

Editorial

Economic Evaluation of Interventions for Osteoporosis

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Health economic evaluation is an increasingly important component of drug development in osteoporosis because of the rapidly-increasing opportunities for prevention and treatment. There is a need to justify resource allocation both for the selection of therapies for prevention and treatment of osteoporosis, and for allocating resources for this condition in competition with other diseases. The field of osteoporosis is immature in terms of pharmaceutical development compared to many established chronic diseases such as cardiovascular disease or diabetes despite the substantial health economic burden of osteoporotic fractures [1]. Treatment and prevention strategies for osteoporosis must therefore be shown to be not only medically justified and possible to implement in clinical practice, but also cost-effective. Model-based health economic studies provide a cornerstone because of their opportunity to integrate epidemiological, clinical and economic data and their flexibility to take account of the many uncertainties that confront such analyses.

This supplement issue provides an update for the health economic assessment of interventions in osteoporosis. It builds on an earlier platform published several years previously [2]. The first paper, developed under the auspices of the two WHO collaborating centers in the field, provides an extensive review of the data available to date on cost utility analysis. The preferred approach is cost utility analysis, involving the calculation of cost per quality adjusted life year gained from intervention, since such analyses provide an established mechanism for comparing cost effectiveness across diseases – an important component of investment strategies. The preferred approach to modeling is the use of a Markov

model. It is suggested that the model developed at the Stockholm School of Economics [3] be used as a reference standard. Different, and usually more complicated approaches are under development, but the advantages of these have yet to be shown. A key factor is the availability of data to populate more sophisticated models. A reference standard is, however, only a platform from which new approaches can be judged in the search for improvements.

With regard to the selection of the primary effectiveness or outcome measure for a model, fracture outcomes are preferred to bone mineral density. Whereas there is a well-established relationship between bone mineral density (BMD) and fracture risk, many factors other than BMD contribute to risk. Moreover, the treatment-induced changes in fracture rate cannot be inferred from the magnitude of treatment-induced changes in BMD with any degree of confidence in that changes in fracture rate are greater than that expected solely from changes in BMD [4]. Where possible, reduction in fracture rates and other outcomes should be modeled from information available from randomized controlled trials (RCTs).

All relevant outcomes should be considered and modeled separately. This increases the complexity of modeling due to the increased number of transition states, but the complexity generated by the great number of potential osteoporotic fractures, can for some applications be reduced by weighting fracture incidence by disutility [5]. For several treatments in osteoporosis, extraskeletal benefits and risks should be accommodated. Examples include the effects of estrogens and selective estrogen receptor modulators on cardiovascular disease and breast cancer. For agents without significant extraskeletal benefits or risks this complexity is redundant. Notwithstanding, drugs do have side effects with very significant implications for cost utility, and models should provide for this contingency.

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It should be acknowledged that our information on fracture risk is incomplete and all assumptions should be made explicit. For example, in modeling cohorts of patients with osteoporosis but without fracture, the relevant fracture risk is the risk of a first fracture. Crude data on incidence overestimate this risk [6]. In patients with established osteoporosis the risk of future fracture may not be linear. In individuals hospitalized for vertebral fracture the risk of further fracture is increased markedly in the several months following admission and then tails off, though not to the risk of the general population [7]. The risk of fracture also varies markedly in different countries so that appropriate data should be used or the assumptions made explicit.

Emphasis is also placed on several aspects of treatment. Treatment effects should be modeled in a base case from randomized controlled trials where available with appropriate assumptions on how long the intervention lasts, compliance and the offset of effects once treatment is terminated. It is appropriate to state the levels of evidence on which efficacy is assumed in line with recommendations for evidence-based medicine. This would help avoid the entrenched positions of dogma, for example the view that hormone replacement provides significant cardiovascular protection – a view that is being challenged as data from randomized controlled trials become available [8]. However, the request for evidence-based data on effectiveness should not prevent the use of sensitivity analysis to address ‘what if’ issues where uncertainty of effectiveness is genuine.

A crucial issue concerning effectiveness of intervention relates to what happens when treatment is stopped. Fracture risk is unlikely to revert to that of the untreated patient at the time of stopping treatment. Rather, the effect will wane over several years. Economic analysis has shown the great importance of assumptions in offset time [9]. Unfortunately, offset times have not been well studied, and this lies behind the recommendations by the WHO for this to be studied as a requisite of drug development [10].

The review also makes recommendations for a defined standard for cost effectiveness. A value of \$60 000 per quality of life year (QALY) gained is suggested for the developed countries. It is relevant to note that this is based on analyses that include the cost of added years [11], and when these are excluded a lower value of \$30 000 per QALY gained provides a reasonable yardstick. The reason for the higher value when costs of added years are included is that cost-effectiveness ratios generally increase when the costs of added life years are included, since most reductions in mortality occur at older ages. The inclusion of costs in added years of life will also change the relative cost-effectiveness of different programs. Mortality reductions at younger ages and QALY gains at older ages will affect cost-effectiveness of interventions aimed at the young or the elderly.

It is important to acknowledge the incompleteness of information. An example is provided by the estimates of mortality following fracture. Excess mortality is

attributed both to hip fracture and spine fracture (though not for Colles fracture). A great uncertainty is the extent to which mortality is reversible by intervention and few studies have yet addressed this point.

The greatest difficulty that arises in making recommendations is the perspective of cost-effective analysis. On the one hand it is argued that cost-effectiveness should include all costs and benefits to society – the societal perspective. On the other hand, healthcare purchasers, regulatory agencies and reimbursement committees are often only interested in costs that affect their budget. A decision maker may also only be interested in costs and benefits over a limited time period suitable for their own decisions. A decision maker may thus decide to ignore costs due to reduced mortality (cost in added years of life) despite the arguments for including these costs in a social perspective that are presented in the report. Thus, the recommendation arises to preserve flexibility intrinsic in the model and to suggest that, where feasible, cost utility analysis should also include an assessment of the societal perspective. There will, for example, be instances where decisions favorable for a purchaser are unfavorable for society and vice versa, and that information may be valuable for understanding the incentives and disincentives for prevention and treatment of osteoporosis that different decision makers face.

A second paper developed by the International Osteoporosis Foundation reviews the information on utilities available in osteoporosis. This highlights several uncertainties. An example is provided by the health states assigned to the same osteoporotic fractures by different methodologies (e.g. standard gamble, time trade off). Differences also arise depending on whether utility values are derived from patients, members of society or expert committees. There is also a lack of empirical data concerning the time course of disutility following many osteoporotic fractures which is clearly an area for further research.

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