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Recommendations for Health Economics Evaluations of Interventions in Osteoporosis

**WHO Collaborating Centre for Public Health
Aspects of Osteoporosis and other Rheumatic
Diseases, Liège, Belgium**



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Recommendations for Health Economics Evaluations of Interventions in Osteoporosis

WHO Collaborating Centre for Public Health Aspects of Osteoporosis and other Rheumatic Diseases, Liège, Belgium

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SUMMARY

Economic evaluation is a critical tool in the evaluation of pharmaceutical interventions. Because these evaluations are complex, good methodology is essential for credible results. The International Federation of Societies on Skeletal Diseases (IFSSD) convened a Working Party to develop recommendations. The purpose of the recommendations is to promote high scientific quality and consistency among economic evaluations in osteoporosis and to help decision makers to properly integrate the results of health economic evaluation into their health policy recommendations. The following methodological recommendations were made:

- The *problem* to be addressed should be clearly stated and defined.
- The *perspective* should be targeted to the appropriate audience. The *societal perspective* permits a global evaluation and, therefore, should be included in the perspectives presented when possible.
- The *target population* should be clearly defined. The intervention should be studied in a population for which the indication has been granted or is sought. As disease prevalence and medical practice vary across geography and social and health care systems, local data will be needed to populate the evaluation. Models may be used to project the economic impact of therapy on different populations.
- Appropriate *comparative interventions* include "no treatment" and the most appropriate comparators, depending on country requirements.
- *Outcomes* to be evaluated should always be based on economically relevant events; i.e., at least fractures. If clinical data exist for only a certain type of fracture, extrapolations may be made to alternative fracture types if data are available to allow such extrapolations. In cases where clinical efficacy data exist only for intermediate endpoints, modeling may be used to link these endpoints to definitive endpoints by means of epidemiological data. Actual fracture data are preferred to any type of extrapolation. Fractures lead to morbidity and mortality variably, depending on the fracture type. The humanistic effect of fractures on patient well being can be studied via quality of life or utility assessment. Later, such quality of life or utility data may be combined with economic analysis to provide cost-utility ratios.
- *Costs* to be considered include those associated with screening and diagnosis, intervention (including costs of drugs, monitoring, side effects), and clinical events related to the disease (including fractures and non-skeletal conditions impacted by therapy). Cost data covering both acute and long-term consequences of the disease should be included. Indirect costs, especially those related to caregiver time, are important to take into account and results should be presented with and without these indirect costs. Results should be presented both with and without costs incurred during future years of life.

- *Data sources* to be used, in order of decreased reliability, include primary data, secondary data, and expert panel opinion.
- *Modeling* techniques may be used to extrapolate costs from primary data and to compensate for the limitations of the clinical trial setting. The applicability of extrapolated data should be carefully assessed.
- *Analytic methods* to be used include Cost-Effectiveness Analysis, which should constitute the basis of the analysis, and Cost-Utility Analysis, which is the preferred method to encompass all aspects of outcomes.
- The *analytic horizon* for studies in osteoporosis, ideally, would be the lifetime of the population. Almost certainly, this time frame will extend beyond the availability of primary data. Therefore, time should be factored into the evaluation to extrapolate costs and outcomes beyond the study period, and to take into account potential changes in disease management, demographics and epidemiology.
- *Discounting* should be applied and performed in accordance with local requirements.
- *Sources of uncertainty*, whether arising through data collection or through assumptions, should be extensively explored through sensitivity and statistical analyses. Different hypotheses of compliance should be explored through sensitivity analysis.
- ***The Working Party concludes that health economic evaluation can be an important part of the decision-making process in this complex disease state if good methodology is used and is described in a clear and stepwise manner.***

INTRODUCTION

Economic evaluation is a critical tool in the evaluation of pharmaceutical interventions and because these evaluations are complex, good methodology is essential for credible results. The International Federation of Societies on Skeletal Diseases (IFSSD) recently convened a Working Party to develop guidelines. The purpose of the guidelines is to promote high scientific quality and consistency among economic evaluations in osteoporosis and to help decision makers to properly integrate the results of health economic evaluation into their health policy recommendations.

As a working definition of osteoporosis, the group used the definition provided by the Consensus Development Conference in 1993¹ "Osteoporosis is a skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture." At the present time, the greatest amount of data showing the relationship between bone mineral density (BMD) and fractures comes from studies performed in postmenopausal women. The relationship between BMD and fractures in male osteoporosis and other osteoporotic conditions (e.g., glucocorticoid-induced osteoporosis) is not nearly as well documented. When more data become available on these other conditions, the applicability of the methods recommended herein to the evaluation of osteoporotic conditions other than postmenopausal osteoporosis can be assessed.

Registration authorities assess the efficacy, safety, and quality of pharmaceutical agents to determine whether they should be licensed for medical use. The recommendations of this Working Party are not intended for use by registration authorities, but by those who conduct health economic evaluations and those who review them; e.g., reimbursement/pricing authorities, formulary committees, patient advocacy groups, public policy makers, and scientific societies.

Several methodological guidelines for the health economic evaluation of pharmaceuticals have already been developed and/or proposed²⁻¹³. The purpose of this task force was to provide recommendations specific to evaluations in osteoporosis that would be consistent with the general guidelines.

PROBLEM TO BE ADDRESSED

The problem to be addressed in the evaluation should be defined clearly, especially with respect to the research question and the population under study.

PERSPECTIVE

The perspective from which the study is conducted should be described and targeted to the appropriate audience. A number of perspectives could be taken, depending upon the decision maker(s) of interest, but the societal perspective, which ensures a global evaluation, is recommended in the field of osteoporosis and should be reported since the consequences of the disease often go far beyond any single health care system.

TARGET POPULATION

In order to facilitate comparisons, the population under evaluation should be fully defined and, as a starting point, it is recommended that the economic evaluation be based on the specific population within the clinical trial. In addition, the evaluation should be targeted to the population for which the indication has been granted or is sought. The sensitivity analysis can simulate alternative populations by varying risk factors such as, but not limited to, BMD, prior fracture history and/or age.

COMPARATORS

The drug treatment should be compared with “no treatment” and the most appropriate comparator(s), depending upon specific regional requirements.

GENERAL RECOMMENDATIONS

For costs and benefits, the usual rules of economic evaluation should be applied:

- Incremental (differential) analysis should be performed.
- Costs and outcomes should be obtained from the same population; however, in cases where this is not possible, data sources should be clear and applicability should be checked.
- Double counting of costs or benefits in the numerator and denominator of a ratio should be avoided.

RELEVANT OUTCOMES

Outcomes should be analyzed on an incremental (differential) basis, showing the difference in outcomes for the alternative treatment regimens under consideration. The types of outcomes to be considered are discussed below.

Clinical Outcomes

Outcomes in economic evaluations should always be based on definitive endpoint(s), and in osteoporosis the definitive endpoints are the number of patients with new fractures (ideally, all types of fractures) and mortality. However, many clinical studies may have reported intermediate (surrogate) endpoints for the reduction in the risk of fracture, such as BMD, which are not usually directly relevant for economic analysis. Evidence linking these intermediate endpoints to the definitive endpoints should be clearly documented and its applicability discussed. When fracture evidence is available for only one fracture type (e.g., vertebral fracture) from a clinical trial, modeling techniques may be used to estimate the effect of the intervention on other fracture types, based on established epidemiological linkages.

Fracture endpoints should be clearly defined, particularly in the case of vertebral fractures, because their definition is complex. Moreover, a subject may not seek medical care until several vertebral fractures have occurred. Therefore, comparable methods of assessment should be used in comparing treatment interventions. Analysis should be based upon the number of women with fracture and not the number of fractures.

Morbidity and Mortality

Different fracture types have different effects on morbidity and mortality, depending upon the specific site. Hip fracture is associated with substantial effects on both morbidity and mortality, spine fracture affects morbidity and, to a lesser degree, mortality, and wrist fracture affects morbidity and does not impair survival.¹⁴ To measure mortality, life-years saved are preferred to number of deaths averted.

Non-Skeletal Outcomes

Relevant non-skeletal consequences of interventions should be considered in the analysis.

Global Outcome Measurements

Outcomes that encompass the effect of definitive endpoints on patient's lives, e.g., life-years saved and life-years adjusted by their quality (e.g., QALYs), should be considered in order to summarize all consequences of intervention. While these two analytic methods allow for a comparison of cost-effectiveness across interventions and disease states, the morbidity associated with vertebral or wrist fractures are better accounted for with the latter method.

Life years saved results should integrate quality of life information (e.g., QALYs gained) and be presented. However, results should be presented before and after the quality of life adjustment. Properly validated and appropriately translated instruments should be used with known scoring systems and statistical tests. Instruments should be used in the way they have been developed (e.g., a single score should not be derived from a multidimensional instrument without proper validation data on global scoring). A generic quality of life instrument can be used to measure the impact of an intervention on a patient population and this type of instrument is appealing in that it can be used across a wide range of interventions and/or disease states. Greater sensitivity, however, is often attainable with a disease or site-specific instrument.

Utility assessment is very useful for the purpose of evaluating the global consequences of multiple outcomes on patient-health-related quality of life and for constructing a cost-utility analysis. Its value is particularly relevant for including the different consequences of vertebral and other fractures; however, due to the rather experimental nature of this field (with different methodologies comprising the standard gamble, time-trade-off and visual analogue scale¹²) results should be examined with caution.

COSTS

Economic evaluations in osteoporosis should consider the costs of screening and diagnosis, the interventions (including costs of drugs, monitoring, and side effects), and clinical events related to the disease (including costs of fractures and non-skeletal conditions impacted by therapy). A comprehensive evaluation of costs should integrate both the immediate consequences of relevant clinical events (e.g., fracture-related hospitalization, surgery, drugs) and the long-term consequences in the time frame of the evaluation (e.g., change in treatment, disability, resulting dependence, institutionalization, mortality)¹⁵.

It is recommended that units of services consumed be collected and reported before costs are determined. Of course, these costs must be linked to local context and cannot be translated from one country to another by the simple application of currency conversion rates.

Costing methods and assumptions should be stated explicitly and their appropriateness should be checked according to the chosen perspective and local guidelines. The values used for costing and their data sources should always be disclosed. Actual economic opportunity costs are preferred; however, charges may have to be used as proxies.

Different types of costs are impacted by interventions and should be evaluated whenever possible (some examples are provided in Table 1 on the following page).

Direct Medical Costs

Direct medical costs are costs for resources consumed in the treatment of disease, or as a result of disease (e.g., drug, hospital, nursing home). The inclusion of direct costs in health economic analysis is universally accepted and considered non-controversial.

Direct Non-Medical Costs

Direct non-medical costs include costs for other resources; e.g., transportation and social care, not directly related to the treatment of disease but resulting from it. These costs should also be included in the analysis, but they are less common due to some difficulty in their measurement.

Indirect Costs

Indirect costs include costs related to loss of time and productivity because of the disease; e.g., time out of work, premature death, caregivers' time. These costs are important from the patient's point of view and should, therefore, be considered; however, many unresolved issues remain about the appropriate method of measurement. Different guidelines make different recommendations regarding the inclusion of indirect costs^{7,8} and for this reason, results should be presented both with and without indirect costs included.

Indirect costs should be presented as physical units (e.g., days lost from work or usual activities). Indirect costs will vary according to the stage of life of the patient population. For example, indirect costs should focus not only on loss of time from work but also on time lost from leisure and family activities of importance to the patient. Also, in younger patients, some types of fracture (e.g., wrist fractures) will have a greater effect on time lost from work than they would for older, possibly retired patients.

Considerable time may be dedicated by caregivers to patients with fractures. Although it may be difficult to assign a value to this time, it should be taken into consideration. Studies of the impact of time spent on care for the patient should be encouraged.

Intangible Costs

Intangible costs include costs related to pain and reduced quality of life which cannot be expressed in monetary terms. In practice, these intangible costs are considered in the denominator of the cost-utility ratio described later.

Table 1. Costs to be included in Economic Evaluations in Osteoporosis*

Reason for Incurring Cost	Unit of Measurement
Treatment of Fractures	
Outpatient Care	Physician office visits
	X-rays
	Laboratory tests
	Outpatient procedures
	Emergency room visits
Pharmacotherapy and its side effects	NSAIDs
	Narcotics
Hospital Care	Length of stay
	Physician visits
	Radiology
	Surgery
	Physiotherapy
	Other professional services
Time lost from work or other activities	Number of days
Rehabilitation Due to Fractures	
Nursing home medical care and	Length of stay
Rehabilitation Center	Physician visits
	Physiotherapy
	Other professional services
Formal home care (professional assistance)	Nursing visits
Medical Care	Physiotherapy
	Medical equipment
	(e.g., wheelchair, walker)
Other Care (housekeeping, transportation, meal delivery)	Units/frequency of utilization of services (x cost per service)
	Time spent by professionals
Informal home care (assistance provided by friends/family)	Number of hours
Caregiver time dedicated to housekeeping, meal preparation, personal care, and other help	
Time lost from work or other activities	Number of Days
<p><i>* The costs included in this table are for illustrative purposes only and do not include all relevant costs for every study. The costs considered in each study should be appropriate to the perspective and country for which it is conducted.</i></p>	

DATA SOURCES

Sources for clinical, epidemiological and resource utilization data should always be clear and their quality should be discussed. Data comparability must be addressed with respect to patient populations and interventions. Acceptable data sources include, in order of decreasing relevance:

- **primary sources** — e.g., dedicated economic studies (which include costs and outcomes); large randomized clinical trials (RCTs); meta-analyses of RCTs; meta-analyses of both RCTs and less rigorous trials; epidemiological surveys; small sample, single clinical trials.
- **secondary sources** — e.g., retrospective studies; bibliographic reviews; expert opinion obtained by valid consensus.

A dynamic approach to the evaluation is advised; i.e., primary data should replace secondary data when they become available.

Because treatment patterns vary across health care systems, country-specific data should be used whenever possible. International data may be used provided that their applicability to the population under study is verified.

MODELING

Models are used to integrate secondary data with primary data (e.g., the effect of intervention on populations not specifically studied in the clinical trial or the consequences of intervention beyond the trial period) and help to describe, for the purpose of analysis, the event pathways, progression of the disease, events associated with both the intervention and the disease itself⁵, and treatment patterns. The specific uses of modeling in health economic evaluations in osteoporosis are discussed below.

Extrapolation of Results to Other Treatment Populations

Trial populations are by necessity smaller than, and non-representative of, the general population. Extrapolation of cost and outcomes data from clinical trial populations to other populations is appropriate in the following two situations:

1. application of results to a narrower, more homogeneous population in which different results in terms of cost-effectiveness may be expected
2. application of results to the whole country to derive financial implications of the intervention to the health care system.

In both cases, hypotheses should be made clear and should be extensively tested in the sensitivity analysis.

Estimation of Fracture Risk

Ideally, data on fracture risk should be available for every sub-population and fracture type. When such data are not available, modeling may be used to extrapolate data from one sub-population or fracture type to another, provided the link is clearly identified. The annual risk for fracture can be computed by using multivariate risk equations that take into account such factors as age, BMD, and fracture history¹⁶⁻¹⁷, or a more straightforward approach is the estimation of age-specific risk of fracture based on rates reported in national hospital admission/discharge Data¹⁸ or epidemiological data. However, the use of age-specific incidence rates may not allow the analysis of sub-populations based on risk and likelihood of benefit from treatment. For example, whereas risk equations would allow one to study the impact of therapy on women with low BMD (i.e., 2 to 2.5 standard deviations below the mean), the use of incidence rate data may not.

Modeling Treatment Effect From Intermediate Endpoints

Definitive endpoints may be modeled from intermediate endpoints when no clinical data are available on definitive endpoints. However, it should be recognized that more modeling increases the possibility of error, and that the use of definitive endpoint data is preferable to the complex modeling of the relationship between surrogate and definitive endpoints.

Modification of risk by the intervention in a population may be sudden, gradual, or apparent only after a lag time. There are no data to suggest that one method of modeling is more realistic than another; the variability of the risk modification observed in the clinical trial should be tested in the sensitivity analysis.

The recent availability of fracture endpoint data for some drugs¹⁹⁻²³ has diminished the need for modeling an extrapolated treatment effect (change in BMD to change in fracture risk) for these compounds¹⁶. Fracture risk reductions observed in clinical trials with these agents can be directly applied to the age-specific probability of fracture¹⁷.

However, it may be necessary to model the relationship between BMD and fracture risk for clinical studies of compounds which lack fracture endpoint data (especially those registered without fracture data) and for trials with small sample sizes. It may be useful to model the relationship between fracture and mortality.

Incorporation of Costs from Different Sources

Modeling costs may be necessary in the following cases:

- When cost data and outcomes data have not been collected in the same manner; if this is the case, differences between different sources should be discussed (e.g., population and clinical environment).
- When resource utilization data and unit cost data have been obtained in different health care settings; if this is the case, verification that the health care settings are similar is necessary.
- When the clinical trial design is not compatible with economic evaluation requirements (see *Loss of follow-up* under *Compensation for the Clinical Trial Setting* below).

- When detailed cost data were not collected during the clinical trial, and results from more detailed studies are necessary to complete the evaluation.
- When prospective collection of long-term costs was not possible in the study.

When cost data are not prospectively collected, decision analysis techniques may be used to integrate costs. In all of these cases, particular care should be taken to verify the applicability of the incorporated data to the population under study and to the local health system and/or social system.

Extrapolation of Effects Beyond the Trial Period

A clinical trial protocol will stipulate appropriate length of therapy during the study period and at the end of the trial; whether patients stop or continue treatment will depend on recommendations for treatment and on patients' motivation to continue being treated. In real clinical practice the population will include patients with different degrees of compliance and lengths of treatment.

Patients who stop treatment

Few data are available on the modification of the fracture risk once therapy stops. Two extreme scenarios can be modeled:

- All benefit is lost immediately (the relative risk of fracture increases to 1.0 immediately after cessation of therapy).
- The relative risk of fracture remains at the level observed at the end of the study.¹⁷

Because neither scenario seems entirely plausible it is likely best to assume some scenario that lies in between; e.g., the relative risk of fracture increases in a linear fashion until death, at which point the relative risk is assumed to be 1.0 at the last year of life. Different plausible scenarios should be tested.

Patients who continue treatment

Some treatments are indicated on a lifelong basis. However, clinical trials are necessarily limited in duration. As in the case of patients who stop treatment, two extreme scenarios can be envisaged:

- No further benefit is obtained by continuing treatment (the relative risk of fracture reaches a plateau, and continuing treatment is required only to maintain benefit).
- The relative risk of fracture continues to decrease with the same pattern as that observed during the study.

Again, because neither scenario seems entirely plausible, it is likely best to assume some scenario that lies in between (e.g., the relative risk of fracture decreases at a decreasing marginal rate). Different assumptions should be tested and reported.

Other scenarios may be envisaged: for example, chronic or sequential administration during life long periods, or chronic or sequential administration during a certain number of years; long-term usage leading to reversal of risk, effects on other risk factors.

Only longer term follow-up of patients may allow for a better understanding of the impact of either stopping therapy or continuing for longer periods. Until data become available, assumptions will have to be made for what happens after the end of the period where data are available, and should be made explicit in the report. In all cases, many parameters should be modeled: efficacy, safety, compliance and, for sequential treatment, duration of cures and treatment interruptions. The impact of these assumptions on the results should be tested in the sensitivity analysis.

Compensation for the Clinical Trial Setting

Efficacy vs. effectiveness

Clinical trials in osteoporosis evaluate the “efficacy” of a drug (i.e., the performance of the agent under idealized circumstances) in that they are undertaken in very specialized centers with more extensive patient management (e.g., more visits and tests for all patients) than usually considered necessary in clinical practice. The result of the extra care taken in the clinical trial setting is that compliance is usually higher than that seen in clinical practice, resulting in optimal treatment effects. Moreover, a drug's effects are frequently compared with that of placebo, which may yield different results than “no treatment” in clinical practice. Also, in osteoporosis clinical trials, calcium supplementation is commonly administered to the placebo group, but in real clinical practice, calcium is not always prescribed by the physician and even when it is, dose may vary and acceptance and compliance with therapy will differ for each patient. In light of the possible discrepancies between the “efficacy” of the drug in clinical trials and the “effectiveness” of the drug in clinical practice, modeling with the use of additional data sources may be useful to adapt data from clinical trials to reflect usual practices.

Loss of follow-up

Patients may stop participating in a clinical trial either voluntarily or because of protocol. These patients incur costs and consequences that are quite different from those incurred by patients who continue with the trial. Also, the rates of, and reasons for, loss to follow-up may be different in the alternatives compared.

Modeling is useful to account for patients lost to follow-up and the methods described in *Extrapolation of Effects Beyond the Trial Period*, above, may be applied.

Compliance

Compliance tends to be greater in the clinical trial setting than in clinical practice because monitoring is more rigorous and the length of treatment is shorter. The sensitivity analysis should account for different hypotheses of compliance.

Modeling Techniques

In health economic analysis it is important that the simulation model be comprehensive and valid. The Markov state-transition simulation model is widely used and has been applied in published economic studies of osteoporosis interventions^{16,17,18}. A typical Markov model run can be characterized as follows: it simulates an equal number of identical patients (cohort) entering the model in two groups (e.g., those receiving and those not receiving the intervention) and transitioning in each time period (e.g., each year) amongst different health states. Examples of health states in osteoporosis may include death from all causes, death from hip fracture, nursing home residence, functional impairment/disability, and return to pre-fracture status. The probability of patients in each cohort (i.e., treatment group) arriving at any health state in each time period may be derived from a clinical trial and/or from secondary data. This can be run over a defined number of cycles (e.g., corresponding to 20 years), until all patients arrive in the absorbing state (death), or until the change in cumulative utility between cycles falls below a certain value. Costs and utilities can be assigned to the health states. This model quantifies the number of patients transitioning in each health state with associated costs and outcomes and thereby calculates the total number of outcomes (e.g., events, life-years, QALYs) and total costs. This model allows the comparison of results between the two groups.

ANALYTIC METHODS

The application of the four most common methods used for health economics analysis to evaluations of osteoporosis specifically is discussed below.

Cost-Minimization Analysis (CMA)

Cost-Minimization Analysis (CMA) is appropriate when it can first be demonstrated that the outcomes (efficacy and safety) of two therapies and the populations that they have been evaluated in are equivalent. For example, the increase in BMD, decrease in fracture risk, and side-effect profile all need to be similar between the two drugs, as does the baseline BMD and fracture risk of the treatment groups. Due to the low likelihood that the study populations and results of any two interventions in two different clinical trials would be completely equivalent, CMA should probably be used relatively infrequently and with extreme caution in health economic assessments of interventions for osteoporosis.

Cost-Effectiveness Analysis (CEA)

Cost-Effectiveness Analysis (CEA) examines and compares the relevant costs and consequences of competing alternatives that have similar outcome measures. This methodology has been the most commonly employed in health economic evaluations in general and in osteoporosis assessment in particular because of the simple practicality of retaining the outcomes in their natural units (e.g., "life-years saved," "fractures prevented"). When only morbidity (fracture incidence reduction) is being considered in osteoporosis, CEA is likely to be the most appropriate method, with "cost per fracture prevented" as the ratio. When mortality is considered, however, CEA is the most appropriate method only when survival alone is the most relevant outcome (with "cost per life-year saved" as the most appropriate ratio). Because osteoporosis is a disease that has an effect on patient quality of life as well as survival, CEA does not provide a complete picture of the effect of an intervention. However, it constitutes the basis of the analysis and the foundation of cost-utility analysis, described next.

Cost-Utility Analysis (CUA)

Cost-Utility Analysis (CUA) adjusts life-years saved results obtained by CEA by utility coefficients. In osteoporosis, CUA is the preferred method to encompass all aspects of outcomes. For example, hip fractures have a well documented association with decreased survival and quality of life, but occur relatively infrequently compared to vertebral and wrist fractures. Although the latter two types of fracture have an impact on quality of life, they have comparatively little direct effect on survival. By taking into consideration both survival and quality of life implications of various types of fracture and of their prevention, CUA gives a more complete picture than CEA.

Cost-Benefit Analysis (CBA)

Cost-Benefit Analysis (CBA) compares the cost of an intervention with its outcomes valued in monetary terms. In light of the fact that both costs and outcomes are in monetary terms, it is possible to assess the net benefit of undertaking an intervention without explicit comparison to a specific alternative. In other words, if the expected benefits of an intervention exceed the expected costs, then the intervention is worthwhile (assuming that there are sufficient funds). CBA is seldom used in health care except in limited primary prevention indications (for example, vaccination), primarily because of the difficulty of assigning monetary value to outcomes such as “improved survival” or “improved quality of life.” The methodology of “contingent valuation” makes monetary valuations based on consumers’ hypothetical willingness to pay for the expected outcomes (as elicited from a questionnaire), but for obvious reasons, this method has many of the limitations of utility assessment. It is important to recognize, however, that CUA and CBA are closely related if one is willing to compare their results either to a benchmark or threshold value. CBA can be a helpful tool and may come to be used more frequently in the future, and partial CBA may be interesting in assessing the economic results for a specific outcome. But at present, the method has limited use in health care.

Regardless of what method of analysis is utilized, other elements will need to be taken into account for decision making, depending on the priorities of the various audiences (e.g., budget considerations).

ANALYTIC HORIZON

Because osteoporosis is a disease that evolves over a long period of time and interventions aimed at prevention or treatment of osteoporosis may begin at middle age (or even earlier in cases of primary prevention), the analytic horizon of an economic analysis is a major question to be addressed. Ideally, the economic analysis should be extended to the life expectancy of the population under study. However, studying a period beyond the trial’s duration adds uncertainties to the evaluation. Indeed, during years potentially saved by the intervention, diseases other than osteoporosis and its consequences may occur and, therefore, incur costs. The analysis should show the impact of the intervention with and without the potential costs resulting from increased life expectancy. In addition, therapies used to treat osteoporosis may have an impact on other body systems, incurring costs. These costs should always be included in the analysis. Several other issues to be considered with respect to the time horizon of the evaluation are discussed below.

Firstly, assumptions must be made for the effects of interventions beyond the clinical trial period for which there are data (see *Extrapolation of Effects Beyond the Trial Period*). Second, future changes in osteoporosis management may have an impact on costs. For example, the availability of new BMD measurement techniques could decrease the cost of measuring BMD in the next decade, thereby potentially reducing the costs of screening and monitoring and, thus, allow for earlier intervention. Early intervention, in turn, has the potential to reduce the natural risk of fracture and, thus, alter the epidemiology of the disease and the future consequences of interventions. Third, changes in demographics and disease epidemiology may impact the economics of intervention and should be included in the sensitivity analysis.

It is important to include these types of anticipated changes in both the evaluation and sensitivity analysis.

Discounting

Because of the long time frame for the economic analysis of interventions in osteoporosis, it is necessary to discount the costs included in the evaluation. However, because discounting of outcomes is still debated, results should be presented with and without discounting. Several discount rates should be used in the sensitivity analysis of this parameter, as recommended in most guidelines for economic evaluation in health care²⁻¹¹. The choice of discount rates should follow local recommendations. However, in order to allow comparison with published studies (until just recently, most health economic analyses used a 5 percent discount rate), future costs should also be discounted at 5 percent per year.

DEALING WITH UNCERTAINTY

Overview of Methods

All guidelines for economic evaluation in health care emphasize the need to deal with the uncertainty that may affect the parameters used in the evaluation as well as the model structure²⁻¹². This need is of particular importance in the field of osteoporosis, given that as discussed above, many parameters used in the evaluation are affected by some uncertainty as well as the model structure. It is useful to classify factors of uncertainty into two categories: those arising in primary data gathering, and those arising in assumptions. In most pharmacoeconomic studies, however, the uncertainty created by assumptions is far greater than that arising from the primary data collection. Therefore, the following discussion will focus only on uncertainty created by assumptions. The standard way of dealing with uncertainty is to conduct a sensitivity analysis and statistical approaches should also be used¹³.

Sensitivity Analysis

Sensitivity analysis involves varying the values of the critical parameters from the values which were initially used in the evaluation. The critical parameters are those that appear to be both key variables for the economic evaluation and most affected by uncertainty. The range of variation has to be both plausible and justified. If the results are insensitive to a reasonable variation of a parameter, then the conclusion of the evaluation may be considered to be “robust” with respect to

this parameter. If the major results are sensitive to the values chosen from a range of plausible assumptions, then the conclusions are not robust¹³. Often, sensitivity analysis is useful in focusing attention on critical variables and posing questions about the need for better or more precise data¹³. Parameters that should be studied in the sensitivity analysis include the following:

- *Cost of fractures by age groups.* Since these data will come mainly from modeling, see *Extrapolation of Results to Other Treatment Populations*, above.
- *The discount rate.* A “zero” discount rate and a 5 percent discount rate should be included to ensure comparability with previous studies. Other rates, as currently recommended by different countries, should be tested.³⁻¹³
- *Treatment effect according to age stratification and baseline BMD.* This parameter should be studied when the population from the economic evaluation is different from the population studied in the clinical trials (see *Extrapolation of Results to Other Treatment Populations*, above).
- *Treatment effect and costs in clinical practice.* This analysis should deal with uncertainty due to factors such as lack of compliance and other factors likely to be different in clinical studies versus clinical practice (see *Compensation for the Clinical Trial Setting*, above).
- *Treatment effect beyond trial period.* This analysis should deal with the uncertainty regarding the relationship between treatment cessation, continuation and efficacy, and it can be especially interesting to vary the treatment length and sequences (see *Extrapolation of Results Beyond the Trial Period*, above).
- *Potential changes in osteoporosis management (see Analytic Horizon), demographics of the treatment population and epidemiology of the disease occurring within the analytic horizon.*
- *Costs due to increased life expectancy.*
- *Type of modification of risk (sudden, gradual, long time).*

Statistical Approaches

It is recommended that statistical tests be added to sensitivity analyses to deal with uncertainty; statistical distributions and confidence intervals of costs and outcomes should be examined. Detailed descriptions of these techniques are beyond the scope of this paper and are described elsewhere¹³.

CONCLUSION

Economic evaluation is a critical tool in the evaluation of interventions in involuntional osteoporosis, including bone-specific agents and agents with actions on multiple organ systems. Like all such evaluations, health economic analyses in this complex disease require clearly defined methodologies. The recommendations from the IFSSD Working Party in this document should help in this process. Thorough, meaningful pharmacoeconomic evaluation requires long-term analysis

which takes into account factors for which complete information is not always available. Modeling can be used to make the analysis more meaningful when data are incomplete; subsequently, the evaluation should be updated upon the availability of new data. In this way, health economic evaluation in osteoporosis can become a useful decision-making aid alongside more traditional tools such as risk-benefit assessment. These recommendations are intended for decision makers such as reimbursement and pricing authorities, formulary committees, patient advocacy groups, public policy makers and scientific societies.

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