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Modelling the Cost Effectiveness of Interventions for Osteoporosis: Issues to Consider.

Abstract

Expenditure on treating osteoporotic fractures and on preventative intervention is considerable and is likely to rise in forthcoming years due to the association between fracture risk and age. With funders such as the National Institute for Health and Care Excellence and the Pharmaceutical Benefits Advisory Committee explicitly considering cost effectiveness analyses within the process of producing guidance it is imperative that economic models are as robust as possible. This paper details issues that need to be considered specifically related to health technology assessments of interventions for osteoporosis and highlights limitations within the current evidence base. A likely direction of impact on cost effectiveness of addressing the key issues has been included alongside a tentative categorisation of the likely level of these impacts. It is likely that cost effectiveness ratios presented in previous models which did not address the identified issues were favourable to interventions.

Declared conflict of interests: Professor Stevenson has received grants from the National Institute for Health Research to undertake health technology assessments within the disease area of osteoporosis. The department in which Professor Selby works has received research support from Amgen who manufacture drugs for the treatment of osteoporosis but he has received no personal financial support.

Key points for decision makers

In order to accurately estimate the cost effectiveness of screening policies costs of identifying people with osteoporosis but without a recent fracture must be included

Rigid adherence to the definition of osteoporosis, or using a single threshold value for fracture risk over a defined period of time in deciding whether to treat or not is unlikely to be optimal approaches in terms of efficient allocation of resources

A tentative categorisation of the level of impact of addressing each issue has been produced.

Background

The internationally agreed definition of osteoporosis is a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] Two thresholds of bone mineral density (BMD) have been proposed for Caucasian women based on the T-score (the number of standard deviations from the average bone mineral density of healthy young women).[2,3] The first, osteoporosis, is defined as a T-score of –2.5 SD or less. The second, osteopenia, is defined as a T-score between –1 and –2.5 SD.

In 2000 the cost of treating osteoporotic fractures in postmenopausal females was estimated to be £1.5 - £1.8 billion per annum in the UK.[4,5] The expenditure on hip fracture in Germany in 2003 was €2.77 billion,[6] whilst fractures in the elderly were estimated to cost $14 billion in 2002 in the USA.[7] The risks of hip and vertebral fractures have been shown to be distributed exponentially in relation to age,[8] using Scottish data.[9] Thus, given the ageing population in developed countries the budgetary impact of osteoporosis, whether through preventative interventions or through treatment of fractures is likely to increase significantly. With funding organisations such as the National Institute for Health and Care Excellence (NICE) in England and Wales and the Pharmaceutical Benefits Advisory Committee (PBAC) in Australia explicitly considering cost effectiveness when appraising interventions there is a requirement for robust economic evaluations.

A recent systematic review of cost effectiveness modelling analyses of identification and treatment of those at risk of osteoporosis or osteopenia was conducted by Müller et al.[10] Twenty-four papers published since 2006 were identified and assessed using the Philips et al checklist.[11] This checklist addresses 15 dimensions of quality which are grouped into three categories: structure; data; and consistency. Each dimension was graded as: being adequately addressed; being inadequately addressed; or unclear or not applicable. A simple scoring system was used with 1 point awarded for meeting demands and -1 for not meeting demands, these results show a considerable range in the quality of reporting, (-4[12] to 14[13]). However, typically the general quality of reporting was high with a mode of 12, a median of 10 and a mean of 8.1 (standard deviation (SD) 4.7)

The intention of this paper is to highlight areas associated with modelling the cost effectiveness of interventions for fracture prevention that warrant further discussion. These areas have been divided into two broad categories: structural issues and model population issues. The remit of this invited paper was to outline, from our experience, issues to consider when modelling the cost effectiveness of interventions for osteoporosis. As such, no formal systematic review was undertaken and this paper would be classified as expert opinion. The issues selected have been those that have been

encountered when undertaking modelling for NICE or the National Institute for Health Research. Both authors were actively involved in informing NICE Technology Appraisals 160 (TA160)[14] and 161 (TA161)[15] which provided guidance on the use of alendronate, etidronate, risedronate, raloxifene and strontium ranelate.

Structural Issues

Including the costs of patient identification

The route by which a person is identified as being a candidate for cost effective treatment with a pharmaceutical intervention can fundamentally change the incremental cost effectiveness ratio (ICER) of a global strategy. Patients who have sustained a fracture that required clinical treatment are effectively self-identifying and would result in one BMD scan per patient with a fracture; in contrast, a patient who is asymptomatic, but who met the criteria for treatment would need to be identified amongst a larger group of people, of whom the majority may not be cost effective to treat, resulting in a large number of BMD scans (and expense) being required. Due to the increased costs of effectively screening people, NICE issued separate guidance for those patients with a previous fracture, (TA161)[15] and for those without (TA160).[14] This division also allowed different cost effectiveness thresholds to be used for each group as it was believed that more caution should be exhibited in treating, and exposing to potential adverse effects, women with asymptomatic osteoporosis than women who had sustained a fracture.

The choice of fracture sites to include

Typically, all cost effectiveness models of interventions to prevent fractures have explicitly incorporated discrete states for: hip; wrist; and vertebral fractures. Often remaining sites have been considered within a homogeneous 'other fracture' health state although this has the disadvantage in that it does not distinguish between the consequences of the fracture which can be widely different, for example between other femoral fractures and rib fractures. However, if the proportions of fractures within the 'other' states are explicitly tracked and different costs and disutilities are used for such fractures, as in Schousboe et al[16] then this limitation is removed.

Within the modelling used to inform TA160[14] and TA161,[15] Stevenson et al[8] grouped: pelvis and other femoral fractures within hip fractures; tibia and fibula fractures within proximal humerus fractures and rib, sternum, clavicle and scapula fractures within wrist fractures, with the class

membership decided on the similarities of the costs incurred and the effect on utility, although on reflection the allocation of pelvis fracture may have overstated the impact of these fractures. Such adjustments (typically a 20% increase in the incidence of 'hip' fracture in the work by Stevenson et al [8]) are needed so a bias against interventions for fracture prevention is not created.

Incorporation of patient history

There is evidence to suggest that the presence of a previous fracture has the effect (albeit of finite duration) of increasing the expected risk of further fractures.[17] To incorporate such patient history whilst maintaining the impacts of all fractures sustained into a model introduces complexity. This would require individual patient modelling approaches or a large number of health states within a cohort model, which would require all combinations of fracture status. Assuming only four fracture sites, but with the requirement to know whether a fracture occurred in the current year or before (for cost and disutility purposes) would require 2^8 (256) fracture health states. Kanis et al report that over one million branches would be required were the individual patient model used within this research, to be replaced with a decision tree which predicted the event in the forthcoming year.[18] The model described in Kanis et al[18] formed the backbone of subsequent models constructed by the independent assessment group to inform the NICE TA160[14] and TA161.[15] Individual patient models can, however, be computationally expensive and may require efficient coding within a computer language / package, such as R, or the use of meta-modelling techniques,[19] in order to run probabilistic sensitivity analyses (PSA). PSA is widely recommended as it produces accurate answers in non-linear models[20] and is preferred within manufacturer submissions to NICE, with the statement that 'The use of model structures that limit the feasibility of probabilistic sensitivity analysis should be clearly specified and justified'.[21] However, individual-based models will allow easier incorporation of factors such as the particularly high risk of fracture in the first year following a fracture which falls gradually afterwards.[22] The level of discrepancy between individual patient models and cohort models may however not be marked, when the individual patient model was populated with data from a Markov-based cohort model[23]the results were reported to be similar.[24]

The use of variable or fixed BMD thresholds

Although clear definitions for osteoporosis and osteopenia exist these were based on epidemiological rather than clinical criteria.[25] As such, this does not mean that recommended BMD thresholds for treatment have to be aligned with these definitions; indeed it is likely to be sub-

optimal in terms of cost effectiveness to have the same treatment recommendations for people with osteoporosis, people with osteopenia and the remaining people. An alternative method would be to allow variable thresholds dependent on the estimated cost per QALY. Such models which assess at what T-Score treatment should be initiated, should produce more efficient allocation of resources, as it allows the more severe patients to have access to treatment when an entire category may not be cost effective to treat, or alternatively, prohibit treatment for less severe patients even though the entire category may be most-effective to treat. These approaches have been refined further by additional sub-division of the population by age, gender and number of potential clinical risk factors resulting in a multitude of mutually exclusive and exhaustive health states. An example of this is the guidance associated with TA161[15] where recommendations for risedronate, etidronate and strontium ranelate use T-Score values, such as -3.0SD or -3.5SD, which are not aligned with the definition of osteoporosis. Historically, results presented by Müller et al[10] showed that more models considered osteoporotic patients as a non-divisible category rather than allowed T-Score thresholds to be defined based on the estimated ICERs.

However, using variable thresholds can result in patients originally identified as requiring treatment with a relatively inexpensive intervention being denied treatment with a more costly treatment due to the ICER being prohibitively high. This can cause concern in the clinical community when an initial treatment has been provided, and then no substitute offered if the patient cannot tolerate the intervention as witnessed in the comments to the NICE technology appraisals.[15,] **Error! Bookmark not defined.** Whilst this could be addressed by using a weighted average of interventions as undertaken in Schousboe et al[26], to ensure treatment is continued this would result in inefficient allocation of resources. This is for two reasons (i) people who could have cost effectively received an initial treatment may no longer receive this as the application of the weighted cost of the bundle of treatments may result in the ICER being deemed too high and (ii) people could receive interventions for which it is known that the ICER in isolation is too high, but it is being subsidised in a weighted bundle of interventions due to highly cost effective interventions earlier in the sequence. In both cases, reallocation of resources would be expected to improve societal health. The tension between efficient allocation of scarce resources and patient-clinician relationship remains unresolved.

Threshold defined in terms of risk of fracture over a defined period versus subgroups of patients in whom interventions are estimated to be cost effective when using annual transition probabilities.

The benefits and disadvantages of assuming a fracture threshold over a period, for example 15% over ten years, at which patients should receive treatment is one of contention, although it is recognised that a single risk value may be easier to implement clinically. Risk calculators such as FRAX®[27] provide risk of hip and major fracture over a 10 year period in a relatively simple to use webpage.

However, in TA160[14] and TA161[15] NICE deemed it more appropriate to provide guidance based on a model that included the annual risks of fractures which were supplied, in confidence, by the FRAX® developers. Briefly, the reasons against using a single risk threshold include: non-differentiation between fracture types in terms of costs and disutility; ignoring the effects of age on cost effectiveness in terms of requiring nursing home care and mortality rates; omission of the increased costs of identification in those without a fracture; the possibility that the funding agency assumes different cost effectiveness thresholds for those with and without a fracture (as NICE did); that given the different prices and efficacy of the interventions that each intervention would have a bespoke risk threshold if efficient allocation of resources was the goal; and that is it unclear whether all components of fracture risk are modifiable by pharmaceutical intervention. Further research on the possibility of using a single threshold has been reported in a NICE Decision Support Unit Paper.[28] This paper concluded that 'it does not appear straightforward to generate an algorithm based on absolute fracture risk (including ratio of hip to major fractures) that could robustly predict a positive recommendation in TA160[14] or TA161'. However, there may be pragmatic reasons to accept under, or over, treatment of people were this to make treatment guidance more simple to implement and this issue is being further explored by NICE.

Assumed length of treatment

One aspect rarely considered within cost effectiveness models is the length of time a treatment is to be provided. Many models have assumed a finite treatment length and then assumed a residual period in which the efficacy of fracture prevention wanes. If patients are to be treated for a longer period then these residual benefits (which are provided without cost) would be less influential and the ICER would increase. If treatment can only be provided for a finite period then strategies that withheld treatment until patients were at most-risk could be considered as alternative interventions.

The longer-term efficacy of alendronate was explored in the FLEX study,[29] where continued treatment for a further five years was observed to reduce vertebral fractures by 55% but not non-vertebral fractures relative to no further treatment. A study using expected value of sample information techniques[30] concluded that an RCT evaluating the long-term efficacy of bisphosphonates in fracture prevention appeared to be cost effective for informing decision making in England and Wales.[31]

Additionally as outlined in the 'Adverse Events' section prolonged treatment may be detrimental to patient well-being.

Adverse Events

Currently the adverse events associated with interventions for osteoporosis, which include osteonecrosis of the jaw or gastrointestinal problems have often not been explicitly incorporated within models. In the modelling undertaken to inform TA160[14] and TA161[15] the costs and potential adverse effects of protein pump inhibitors were included, however the NICE Appraisal Committee were content purely to note that osteonecrosis of the jaw was a potentially side effect that would be unfavourable to bisphosphonates.. However, as the observational evidence base grows for current interventions or with the advent of more efficacious, but potentially more harmful interventions these conclusions may change, as such adverse events should be reviewed prior to any new economic analyses.

Emerging data on atypical subtrochanteric and diaphyseal femoral fractures in patients receiving long-term bisphosphonates (approximately 1 per 1000 person years)[32] indicate that this may need to be considered in patients modelled to receive prolonged bisphosphonate treatment. The authors are not aware of modelling work that has incorporated such fractures.

Adherence

Müller et al[10] comment on the frequent omission of the effects of non-adherence within published models of osteoporosis interventions. Within the modelling used to inform TA160[14] and TA161[15] adherence was modelled crudely as either fully adherent or non-adherent, where the costs of 3 months' prescription were assumed to be incurred without benefit. In the results produced non-adherence did not significantly change the ICER, as the cost implications were relatively small given five-year treatment periods. However, this may be too simplistic an approach and would ignore

people who may remain on an intervention but be less than fully adherent. This was explored by Hiligsmann et al[33] where real-world adherence in Ireland was shown to halve the benefits associated with treatment and double the ICER when assuming a relative risk of 1.17 in the increase in fractures associated with patients with a medical possession ratio of less than 0.8.[34] More sophisticated methods such as those by Hiligsmann et al should be used, particularly with the advent of interventions where adherence is maintained through the delivery mechanism (such as the once-yearly injections for zolendronic acid) where differential adherence levels could result in marked changes to the ICER.

Model population issues

Calculation of fracture risks for the referent woman

It is typical that clinical risk factors are reported in terms of their impact on risk per Z-Score (the SD from the average person of that age), as for example is the effect of low BMD on fracture risk.[35] Care is needed to calculate correctly the risk values for women without risk factors having taken into account the prevalence of clinical risk factors in the group for which an average fracture rate is reported. An example of this is provided in Stevenson et al.[8] where, adjusting only for age and previous fracture, it was estimated that the risks of hip fracture for women aged 70-74 years, with average BMD and no fracture were 54% lower than those for the average of women aged 70-74 years. Failure to adjust average fracture rates will lead to over-estimation of fracture rates; an error that will increase the greater number of risk factors considered and will bias analyses in favour of interventions for fracture prevention.

Synthesising efficacy data from randomised controlled trials

Historically, interventions have been tested in randomised controlled trials (RCTs) against placebo, which resulted in only indirect comparisons being made between competing interventions.[36] However, as placebo controlled trials become less ethical, as patients should not be randomised to treatment of proven non-effectiveness when effective (and inexpensive due to generic formulations) treatments are available, it is likely that head-to-head RCTs will be conducted and that network meta-analysis would be required.[37] Such analyses would require explicit assumptions to be made regarding whether drugs within the same class, for example alendronate and risedronate, truly

exhibit a class effect, or whether there are actual differences between the efficacies of these interventions. The uncertainty in the relative effectiveness of interventions will be greater when compared with active interventions rather than placebo unless the numbers recruited are significantly increased as the incremental benefit will be smaller. Synthesis of the efficacy will be made more complex if it is believed that different components of fracture risk are less modifiable through pharmaceutical intervention as discussed in the next section.

Application of estimated efficacy levels to overall risk level when it is possible that efficacy differs between components of fracture risk

Typically, the pivotal RCTs that have proven treatment efficacy for each intervention have recruited elderly, females based on the presence of low BMD and/or a previous fracture. As such, it has been shown that interventions reduce fractures in such women but not people who do not have these characteristics. For example, there is significant circumstantial evidence that the non-vertebral fracture reduction efficacy of bisphosphonates and denosumab are much greater in those with femoral neck T-score <=-2.5 compared to those with femoral neck T-score > -2.5.[38 39 40] Additionally there is little evidence that the interventions would reduce the risks conveyed by factors (that are contained within FRAX®) such as current smoking, relatively high alcohol consumption and rheumatoid arthritis.

Accordingly NICE requested that analyses be undertaken allow a differential (and greater) efficacy for risks conveyed through age, sex, low BMD and prior fracture than through other patient characteristics. In calculating the respective efficacies associated with each group care was taken to maintain the average efficacy reported in the RCTs. Until robust data on whether interventions have similar efficacy across all components of risk are obtained this will remain a key area of uncertainty.

Uncertain, or dated, parameter values

Whilst the costs of treating fractures are relatively known, due to the large proportion that result in either hospitalisation or hospital treatment there is less certainty in the values assumed for other parameters. The disutility associated with vertebral fractures often have been derived from Swedish data [41] and which Müller et al.[10] state leaves a 'study susceptible to bias' due to the lack of a utility value prior to the fracture. The emergence of research to identify more accurately the disutilities associated with fractures will increase the robustness of the results.

Whilst data reporting the rate of mortality following a hip fracture exist,[42] it is likely that a substantial component can be attributed to comorbidity;[43,44] precise and recent data are not available. The same issues relate to estimated mortality following a clinical vertebral fracture where data from Australia[45,46] and the UK[47] show a significant increase in mortality, although the proportion judged to be causally related is uncertain and has been estimated from a Swedish hospital admission registry.[48]

Admission to nursing home has both a large impact on both costs and quality of life, although the data on the incidence attributable to a hip fracture and on utility remain uncertain. Where possible, we recommend that the impact of these uncertainties be formally reported via expected value of partial perfect information techniques,[49] which would provide funders with further evidence when considering whether to commission research studies.

Schwarz et al[50] report that they identified no RCTs that evaluated the efficacy of pharmaceutical interventions for males using fracture as an outcome measure, however, studies were identified that used the surrogate outcome of BMD change. Currently treatment recommendations for men have been generated based on inferences between the BMD changes in males and those observed in females and thus are less certain than were data on fracture reduction available.

Relative importance of the issues considered.

The issues considered have been tabulated, in order of appearance, with the authors estimating the direction of impact of each issue on the cost effectiveness of a specific intervention compared with no treatment and the estimated level of impact (Table 1). The categories used are broad: favourable, unfavourable and unknown for the direction of impact; and large, moderate, slight and unknown for the level of impact. There is little evidence regarding the level of impact and thus there is uncertainty in this categorisation. It is seen that the incorporation of additional factors within the model is likely to be unfavourable to interventions in terms of cost effectiveness as the number of unfavourable impacts are greater than the favourable ones. Whilst the level of impact for: the use of variable BMD thresholds; the use of patient specific thresholds ; and on evaluating interventions directly cannot be estimated *a priori,* from a funder's perspective addressing these issues would allow more efficient allocation of resources.

[Table 1 near here]

Discussion

A large limitation to this paper is that it is, in essence, expert opinion with the inherent biases that are associated with such work. As the authors reside in England and have undertaken significant amounts of work for NICE the paper is likely to be UK-centric although we believe that all of the issues raised are relevant to cost effectiveness modelling of osteoporosis interventions in all regions. A systematic review was not undertaken and references are largely limited to those that were already known by the authors; it is probable that newer values for some parameters exist although these would not change the intrinsic message regarding the issues that need to be considered when undertaking health technology assessments for interventions to prevent fracture.

Modelling the cost effectiveness of interventions for reducing the risk of fractures is complex. The asymptomatic nature of the disease means that people with osteoporosis often remain undetected until a fracture occurs. Additionally, BMD is measured on a continuum where people with similar T-Scores can have different cost effectiveness ratios, and subsequent funding decisions, based on characteristics such as age and the number of associated clinical risk factors. Whilst a single 10-year risk of fracture threshold may be appealing there are a number of reasons why this concept is limited.

Challenges remain in terms of data collection with pressing concerns relating to: which components of risk can be modified by pharmaceutical interventions, with currently only age, sex, low BMD and previous fracture being clearly linked to efficacious treatment; robust data on mortality following hip or vertebral fractures, and the rates attributable to the fracture; robust data on nursing home admissions which are costly; the reduction in utilities associated with fracture; and the efficacy of interventions in males.

This paper has attempted to summarise the key issues and to provide a likely direction of any impact in terms of cost effectiveness of incorporating features as well as the estimated level of the impact. However, it is acknowledged that the categorisations are the authors' opinions and there is little hard evidence available. It is recommended that the features which we believe to have at least a moderate impact should be included in any future osteoporosis model, although as complexity of models increase it may be that individual patient models are needed. Whilst some published models have included the majority of these features, to the authors' knowledge no model has adequately incorporated all of the features. In addition, we recommended that the default analysis would use

variable BMD thresholds, use patient specific T-Score thresholds and analyse interventions directly rather than as a package of care in order to efficiently allocate resources.

Based on our estimate of the likely favourable or unfavourable impact of including each feature it is likely that previous estimates of cost effectiveness are likely to be favourable to interventions; addressing all of the issues identified within this paper is likely to increase the ICER.

Different jurisdictions may have different recommendations for whether the costs of home help, lost productivity, or of future added life years should be included in the base case analyses. Therefore these are not discussed within this paper although it is recommended that modellers adhere to the reference case for each jurisdiction.

Conclusion

Whilst complex modelling work has been undertaken to estimate the cost effectiveness of interventions to reduce fracture in patients with osteoporosis or osteopenia there remain outstanding issues. This paper has attempted to detail the issues that need to be considered when constructing such a cost effectiveness model, highlight the likely direction and level of impact for methods of addressing these issues and also to highlight the gaps in the evidence base that need strengthening in order for more robust estimates of cost effectiveness to be determined. If all of the issues identified were adequately addressed it is likely that the resultant change in ICER would be unfavourable to interventions.

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