FRAX® and its applications in health economics—Cost-effectiveness and intervention thresholds using bazedoxifene in a Swedish setting as an example

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ABSTRACT

Background: An important aspect of cost-effectiveness analysis of osteoporosis is to accurately model the fracture risk and mortality related to the patient groups in the analysis. The estimation of fracture risk is based on a number of factors, such as the level of general risk of the normal population, the effect of treatment and the prevalence of clinical risk factors (CRFs) for fracture. Fracture risk has traditionally been calculated with risk adjustments based on age, bone mineral density and prior vertebral fracture. The treatment effect has been derived from clinical trials and, in the absence of subgroup analyses, the same efficacy has been assumed irrespective of the fracture risk of the population. The FRAX® tool enables the estimation of risk based on a wider range of risk factors, and treatment efficacy that is dependent on the level of risk in the analyzed population. The objective was to describe the implementation of the FRAX® algorithms into health economic osteoporosis models and to highlight how it differs from traditional risk assessment.

Methods: The selective estrogen receptor modulator, bazedoxifene, was evaluated in a Swedish setting with traditional and FRAX®-based risk assessment in a previously developed Markov model that included fractures and thromboembolic events, and also was adapted to accommodate risk-dependent efficacy, which is available for bazedoxifene.

Results: The traditional approach gave lower ICERs at ages up to 60 years compared to the FRAX® method when only considering age, BMD and prior fracture. At 70 years and older and when adding more CRFs with the FRAX® approach, the FRAX® ICER decreased and fell below the traditional approach. The risk dependant efficacy was the main reason for lower ICERs with FRAX® in women at higher risk of fracture.

Discussion: FRAX® applied in cost-effectiveness analyses is a more granular method for the estimation of fracture risk, mortality and efficacy compared to previous approaches that can also improve case finding. Furthermore, it facilitates the estimation of cost-effectiveness for various types of patients with different combinations of CRFs, which more closely matches patients in clinical practice.

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Introduction

An important aspect of cost-effectiveness analysis (CEA) of osteoporosis is to accurately model the fracture risk and mortality related to the patient groups targeted in the analysis. The estimation of the fracture risk is based on a number of factors, such as the level of general risk of the normal population, the effect of treatment and the prevalence of clinical risk factors (CRFs) for fracture. The fracture risk has traditionally been calculated with risk adjustments based on age, bone mineral density (BMD) and prior vertebral fracture. The treatment effect has been derived from clinical trials and, in the absence of subgroup analyses, the same efficacy has been assumed irrespective of the fracture risk of the population.

The recently introduced WHO FRAX® algorithms consider multiple risk factors and are intended to be used to identify patients eligible for treatment based on fracture probability [1–3]. The FRAX® algorithms can also be used to estimate efficacy as a function of fracture probability in clinical trial populations [4,5]. Implementing the FRAX® tool in health economic models for osteoporosis can facilitate the estimation of cost-effectiveness for patients with different sets of risk factors, which has not previously been possible. Combining the FRAX® algorithms and cost-effectiveness modelling will also facilitate the estimation of coherent intervention thresholds, i.e. the fracture risk at which a given treatment should be initiated. Such a development will provide useful data to inform treatment guidelines that are increasing based on absolute fracture risks [6–13].

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The implementation and interpretation of the FRAX® algorithms when used in cost-effectiveness analysis are fairly complex. It is important to be aware of the differences between the previously used traditional method and the FRAX® method to assess risk when comparing results from studies using these different approaches. The use of FRAX® in the context of health economics has not previously been described in detail. The purpose of this article is to describe the implementation of the FRAX® algorithms in a health economic model of osteoporosis and to determine its impact on cost-effectiveness. For this purpose, the use of the FRAX® algorithms is illustrated with data derived from the selective estrogen receptor modulator (SERM) bazedoxifene [14]. The main objective of this study was not the evaluation of the cost-effectiveness of bazedoxifene, which has been done more extensively elsewhere [15]. Rather, the specific objective was to describe the implementation of the FRAX® algorithms into health economic osteoporosis models and to highlight how it differs from traditional risk assessment. The manuscript is therefore less comprehensive with regard to sensitivity analysis, risk scenarios, and interpretation.

Methods

The FRAX® algorithms

The FRAX® tool⁸ was developed by the World Health Organization Collaborating Centre at Sheffield and permits the assessment of fracture probabilities in men and women [3,16]. The tool uses easily obtainable CRFs to estimate probabilities with or without femoral neck bone mineral density (BMD). The inclusion of BMD enhances fracture risk prediction. Poisson regression is used to derive hazard functions of death as well as fracture. These hazard functions, continuous as a function of time, permit the calculation of the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture.

Probability of fracture can be calculated from gender, age, body mass index (BMI, computed from height and weight), and dichotomised risk variables that comprise:

- prior fragility fracture,
- parental history of hip fracture,
- current tobacco smoking,
- ever long-term use of oral glucocorticoids,
- rheumatoid arthritis,
- other causes of secondary osteoporosis and daily alcohol consumption of three or more units.

The relationships of risk factors with fracture risk and death incorporated within FRAX® have been constructed using information derived from primary data of nine population based cohorts from around the world. These include centres from North America, Europe, Asia and Australia and have been validated in 11 independent cohorts with a similar geographic distribution with observations comprising more than 1.2 million patient years [2]. The use of primary data for the model construct permits the determination of the predictive importance in a multivariable context of each of the risk factors, as well as interactions between risk factors, thereby optimising the accuracy with which fracture probability can be computed. The use of primary data also eliminates the risk of publication bias.

In addition to the clinical risk factors, fracture probabilities vary significantly across different regions of the world [17]. The FRAX® models are therefore calibrated to those countries where the epidemiology of fracture and death are known. At present, FRAX® models are available for 18 countries.

How FRAX® algorithms assess fracture risk in cost-effectiveness analysis

Most cost-effectiveness models for osteoporosis are simulated on the risk of fracture events. As a base, the models are populated with the population risk of fracture, which needs to be adjusted to fit the risk for the patient group targeted in the analysis, e.g., a population with a T-score of −2.5 and a prior fracture. In most previous studies, this adjustment has been based on age, BMD and prevalence of fracture [18–23]. All other CRFs have implicitly been assumed to be prevalent at the same level as in the normal population. Using the FRAX® algorithms, it is possible to assess the risk of fracture in much more detail based on any combination of the CRFs included. In addition to the estimation of 10-year probabilities, FRAX® also allows the estimation of relative risk of both hip and major fractures. In health economic modelling, the 10-year probability of major osteoporotic fracture only functions as an indicator variable that is linked to relative risks. The relative risks are then applied to the general population incidences of these individual fracture types to generate annual fracture risks for a specific patient population in the model. The FRAX®-derived relative risk of major osteoporotic is used for vertebral, wrist, and other fracture. To avoid overestimation of the total risk, the relative risks are also inherently adjusted to consider the impact of the prevalence of the CRFs on the normal population incidence. The relative risks derived can thus be used to adjust the population fracture risk for any clinical scenario modelled. Therefore, the traditional and the individual FRAX®-based risk assessment are not directly comparable, as illustrated in Fig. 1. In contrast to the traditional method, FRAX® estimates the CRFs to be either present or not. Thus, a 70-year-old woman with a T-score of −2.5 and no other risk factors will be estimated to have a somewhat lower relative risk of fracture when estimated with FRAX® compared with the traditional method (Table 1).

There are other differences between the traditional method and FRAX® that need to be considered. In the traditional approach, the relative risk of fracture most often employed has been that associated with a prior vertebral fracture, whereas in FRAX® the relative risk is estimated based on any prior fracture. Another difference is that with FRAX®, two estimates of relative risk are estimated (i.e. hip and major fracture) while the traditional approach estimated the relative risks for hip, vertebral, wrist and other fracture separately. Given the differences between the two approaches, it is not actually relevant to directly compare the estimated relative risks, since they each reflect different types of patient populations. As can be seen in Table 1, using the FRAX® algorithm results in lower relative risks for fracture as compared with the traditional method. As noted above, this is because the prevalence of CRFs other than BMD, age and prior fracture with the traditional method are assumed to be the same as in the normal population.

Fig. 1. The difference between the traditional and FRAX®-based risk assessment methods.

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¹ Available at http://www.shef.ac.uk/FRAX.
How FRAX<sup>®</sup> accounts for mortality in cost-effectiveness analysis

After a fracture, the mortality increases [24–26]. The difficulty of incorporating the change in mortality after fracture, compared to before fracture, in CEA is not in obtaining estimates on the absolute mortality rates after fractures. The main problem is that individuals with osteoporosis have a higher degree of frailty compared to the general population [27,28] with its attendant mortality, so that only some fraction of the excess mortality after a fracture is causally related. Only this causal component should be accounted for in estimating the potential gain of avoiding a fracture. Traditionally, this adjustment has been done by assuming that only a proportion (e.g. 30%) of the excess mortality (compared to normal mortality) after a fracture was directly caused by the fracture. Sometimes an adjustment assumption has also been made for pre-fracture mortality by using published estimates on the relation between BMD and mortality [29]. This approach is not optimal, since it provides some inconsistency in the balance of estimated gains related to the life years and quality of life parts in the QALY estimate. An optimal approach would require the possibility of adjusting the mortality before fracture according to the co-morbidity profile of the target patients instead of afterwards. However, this is an obstacle that is difficult to address, since it is likely that the co-morbidity profiles among those that fracture and those that do not fracture differ, implying that the pre-fracture mortality will differ between these patients. This is especially true since it is not empirically possible to observe and estimate the pre-fracture mortality among those that will fracture.

A CRF-dependent relative risk of death related to normal population mortality can be estimated by the FRAX<sup>®</sup> algorithms. This relative risk is used to adjust the baseline mortality in the CEA, as well as the mortality after fracture. We acknowledge that this assumes that the CRF-dependent mortality adjustment is maintained also after fracture. This assumption is made, since the relationship between the CRFs and the risk of mortality after fracture has not yet been investigated. The main consequence of using the FRAX<sup>®</sup> mortality relative risks is that high-risk populations will have a higher overall mortality, thus benefiting less from avoiding fractures, compared to modelling without the mortality adjustment.

Thus, by using the FRAX<sup>®</sup> algorithms to adjust mortality in the CEA, the prediction of the mortality is improved. However, some of the problems of accurately modelling the mortality remain. For example, FRAX<sup>®</sup> only adjusts mortality related to the CRFs. Other factors that might differentiate the mortality in osteoporosis patients compared to the normal population are not accounted for. Therefore, we recommend to conservatively retain the assumption that only a proportion of the excess mortality after fracture is directly related to the fracture event.

### FRAX<sup>®</sup> algorithms to assess efficacy

By estimating the risk for an entire clinical trial population using FRAX<sup>®</sup> and treating this risk as a continuous variable, it is possible to use the whole patient sample to analyze the impact of fracture probability on treatment efficacy, thus avoiding subgroup analysis and the associated loss of statistical power. In recent studies using this approach, it has been shown that treatment efficacy increases with higher fracture risk [5,30]. The present analyses are based on the randomized, double-blind controlled Osteoporosis Study that analysed the efficacy of bazexofenone compared to placebo and raloxifene [14]. The efficacy of BZA (20 mg and 40 mg dosages combined) compared to placebo was estimated as a function of risk and showed that the relative risk reduction increased with increasing 10-year probability of major osteoporotic fracture. On average, bazexofenone was associated with a statistically non-significant 11% decrease in non-vertebral fractures (hazard ratio HR = 0.89; 95% CI = 0.70–1.14) compared to placebo. The hazard ratio for the effect of bazexofenone on fractures decreased with increasing fracture probability when analysed as a function of FRAX<sup>®</sup> 10-year fracture probability as shown in Table 3. In patients with 10-year fracture probabilities at or above 16%, bazexofenone was associated with a significant decrease in the risk of all clinical fractures. Morphometric vertebral fractures showed a significant 39% average decrease in risk compared to placebo (hazard ratio HR = 0.61; 95% CI = 0.43–0.86; p = 0.005) and a similar risk-dependent pattern using FRAX<sup>®</sup> (Table 3).

Incorporating an efficacy dependent on fracture risk will have implications for CEA compared to the traditionally used approach of using average efficacy as observed in the clinical trial. For example, in high-risk populations, the cost-effectiveness would be improved by the addition of risk-dependent efficacy, whereas in low-risk populations it would be worsened.

### Analysis framework for comparing the two approaches

The cost-effectiveness of bazexofenone using FRAX<sup>®</sup> and the traditional approach were compared. Bazexofenone was chosen because its efficacy has been examined using the FRAX<sup>®</sup> tool [5]. Bazexofenone was compared with a “no treatment” alternative because the efficacy using the FRAX<sup>®</sup> algorithms has not been estimated for any other relevant treatment alternative.

A previously developed Markov model for postmenopausal symptoms and osteoporosis [31], of which the structure is depicted in Fig. 2, has been adapted to accommodate bazexofenone and risk-dependent efficacy [32,33]. In short, the model version used in the study simulates patients in yearly cycles from start of treatment until they reach either 100 years of age or death. The model includes fracture states for hip, vertebral, wrist and other fractures (including pelvis, rib, humerus clavicle, scapula, sternum, tibia, fibula, and other femoral fractures). A state considering venous thromboembolic events (VTE) has also been included, since bazexofenone has been found to increase the risk of such events. All states are always accessible and no structural restrictions were thus put in place. By using tunnel techniques for all health states [34], it was possible to implement a “memory” of one previous event into the cohort structure. The method allows for example that long-term consequences of hip and vertebral fractures can be accounted for while patients also can incur any one subsequent event without losing “memory” of the last event. This means that the model will give results that are largely comparable to a Monte Carlo model that can

**Table 1**

Relative risks of fracture for women with a T-score of -2.5 in Sweden using the traditional and FRAX<sup>®</sup>-based risk assessment methods.

<table>
<thead>
<tr>
<th>Age</th>
<th>FRAX approach</th>
<th>Traditional approach</th>
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<tbody>
<tr>
<td></td>
<td>Without prior fracture</td>
<td>Without prior vertebral fracture</td>
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<tr>
<td>Major Fx</td>
<td>Hip Fx</td>
<td>Vertebral Fx</td>
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<tr>
<td>50</td>
<td>1.21</td>
<td>4.08</td>
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<tr>
<td>60</td>
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<td>70</td>
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<td>80</td>
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incorporate any number of events. As the probability of having more than two events is very small, the information lost by using this approach will be negligible. The model was populated with Swedish data, which are summarized in Table 2. The traditional approach gave lower ICERs at ages up to 60 years compared to the FRAX® method when only considering age, Tables 3 and 4. The traditional approach, all other risk factors are assumed to be at the same level as the population prevalence, whereas in the FRAX® approach, the FRAX® ICER decreased and fell below the traditional approach ICER. One reason for this is that, in the traditional approach for fracture risk estimation, the patients are not assumed to have any prevalent CRFs (besides low BMD). Also, with increasing age, the fracture risk increases, which improves the efficacy and thus the cost-effectiveness estimated with the FRAX® approach.

The impact of using fracture risk dependent efficacy and mortality adjustments with FRAX® is shown in Table 5 and Table 6. The ICER was lower using the FRAX® approach at T-scores lower than −1.5. The main reason for these differences is the variable efficacy, which increases with higher fracture risk and more than offsets the higher relative risk of fracture used in the traditional approach. The FRAX® recommendations [37] and Swedish guidelines [38]. Since a population's production is lower than its consumption above the age of 65 years, the inclusion of this cost will generate a non-medical cost of increased longevity in the elderly.

Results

Comparison of the two approaches for fracture risk estimation

The incremental cost per QALY gained of bazedoxifene compared with no treatment for a woman with a T-score of −2.5 at different starting ages for the FRAX® approach with risk-dependent efficacy and the traditional approach with constant efficacy are shown in Tables 3 and 4. The traditional approach gave lower ICERS at ages up to 60 years compared to the FRAX® method when only considering age, BMD and prior fracture. At 70 years and older or when adding more CRFs with the FRAX® approach, the FRAX® ICER decreased and fell below the traditional approach ICER. One reason for this is that, in the traditional approach, all other risk factors are assumed to be at the same level as the population prevalence, whereas in the FRAX® analysis, the patients are not assumed to have any prevalent CRFs (besides low BMD). Also, with increasing age, the fracture risk increases, which improves the efficacy and thus the cost-effectiveness estimated with the FRAX® approach.

The difference between consumption and production [36] or cost in added life years (QALYs), was included in line with academic recommendations [37] and Swedish guidelines [38]. Since a population's production is lower than its consumption above the age of 65 years, the inclusion of this cost will generate a non-medical cost of increased longevity in the elderly.

Cost in added life years

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mortality adjustment did not have a major impact on the cost-effectiveness.

**Intervention thresholds**

Another way of displaying the results from a cost-effectiveness analysis using the FRAX® tool is to estimate the cost-effectiveness for a number of different CRF combinations and correlate the ICER with the 10-year probability of a major fracture. This is shown in Fig. 3, and as can be seen in the figure, the relationship between 10-year probability and risk and the cost per QALY gained is evident. Based on such an analysis, it is possible to derive intervention thresholds for treatment, i.e. to estimate the 10-year probability at which it becomes cost-effective to start treatment at a given willingness to pay (WTP) for a QALY. For example, at a WTP of EUR 60,000, a commonly used reference value in Sweden [39], it would be considered cost-effective to initiate bazedoxifene treatment when the 10-year probability of a major fracture was 15% or higher for 70-year-old women.

It should be noted that the distribution of estimated ICERs in Fig. 3 is not a true representation of the prevalence of CRF combinations for patients in the population but is based on estimated ICERs for a range of different combinations of CRFs and BMDs. However, this will not have an impact on the assessment of the risk at which treatment is cost-effective provided that a sufficient number of scenarios are analyzed.

**Discussion**

The main differences between the traditional and the FRAX® approach are first that FRAX® accounts for ten CRFs in its fracture risk estimation and second that FRAX® facilitates the use of fracture risk dependent efficacy and adjustment of the mortality related to these CRFs. It is important to be aware of these differences when comparing cost-effectiveness studies using the traditional and the FRAX® approach for fracture risk and mortality estimation, since the methods target populations at different risk of fracture (Table 3).

The FRAX® tool can improve case-finding when used in cost-effectiveness analyses and the 10-year probability of major fracture provides a risk indicator that combines and weights together several CRFs into one measure. It also facilitates the estimation of the cost-effectiveness for patients based on any combination of CRFs included in the FRAX® algorithms, which provides a closer matching of patients in clinical practice compared to the traditional approach which considers only a limited number of CRFs.

There is currently a shift in clinical guidelines to move from treatment recommendations based primarily on BMD and prior fracture to recommendations based on absolute risk [7-11,40,41]. This shift will make FRAX® a valuable tool in clinical practice to identify high risk patients eligible for treatment. However, in order to be useful in decision making, intervention thresholds need to be determined. These thresholds could be based either on judgments for which patients it is most clinically relevant to treat, or on health economic arguments, such as estimating at what 10-year fracture probability it is cost-effective to treat. A combination of these two will probably be the most suitable approach. Cost-effectiveness analysis incorporating the FRAX® tool could therefore be useful in informing treatment guidelines and HTA agencies regarding the 10-year fracture risk at which a given treatment becomes cost-effective. The example in this study was based on bazedoxifene, but similar analyses could be appropriate also for other available osteoporosis drugs in order to optimize treatment strategies. It should also be noted that intervention thresholds based on cost-effectiveness need to be defined on a per country basis since e.g. fracture risks, costs, WTP and treatment guidelines differ considerably between countries.

Although cost-effectiveness modelling based on FRAX® confers several advantages, it is not without limitations. Several of the clinical risk factors identified take no account of dose-response, but give risk ratios for an average dose or exposure. By contrast, there is good evidence that the risks associated with excess alcohol consumption, cigarette smoking and the use of glucocorticoids are dose-responsive [42,43]. In addition, the risk of fracture increases progressively with the number of prior fractures [44].

One of the advantages of using FRAX® for assessing the efficacy in a clinical trial is that it avoids the issue of subgroup analysis and its loss of statistical power. Another advantage is that when introduced in cost-effectiveness modelling it will provide a better efficacy estimate for the target population under analysis. Using fracture risk dependent efficacy estimates showed a clearly improved cost-effectiveness among patients at high risk of fracture, suggesting that the cost-effectiveness in these populations has been underestimated in previous studies. The use of risk dependent efficacy in health economic evaluations will thus favour preventative treatment in high risk groups at the expense of low risk groups. Decision makers and payers should judge how to spend the available resources. Society could for example choose to prioritize equality aspects over efficiency, and thus pay more per QALY in low risk groups. One could conversely also argue that efficiency is equality when those who would benefit most from treatment are the ones who receive it. The introduction of

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<th>Table 5</th>
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<td>The cost per QALY gained (EUR) of bazedoxifene compared to no treatment for 70-year-old women with prior fracture and BMD = 26 at various T-scores using the traditional approach.</td>
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<td>Traditional risk assessment</td>
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N/A: not applicable.

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<td>The cost per QALY gained (EUR) of bazedoxifene compared to no treatment for 70-year-old women with prior fracture and BMD = 26 at various T-scores using FRAX®.</td>
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<td>Risk assessment based on FRAX®</td>
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Cost saving Cost saving Cost saving Cost saving

$2.5$ 36%/47% 2.46/2.16 Cost saving $395 38,931 23,490 23,754 Cost saving Cost saving $33,691 15,568 15,388 Cost saving Cost saving $2.123 10,428

$3$ 39%/11% 4.03/5.39 16,454 21,763 30,628

$2$ 39%/11% 1.43/3.00 22,203 28,702 35,794

$–3.5$ 39%/11% 6.77/7.23 11,813 16,164 26,723

$1.5$ 39%/11% 0.85/2.23 40,379 50,833 53,813

$–2$ 39%/11% 1.43/3.00 29,811 37,918 43,108

$–2.5$ 39%/11% 2.40/4.02 22,203 28,702 35,794

$–3$ 39%/11% 4.03/5.39 16,454 21,763 30,628

$–3.5$ 39%/11% 6.77/7.23 11,813 16,164 26,723

Relative risk (hip/vertebral)

Relative risk (hip/vertebral)

Relative risk (hip/vertebral)

Relative risk (hip/vertebral)

Relative risk (hip/vertebral)

Relative risk (hip/vertebral)
generic alendronate has however ensured that most patients at elevated risk of fracture can be treated cost-effectively. Risk dependent efficacy, as estimated with FRAX®, has to date only been demonstrated for clodronate [4] and bazedoxifene [5] and more research is needed to establish whether the same pattern exists for other treatments. Bazedoxifene was used as an example intervention in this study. Even though cost-effectiveness was estimated with appropriate methods and data, the reader should, when interpreting the results, keep in mind that a full analysis, addressing also treatment persistence and causally related mortality, not was provided. For a more complete analysis and interpretation of the cost-effectiveness of bazedoxifene the reader is referred to a recently published study exploring this in a pan-European setting [15].

A concern that has been raised is whether the total risk given by the CRFs in FRAX® is responsive to a therapeutic intervention. For example, in recent NICE HTA appraisals on osteoporosis it was assumed that only 50% of the treatment effect is accounted for in the fracture risk that can be related to CRFs other than BMD, age and prior fracture [45,46]. To test this hypothesis, it would be necessary to recruit individuals selected on the basis of the risk factor(s) to a randomised controlled trial. The risk factor that is best evaluated in this way is BMD, and indeed, the vast majority of therapeutic studies have recruited on the basis of low BMD as recommended by regulatory agencies in the US and Europe [47,48]. In recent years, other trials have recruited on the basis of age, gender, a prior vertebral fracture and current exposure to glucocorticoids irrespective of BMD, and have shown therapeutic effects similar to those noted in RCTs.

![Fig. 2. Structure of the model.](image)

![Fig. 3. Correlation between the 10-year probability of a major osteoporotic fracture (%) and cost-effectiveness of bazedoxifene at the age of 60, 70 and 80 years in women (BMI set to 26 kg/m²). Each point represents a particular combination of clinical risk factors and T-score. Note: A Cost/QALY of 0 means that the treatment is cost-saving.](image)
based on BMD selection [49–51]. By contrast, the HIP study of risendronate failed to show significant reduction of hip fracture risk in women ≥ 80 years of age, which also had at least one clinical risk factor [52]. For many risk factors, comparable data are lacking, but several considerations suggest that this concern is misplaced in the context of the FRAX® risk factors. First, several studies have shown that intervention in the general population induces therapeutic results similar to those expected in individuals selected to be at high risk [2,53,54]. Second, the clinical risk factors are not totally independent of BMD and when clinical risk factors alone are used in women aged 70 years or more, BMD is approximately 1 SD lower in the high-risk group compared with a low-risk group [55]. Perhaps the best evidence is that the response to intervention in elderly women analyzed without including BMD is greater when the probability of fracture estimated from FRAX® is higher [5]. These considerations suggest that the risk factors chosen are appropriate, but a larger prospective experience of phase III studies is still needed.

The incorporation of FRAX®-adjusted mortality gives a better reflection of the mortality related to the specific patient group that is analysed compared with the traditional approach. However, the incorporation of FRAX®-adjusted mortality did not have any major impact on the cost-effectiveness in the present study. Although the FRAX® approach provides a more accurate prediction of mortality, it does not overcome the main issue related to co-morbidity and its impact on excess mortality after fracture. A partial solution to this problem could be to estimate the impact on post-fracture mortality related to the FRAX® CRFs. However, that is an area for future research.

Another limitation of the FRAX® approach is that the relative risks are only differentiated on hip and major fracture. For example, a prior fracture might incur different risk increases, depending both on the type of prior fracture and the fracture type it will predict. This is not likely to lead to any major consequences on the cost-effectiveness since the relative risk will be underestimated for some fracture types and overestimated for others, which will balance this discrepancy. However, the estimation of risk for various fracture types should be investigated further in future analyses of the FRAX® data.

We conclude that the implementation of FRAX® in cost-effective ness analyses refines the estimation of fracture risk, mortality and efficacy compared to previous approaches. It also facilitates the estimation of cost-effectiveness for various types of patients with different combinations of CRFs, which more closely matches patients in clinical practice.

As clinical guidelines shift to recommendations based on absolute risk and FRAX® becomes more widely used in clinical practice, it is important that the health economic evaluations of osteoporosis interventions follow suit and produce results that can be interpreted in this context.

Acknowledgments

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