Towards a Reference Case for Economic Evaluation of Osteoporosis Treatments

INTRODUCTION

The growing number of economic analyses in the general medical literature and the increasing requirements for economic evidence with regard to reimbursement of pharmaceuticals have led to a number of attempts to provide guidelines for the conduct and reporting of studies[1-5]. Guidelines may undertake any of 3 specific roles: to promote the standardization of methods to allow comparison across studies, to facilitate the interpolation of studies across jurisdictions, and to act as an educational tool for both users and producers of studies.

Guidelines often focus on promoting the use of either a set of minimum or core requirements or a reference case[1,5]. For many issues in the conduct of economic evaluations, guidelines reflect the consensus within the research community. For example, the need for discounting, sensitivity analysis, and the separate reporting of costs and resource use is widely recognized and accepted. However, there are still areas where consensus has not and may never be reached.

The objective of this article is to present a draft reference case for economic evaluations in osteoporosis. The article builds on ongoing work to develop standards within the conduct of economic evaluations in rheumatology especially for rheumatoid arthritis[6]. The paper provides definitive guidance for those issues within an evaluation for which consensus has been reached and also highlights those areas for which consensus has not been reached. Recommendations with respect to the latter issues are suggested primarily to facilitate further debate.

ISSUES OF CONSENSUS

Study Purpose and Population

Studies should report patient characteristics relevant to the evaluation of therapies for osteoporosis. Important characteristics include age and whether the patient had previous fracture, both strong predictors of the baseline risk of fracture[7,8]. If possible, studies should incorporate a stratified analysis where the costs and benefits of therapies are estimated for alternative patient profiles[9].

Clinical Data

The effectiveness of therapies should be based on efficacy data from clinical trials. Where possible, evaluations should be conducted based on the results of metaanalysis rather than single trials, as this limits the potential for bias[10]. When conducting such analyses, attention should be given to the use of bone mineral density t scores for trial inclusion. Baseline rates of fractures and mortality should be obtained from relevant population databases for the geographical location for which the analysis is being conducted[7,11,12].

Resource Use

Evaluations should consider the costs of drug therapies including health care costs associated with monitoring of drug therapies (e.g., additional health care provider visits) and/or managing treatment-emergent side effects. In addition, both the acute and longterm costs associated with fracture should be included in analyses. If any extraskeletal effects of the treatment are documented, then related resource use should be included in the analysis.

Discounting

Future costs and benefits should be discounted. Base case analysis and sensitivity analysis should include at least 0, 3, and 5%[1,5].

Source of Study Funding

There has been concern over the potential bias from studies funded by the pharmaceutical industry[13,14]. However, it is unlikely that sufficient economic studies could be produced without industry funding. Therefore, in addition to a statement on funding source, authors of industry-sponsored studies must demonstrate their independence in the conduct and reporting of the economic evaluation. Only studies that were conducted under contracts that allowed for independence over all aspects of study design, analysis and interpretation, and reporting of results should be considered for publication.

ISSUES OF DEBATE

Here we highlight the major issues of debate within the conduct of economic evaluations in osteoporosis. The issues identified have been highlighted in previous work and primarily reflect the lack of specific data to facilitate analysis[15-18].

Study Perspective

Where possible, studies should adopt the societal perspective. The effect of adopting a societal perspective will be dependent on whether the productivity losses associated with informal caregivers are deemed appropriate to include. Treatment of osteoporosis is ostensibly for patients who are past working age. Thus, if costs related to informal caregivers are excluded, evaluations incorporating costs to both the health care and social care sectors should be accepted as close approximations to the societal perspective[19]. However, if informal caregiver costs are included, their incorporation may lead to lower cost effectiveness ratios than from a health care perspective.

Recommendation. Studies should at least adopt a perspective incorporating costs to the health and social

care systems. Analysts should be encouraged to adopt the societal perspective and further studies should be conducted to estimate informal caregiver costs.

Basis of Modeling Osteoporosis Outcomes

Previous models used in economic analysis in osteoporosis can be categorized as either age-specific fracture incidence based on models or bone mineral density (BMD) based models[16,17]. To model treatment effectiveness, fracture incidence-based models directly apply the relative risk reduction for therapy reported in clinical trials to baseline age-specific fracture incidence rates in the population of interest.

Relative risk reductions from randomized controlled trials usually are reported separately for vertebral and nonvertebral fracture sites. However, for different nonvertebral fractures the proportion of fractures attributable to osteoporosis varies substantively, suggesting that the relative risk reductions from therapy will vary by the location of nonvertebral fractures[20]. In addition, there are substantive differences in the costs, mortality, and quality of life effects associated with fractures[21]. Thus, for economic analysis it is necessary to obtain relative risk reductions for specific fracture sites: vertebral, wrist, and hip.

BMD-based models utilize epidemiological evidence to parameterize fracture incidence as a function of BMD and age. A caveat to this approach is that the evidence provided in epidemiological studies linking BMD changes to fracture risk often reflect cross-sectional population differences and may not be valid for interpreting the likely effect of longitudinal BMD differences observed in clinical trials.

Thus the BMD-based approach is more complex than the fracture incidence-based approach and has a greater potential of error. However, it has been attractive in that previously trials of osteoporotic therapy tended to focus on detecting differences in BMD rather than a decline in fracture rates. As evidence of reduction in fractures has become required more by regulators, the need for BMD-based models is less clear[22]. Further, for newer osteoporotic treatments such as bisphosphonates it is unclear that a BMD level obtained through treatment will be associated with the same level of fracture risk if fracture occurred without treatment[23]. Ultimately, for economic modeling and clinical trial planning purposes it would be desirable to develop a comprehensive model that could accurately predict fracture on the basis of both BMD changes and markers of bone resorption and formation.

Recommendation. We propose that future economic analyses of interventions for osteoporosis follow previous recommendations of adopting fracture-based models[16,24] until a more comprehensive modeling framework is validated. In addition, we propose that relative risks should be obtained for at least the 3 primary fracture sites and should be based on symptomatic fractures.

Mortality Following Fracture

There is convincing evidence of mortality post-hip fracture[25,26]. However there is less convincing evidence of a mortality effect associated with vertebral fracture[25,27].

Recommendation. We propose that economic evaluations in osteoporosis should incorporate a mortality effect associated with hip fractures, and where possible such data should be based on the specific geographical location for which the study is conducted. For mortality following vertebral fractures we recommend analysis should be conducted with and without such effects and reiterate that further clinical research is needed in this area.

Longterm Care Admission Post-Hip Fracture

Hip fractures are associated with increased admission to longterm care facilities, although this will vary by country due to differences in the availability and funding of such care[26]. However, it is unclear whether prevention of fractures will reduce admission to such facilities or merely delay it. A recent population-based study from Olmsted County, Minnesota, USA, suggests that savings due to nursing home stays averted through hip fracture prevention are likely to be overly optimistic[28].

Recommendation. We propose that studies should incorporate data on longterm care admission specific to the geographic location for which the study is conducted. Further, we propose that analysis should be conducted based on 2 assumptions: that all future longterm care costs can be attributed to fracture; and that only the costs of LTC in the first year post-hip fracture are assumed to be directly attributable to fracture. The latter can be seen as a more conservative assumption that will bias against effective therapies. Further research addressing fracture-attributable length of stay in longterm care is needed.

Lack of Head-to-Head Trials

Within economic evaluation, the cost effectiveness of therapies is assessed relative to other available interventions. The choice of comparator therapy is a major determinant of the results of an analysis. Existing guidelines tend to differ modestly in their preferred choice of comparator — however, they tend to favor adoption of usual practice as at least one of the comparators. A major limitation in the conduct of economic analyses, however, is the lack of head-to-head trials comparing the therapies of interest. This problem exists primarily as a result of the requirement for placebo-controlled trials with respect to the licensing of pharmaceuticals. Thus, if we wish to compare treatment options, it is necessary to estimate the relative effects of treatments through synthesis of placebo-controlled trials. The Australian guidelines for pharmacoeconomics disallow any claim of superiority for a pharmaceutical based on

synthesis of trials[2]. Other guidelines tend to have less rigorous positions with respect to this issue, allowing comparisons through carefully designed synthesis.

Recommendation. We propose that head-to-head comparisons can be made through careful synthesis of similarly designed trials and application of model-based economic evaluation techniques. However, we also recommend that pharmaceutical manufacturers be encouraged to conduct head-to-head trials.

Incorporating Extraskeletal Effects

In addition to their effect upon osteoporotic fractures, therapies may have extraskeletal effects. Depending on the therapies under consideration within an analysis, the importance of such effects will vary. Thus, the selection of health states to include in model-based economic evaluations of osteoporosis treatment is one that warrants careful consideration. Until recently, postmenopausal hormone replacement therapy (HRT), a treatment with widely recognized beneficial (e.g., reductions in menopausal symptoms and protection against colorectal cancer) and harmful (e.g., increases in breast cancer, thromboembolic events) extraskeletal effects, was a mainstay for osteoporosis prevention and treatment. Thus, model-based analyses for postmenopausal HRT required explicit attention to health states related to these extraskeletal effects. Failure to include the full complement of health states likely to be affected by a therapeutic agent could produce misleading economic evidence. For example, a treatment that reduced hip fracture incidence by 90%, but increased breast cancer incidence by 50%, may appear as a great success unless the harms were appropriately modeled. For other therapies, incorporation of extraskeletal effects will have minimal effect on analysis. For example, with bisphosphonates a possible adverse effect is an increased risk of gastrointestinal problems, which can be alleviated by discontinuation of therapy or improved adherence. Such effects can be considered by accurate modeling of treatment discontinuation rates.

Recommendation. We propose that in future studies, analysts consider the effect of therapies on extraskeletal effects and incorporate these as necessary to accurately assess the incremental cost effectiveness of alternative treatments. Such effects should be incorporated adopting methods consistent with those discussed with respect to fractures.

Benefit Beyond Therapy

There is evidence that patients experience continued reductions in the risk of fracture after stopping therapy (e.g., Tonino, *et al*[29]). Previous studies have assumed that a patient will experience continued benefit in terms of fracture reduction over a time period equal to therapy duration, while it is assumed that magnitude of benefit will decrease linearly over this period[16,17]. However, evidence of continued benefit comes from studies where the followup of patients has been for no more than 2 years post-treatment curtailment[29].

Recommendation. We propose that future studies should conduct multiple analyses based on assumptions relating to benefit to be obtained beyond therapy duration. As a minimum, analysis should be based on 3 assumptions: (1) no benefit beyond treatment, (2) a linear decline in benefit in terms of fracture reduction over a time period post-therapy equal to therapy duration, and (3) a linear decline in benefit for a period up to 2 years.

Model Validation

Model validation should focus on calibration; that is, that the model replicates all population estimates for each individual parameter[30]. This is necessary because in certain instances, the specific data required for modeling are unavailable though sufficient data are available for the interpolation of such parameters. For example, age-specific mortality (excluding mortality post-fracture) may be unavailable, although age-specific all-cause mortality and age-specific mortality post-fracture is available. Thus, a model should be calibrated such that the combination of mortality rates post-fracture and mortality rates without fracture replicates age-specific all-cause mortality. Failure to replicate models can lead to a major overestimation of the benefits of treatment.

Recommendation. We propose that for future studies, all models are fully calibrated.

Compliance with Therapy

Consideration of patient compliance raises 4 specific issues: measurement of compliance versus continuation; how to measure compliance; how soon do patients obtain benefits of treatment given noncompliance; and compliance beyond the duration of clinical trials.

It is generally much easier to document whether patients have obtained prescriptions for medication than to determine whether they have taken medications correctly. This is the distinction between treatment continuation and compliance with therapy. The difference between these concepts should be recognized within an economic evaluation: the analyst often models continuation due to a lack of complete data on compliance. When clinical trial results are reported on an intention-to-treat basis, it is noted that estimates of treatment efficacy are likely to already be influenced by treatment noncompliance.

Estimating compliance levels is problematic. Two distinct approaches are available: prescription-based records and patient-based reports. Prescription-based records typically involve the use of administrative databases from health care insurers — for instance, the Ontario Drug Benefit Program's database can be used to estimate compliance with therapies at 6 and 12 months. These can be seen as measures

of patient's continuation with therapy, but they do not necessarily suggest compliance. Alternatively, therapy use can be estimated through such measures as pill counts and diaries; however, again, these may not be accurate measures.

Clinical trial evidence on continuation is possibly more optimistic than evidence in routine clinical practice. Therefore, clinical trial evidence should be augmented with real-world patient compliance information whenever possible. For example, a recent paper on early osteoporosis treatment discontinuation among women initiating treatment with low BMD showed self-reported rates of discontinuation of approximately 1 in 4 for postmenopausal hormone therapy and 1 in 5 for raloxifene and alendronate[31].

Thus, it is necessary in economic evaluation to consider when the benefits of therapy are likely to commence. In clinical trials reporting fracture reductions by year of study, there is clear evidence that for many therapies treatment effect begins within 1 year of therapy[32].

Most clinical trials of therapies for osteoporosis are conducted over a short period of time, 2 to 3 years. As duration of therapy can be longer than trial duration it is necessary to model the effects of therapy beyond the period for which efficacy data are available. Generally, previous studies have adopted the same relative risks of fractures beyond the trial duration. This seems justified given that there is evidence of continued benefits from therapies for up to 7 years[29].

Recommendation. In all evaluations, some empiric measure of compliance should be used, although sensitivity analysis based on different rates of treatment continuation is required. We recommend that for economic evaluations in osteoporosis, it is assumed that for individuals taking therapy for less than 1 year no treatment effect is obtained, but for individuals taking therapy for at least 1 year the full treatment effect is obtained. Further, we recommend that for therapy taken beyond the duration of trials, benefits are assumed to continue to the same extent.

Incorporation of Utilities

The principal influence of the sequelae of osteoporosis is decreased quality of life in individuals with symptomatic fracture. For economic evaluation this is best incorporated by obtaining utility values for the specific fracture health states. Typical health states will relate to the fractures modeled within the analysis: hip fracture, wrist fracture, and vertebral fracture, as well as a "normal health" state relating to the absence of fracture[33]. With respect to utility measurement there are 2 specific areas where there exists a lack of consensus: the duration of quality of life effects associated with fracture; and what should be the preferred approach for obtaining utility weights.

Previous studies have typically assumed that the quality of life effects of vertebral and wrist fractures are limited to the first year post-fracture. However, for hip fractures the quality of life effects may be longer lasting. In addition, previous model-based economic evaluations have typically assumed that the "worst" post-fracture health state is that associated with hip fracture. However, recent evidence has challenged this assumption by findings of lower health utility among persons with hip and vertebral fracture relative to those with hip fracture alone[34].

There are several methods of obtaining societal utility values for osteoporotic health states[35,36]. Direct utility elicitation methods, such as the standard gamble and time tradeoff, can be undertaken to investigate osteoporotic health states since they are more meaningful to individuals unfamiliar with health state scenarios. Alternatively, an indirect approach to health state valuation can be undertaken by having osteoporotic patients complete a standardized utility questionnaire, which has been linked through construction of a scoring algorithm to societal health state values[37-39]. A study that considered the effect of health state utility values on the cost effectiveness of an intervention that reduced hip fracture incidence by 50% suggested that the 2 approaches could result in qualitatively different results[40].

Table 1. Summary of recommendations for areas of debate regarding reference case.

Methodological Issue	Recommendation
Study perspective	Perspective should be that of the health and social care system
Modeling fractures	Adopt models that use age-specific fracture incidence models using rates from the reference population
Mortality following fractures	Incorporate attributable mortality following hip fracture; assess the impact of mortality following vertebral and other fractures in sensitivity analyses
Longterm care admission post fractures	Consider 2 assumptions: that all future longterm care costs are attributable to fractures and that only the first year costs post fracture are attributable
Head to head comparisons	Achieved through careful synthesis of similarly designed trials.
Extraskeletal effects	All effects that will impact cost effectiveness should be included.
Benefit beyond therapy	The impact of assumptions should be assessed through sensitivity analysis.
Model validation	All models should be fully calibrated
Compliance with therapy	Empiric measures of discontinuation should be incorporated into analysis
Utility values	Values should be incorporated but treated with caution.
Accommodating uncertainty	At a minimum, univariate and multivariate sensitivity analysis.

Recommendation. In economic evaluations in osteoporosis, 2 distinct quality of life weights should be adopted for all fractures: one relating to the first year post-fracture and a second relating to longterm effects (for some fractures may be equivalent to normal health). Indirect elicitation has the advantage of providing societal health state values to the full range of outcome health states experienced by individuals with osteoporosis. It is recommended that analysts treat all utility values with caution and conduct appropriately detailed sensitivity analyses.

Accommodating Uncertainty

Previous recommendations for sensitivity analysis for studies in rheumatoid arthritis suggest that the minimum requirement should be for simple one-way analysis of the major clinical, cost, and quality of life variables[6]. In recent years there have been considerable developments in the methods of analyzing uncertainty in economic analysis (e.g., Briggs, *et al*[41] and Felli, *et al*[42]). Given the wide range of uncertainty concerning many variables within an osteoporosis-based economic evaluation, more advanced techniques for sensitivity analysis should be explored. Monte Carlo simulation techniques can both identify those variables that have major impact in the results of analyses and provide a more accurate expression than simple deterministic analysis of the expected value of outcomes of interest[43,44]. Such techniques are more easily conducted through the development of appropriate analytical software[45,46].

Recommendation. As a minimum, economic analysis in osteoporosis should adopt simple univariate and multivariate sensitivity analysis. However, analysts should be encouraged to adopt advanced methods for analyzing uncertainty with preference for the use of Monte Carlo simulation techniques.

CONCLUSIONS

Defining standards for economic evaluations in osteoporosis should improve the quality of future studies and facilitate comparisons between studies. This should ultimately allow more efficient health care provision in this disease area.

In our article we have worked towards defining such standards by recognizing both areas of consensus and areas of debate. The latter require further consideration by researchers in the field. Although we have provided tentative recommendations addressing these issues, we recognize that the ultimate reference case for osteoporosis will be resolved through further discussion and research.

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