Review of the published literature on cost-effectiveness of osteoporosis interventions

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Background

The ScHARR Economic Model of Osteoporosis (SHEMO) was used in the NICE Technical appraisal of interventions for the prevention of further fracture in women with a previous fracture. An updated version of this model, incorporating more fracture sites, has been used for the economic modelling for prevention strategies and is being used by the NICE Guideline Development Group.
The DSU was commissioned to review economic models of osteoporosis, and comment whether the methodology, assumptions and data population were applicable to the UK. Published literature from 2002 onwards, written in English were sought. 11 papers were found, 2 of which related directly to SHEMO (* Stevenson et al MDM (2004). Stevenson et al. JORS (2005) and thus have not been critiqued against the current model.

Outline of SHEMO

Fracture Data used in SHEMO

- o The risks of hip, wrist and proximal humerus fractures were taken from a UK epidemiological study (Singer et al. J Bone Joint Surg, 1998)
- o The risk of spine fracture was calculated assuming that the ratio of hip to spine as seen in Sweden (Kanis et al. Ost Int , 2000)
- o It was assumed that pelvis and other femoral fractures were equivalent to hip fractures. The risk of other fractures were calculated assuming that the bed-days in Sweden reflected the incidence (Kanis et al. Ost Int , 2001)
- o The risks of hip, wrist and proximal humerus fractures were taken from a UK epidemiological study (Singer et al. J Bone Joint Surg ,1998)
- o The risk of spine fracture was calculated assuming that the ratio of hip to spine as seen in Sweden (Kanis et al. Ost Int , 2000)
- o Other fractures were approximated to hip, proximal humerus or wrist fractures based on similarity of costs and disutility.

The incidence of other fractures were estimated assuming that the ratio of incidence for a site compared with the ‘equivalent fracture type’ as seen in Sweden was applicable to the UK. (Kanis et al. Ost Int , 2000)

Cost Data

Source : Inflated UK data from Dolan and Torgeson (Ost Int ,1998), adjusted by length of stay data to produce age weightings.

Cost of hip, pelvis and other femoral fracture in year 1. *
£5,157 at 50 and 60 years
£6,487 at 70 years
£8,538 at 80 years
No costs assumed in subsequent years
For patients assumed to enter a nursing home a cost of £23,562 per year was applied.

Cost of vertebral fracture in year 1.
£477 at 50 and 60 years
£539 at 70 years
£581 at 80 years
£222 assumed in subsequent years

Cost of wrist,sternum, rib and scapula fracture in year 1. *
£359 at 50, 60 and 70 years
£585 at 80 years
No costs assumed in subsequent years

Cost of proximal humerus, tibia and fibula fracture in year 1. *
£1,024 at 50, 60 and 70 years
£1,674 at 80 years
No costs assumed in subsequent years

Utility Data
These were based on Kanis et al. Ost Int , 2004. It was assumed that
- o pelvis and other femoral fractures were equivalent to hip fractures.
- o tibia and fibula fractures were grouped with proximal humerus fractures and a weighted average fro disutility calculated.
- o scapula, sternum and rib fractures were equivalent to wrist fractures.

Multiplication factors in year 1 and subsequent years respectively.
Hip, pelvis and other femoral fracture 0.792, 0.813
Vertebral fracture 0.626, 0.909
Wrist, sternum, ribs and scapula fracture 0.977, 1.00 Proximal humerus, tibia and fibula fracture 0.794, 0.973
Nursing home following hip fracture 0.400,0.400

Mortality Data following hip, pelvis and other femoral fracture

Source :
Unpublished Data from East Anglian audit for hip fracture, combined with attributable rates from Parker and Anand (Public Health, 1991).
Value: Rising from 2% at ages 50 – 59 years to 16% at 90 years and over in the year of a hip, pelvis and other femoral fracture

Mortality Data following vertebral fracture
Source: Jalava et al. Journal Bone and Mineral Research (2003)

Value: A hazard ratio of 4.4 in the standard mortality rate in the year following fracture was assumed. 28% of these deaths were assumed attributable to the fracture as reported by Kanis et al Ost Int (2004)

Mortality Data following proximal humerus, tibia and fibula fracture
Source: Kanis et al. Ost Int 2004
Value: A hazard ratio of 2.0 in the standard mortality rate in the year following fracture was assumed. 28% of these deaths were assumed attributable to the fracture

Mortality Data following wrist fracture
No mortality was assumed to be associated with wrist fracture.

Nursing Home entry following hip, pelvis and other femoral fracture

50 – 59 years	0%
60 – 69 years	4%
70 – 79 years	4%
80 – 89 years	12%

Critique of Studies.

Comments applicable to all published models

- All models were of a Markov design. SHEMO used an individual patient modelling approach in order to incorporate more sophisticated features within the modelling.
- The quantative effect of the differences in methodologies is unknown, however comparison of data submitted in the established osteoporosis TAR suggests that the results are not markedly different.

1. <u>Johnell et al Pharmacoeconomics (2003)</u>

Funding: Merck, Sharpe and Dohme.
Intervention : Alendronate
Model Structure : Markov cohort model
Fracture Sites considered : Hip, Spine, Wrist
Population studied in base case : 71 year old women with a previous spinal fracture.
Underlying Fracture Incidence : General Swedish population data adjusted for greater risk of cohort (Kanis et al. Ost Int , 2000)
Methodological weaknesses compared to SHEMO.

- Following a hip fracture the only possible transition was to death
- Only hip fractures were associated with mortality
- No allowance for fractures to increase risk during the simulation

Cost Data
Taken from previously published data from Sweden. Zethraeues et al. Acta Orthop Scand 1997 Jonsson et al. Scand J Rheumatol Suppl 1996
Hip fracture cost: SEK 181,000 in the first year and SEK 41,000 in subsequent years.
Spine Fracture : SEK 16,000 in first year
Wrist Fracture : SEK 4,000 in first year
Utility Data
Assumption of 76% of utility in the first year following a hip fracture and 87% of utility in subsequent years
Assumption of 90% of utility in the first year following vertebral fracture and 95% of utility in the first year following a wrist fracture. Neither fracture was assumed to have impact in subsequent years
Mortality Data
Assumption of 10%, 20% and 50% mortality in the first year following a hip fracture at 65-74, 75 – 84 and 85 years and over respectively. All were assumed attributable to the hip fracture.

Overview.
The high percentage of hip fractures associated with mortality will mean that the results from this model will be more favourable to treatment than those produced by SHEMO. However, the increased number of fracture sites used by SHEMO will redress the balance somewhat.

2. Fleurence. International Journal of Technology Assessment in Health Care (2004)

Funding: None.
Intervention : Vitamin D and calcium, and hip protectors
Model Structure : Markov cohort model
Fracture Sites considered : Hip, Spine, Wrist, Other
Population studied in base case : Hypothetical cohort of male and females, with and without fracture.
Underlying Hip Fracture Incidence : HES data from the UK.
Methodological weaknesses compared to SHEMO.

- Only hip fracture was associated with utility decreases
- Only hip fractures were associated with mortality
- No allowance for fractures to increase risk during the simulation
- No lowering of average population risk to take into account high risk sub-sets of the population.

Cost Data
Taken from Dolan and Torgerson, but not age-weighted and not adjusted for patients already in a nursing home.
Hip fracture $19,350
Spine fracture $764
Wrist fracture $746
Other fracture $2,135
All Costs for the first year only.Utility Data taken from Brazier et al. Ost Int (2002)A multiplier of 0.797 in all years following a hip fracture.
No utility decreases for other fractures
Mortality Data
Assumption of a 15% mortality rate in the first year following a hip fracture, irrespective of age. All were assumed attributable to the hip fracture.

Overview.
The results from this model are not expected to be markedly different from those produced by SHEMO assuming only hip fractures were considered. This approach will not be applicable to interventions which are known to have a beneficial effect at other sites such as the vertebra.

3. Willis. International Journal of Technology Assessment in Health Care (2002)

Funding: Recip AB.
Intervention : Calcium and Vitamin D.
Model Structure : Markov cohort model
Fracture Sites considered : Hip
Population studied in base case : Women at varying risk levels
Underlying Fracture Incidence : Swedish data Kanis et al. Ost Int (2000)
Methodological weaknesses compared to SHEMO.

- Only hip fracture were considered.
- No lowering of average population risk to take into account high risk sub-sets of the population.

Cost Data
Taken from Swedish data.
Hip fracture SEK107,000 at age 50 years to SEK 346,000 at age 100 years in the initial year.
Ongoing costs of SEK 27,000 per year for all ages.
Utility Data
Taken from Jonsson et al. (Ost Int 1998 supp 1: S13-S16)
A decrement of 0.2 in the year following hip fracture.
A decrement of 0.1 in the year following hip fracture.
Mortality Data
A relative risk of death over the next 5 year period of 2.2 and 1.3 for women aged 50-74 years and 75-84 years respectively.

Overview
By only analysing effects on the hip it is likely that this results will be less favourable to the treatment than those produced by SHEMO. This approach will not be applicable to interventions which are known to have a beneficial effect at other sites such as the vertebra.

4. Iglesias et al. QJ Med (2002)

Funding: Procter and Gamble Pharmaceuticals and Aventis Pharma.
Intervention : Risedronate.
Model Structure : Markov cohort model
Fracture Sites considered : Hip, Spine and Other
Population studied in base case : Women aged approximately 75 years
Underlying Fracture Incidence : UK epidemiological study (Johansen et al. Injury, 1997)
Methodological weaknesses compared to SHEMO:

- No lowering of average population risk to take into account high risk sub-sets of the population.
- Note that the efficacy assumed for Risedronate does not match that calculated by ScHARR (which is markedly less effective)

Cost Data taken from Dolan and Torgerson (Ost Int, 1998)
Not reported in the paper but will be similar, but lower than those used in SHEMO.
Utility Data taken from unpublished data.

- A decrement of 0.264 in the year following a hip fracture.
- A decrement of 0.080 in the year following a spine fracture.
- A decrement of 0.025 in the year following a wrist fracture.
- Utililty decrements in subsequent years are not reported.

Mortality Data: not clearly reported. Reference to a 30% increase in mortality compared to the population in the second year following hip fracture.

Overview. The epidemiological data for the fractures considered will be fairly similar to that in SHEMO, however the increased number of fractures used in SHEMO will be more favourable to the intervention. However the markedly better assumed efficacy of Risedronate used in Iglesias et al, will be very favourable to the intervention.

5. Borgstrom et al. Bone (2004)

Funding: Merck, Sharpe and Dohme.
Intervention : Alendronate.
Model Structure : Markov cohort model
Fracture Sites considered : Hip, Spine and Wrist
Population studied in base case : Men aged approximately 71 years with a prior spine fracture
Underlying Fracture Incidence : Swedish observational data (Kanis et al. Ost Int, 2000)
Methodological weaknesses compared to SHEMO:

- o Following a hip fracture, no further fractures are modelled. Following a spine fracture only a spine or hip fracture can occur.
- o The costs associated with Spine and Wrist fracture include indirect costs. Note the direct costs estimated for these fracture types are very high.

Cost Data
Taken from Zethraues et al. (Acta Orthop Scand, 1997)
Hip fracture costs in year 1
€6,996 (50 – 64 years)
€12,325 (65 – 74 years)
€15,028 (75 – 84 years)
€21,251 (85 years and older)
€5,354 in subsequent years assuming 10% of patients with a hip fracture transit to nursing home.
Cost Data
Taken from Zethraues et al. Working Paper (2002)[1]
Spine fracture costs in year
€6,716 (€3,326 direct costs, €3,390 indirect costs) ages 50 – 64 years
€3,326 (€3,326 direct costs) ages 65 years and over.
No costs in subsequent years.
Wrist fracture costs in year 1
€2,476 (€2,114 direct costs, €362 indirect costs) ages 50 – 64 years
€2,114 (€2,114 direct costs) ages 65 years and over.
No costs in subsequent years.
Utility Data in <u>the year of</u> the event taken from Zethraeus et al. Working Paper (2002)

- o A multiplier of 0.79 following a hip fracture.
- o A decrement of 0.62 following a spine fracture.
- o A decrement of 0.98 following a wrist fracture.

Utility Data in <u>subsequent</u> years

- o An assumption of a multiplier of 0.90 following a hip fracture.
- o An assumption of a multiplier of 0.95 following a spine fracture.
- o An assumption that wrist fractures had no effect on utility in subsequent years.

Mortality Data
Age differentiated mortality in the first year during hip fracture was calculated for men using the methodology reported in Oden et al. (Ost Int 1998)
Following spine fracture an age-standardized mortality ratio of 2.35 was used (Center et al. Lancet 1999)Attributable mortality following all fractures was set at 50%.

Overview
The high costs for hip fracture assumed in this model will be favourable to alendronate, however the smaller number of fractures considered will be unfavourable to treatment. The reduced number of fractures that can occur after some fractures will be unfavourable to alendronate

6. Kanis et al. Bone (2002)

Funding: Lilly, Hologic, Novartis and Roche.
Intervention : Hypothetical drug.
Model Structure : Markov cohort model
Fracture Sites considered : All osteoporotic fractures
Population studied in base case : Hypothetical women with the average population risk
Underlying Fracture Incidence : Swedish epidemiological studies (Zethraeus et al. Working Paper, 1998; Kanis et al. Ost Int, 2000; Kanis et al. Ost Int, 2001)
Methodological weaknesses compared to SHEMO:
The costs of osteoporotic fractures are assumed proportional to utility decrement with hip used as the reference case. The costs are US based, and may not be applicable to the UK. Additionally the hypothesis of costs being proportional to disutility was derived with assumed small disutility for peripheral fractures. Newer data on disutility has shown the disutility to be much higher, resulted in the known costs also being transformed by a similar proportion. In SHEMO the disutility from hip and spine fractures are broadly similar, but there is a marked difference in price. In this paper the costs associated with hip and spinal fractures would be assumed to be similar
Cost Data

- Hip fracture first year costs (Zethraues et al. Acta Orthop Scand, 1997)
- $7,900 between 50 and 64 years rising to $21,100 for women aged 85 years or over.
- $4,100 costs assumed in subsequent years.

Utility Data taken from unpublished data.

- A decrement of 0.2 QALYs in the year following a hip fracture.
- A decrement of 0.1 QALYs in subsequent years.
- The utility loss from other fractures are proportionate to the cost ratio between the appropriate site and hip. Detailed data not given in the report.

Mortality Data: not clearly reported. Reference to Kanis et al. Ost Int (2001)
Other fractures are said to increase the mortality expected from hip fractures by a ratio of 3.34 between the ages of 50 –54 years and 1.25 between 85 and 89 years.

Overview.
Assuming that costs are proportional to disutility results in the costs associated with peripheral fractures being greatly increased. This has most effect in the younger patients where peripheral fractures are relatively more common and is significantly favourable to the drug.

7. Buckley and Hillner. J Rheumatology (2003)

Funding: SmithKline Beecham.
Intervention : Calcium and Vitamin D, Etidronate, Alendronate.
Model Structure : Markov cohort model
Fracture Sites considered : Spine fractures only
Population studied in base case : Hypothetical women at varying risk using glucocorticoids
Underlying Fracture Incidence : An assumption of 4% per annum in women aged 70 years, halved for each 10-year reduction in age.Methodological weaknesses compared to SHEMO.
Only spine fractures considered.
Cost per spine fracture avoided presented, not cost per QALY
Cost Data
The cost per spine fracture is assumed to be $840 (Chrichilles et al. Bone, 1994).
Utility Data:
No utility data are provided, although comment is made that 38 days of disability per clinical spine fracture is expected (Nevitt et al. Ann Intern Med, 1998)
Mortality Data
No mortality from spine fractures were assumed.

Overview
This approach is not suitable for the interventions covered within the technology assessment as only spine fractures are considered.

8. Brecht et al. Int J Clin Pharm Res (2003)

Funding: Alliance for Better Bone Health.
Intervention : Risedronate.
Model Structure : Markov cohort model
Fracture Sites considered : Hip, Spine, Wrist and Other fractures
Population studied in base case : Women aged 70 years with low spine BMD and a prevalent vertebral fracture
Underlying Fracture Incidence : Hip and spine fracture incidence was taken from 1999 German Hospital discharge statistics. Statistisches Bundesamt (2000) Incidence of wrist fractures were taken from the “ADT—survey”
Methodological weaknesses compared to SHEMO.
No major flaws.
Cost Data
Taken from Pientka and Friedrich. Z Gerontol Geriat(1999)

- The cost per hip fracture is assumed to be €17,326 in the year of the fracture and €8,576 in subsequent years. [1]
- The cost per spine fracture is assumed to be between €5,035 and €6,171 in the year of fracture (depending on patient age). [1] No costs were assumed in subsequent years

Utility Data:
Have been taken from Jonsson et al Osteoporosis (1998)

- Reduction in utility of 0.2 and 0.1 in the year following a hip fracture and subsequent years respectively.
- Reduction in utility of 0.1and 0.09 in the year following a spine fracture and subsequent years respectively.

Mortality Data
The paper assumes that mortality following a hip fracture was equal to that reported by Keene et al. BMJ (1993). It is implied that all excess mortality was due to the hip fracture

Overview.
The results produced in this paper will be more favourable to the intervention that that in SHEMO due to the higher assumed cost of fracture. It is unclear whether the assumed incidence is greater or smaller than that used in SHEMO.

9. Brecht et al. Int J Clin Pharm Res (2004)

Funding: Alliance for Better Bone Health.
Intervention : Risedronate, Alendronate and Raloxifene.
Model Structure : Markov cohort model
Fracture Sites considered : Hip and Spine fractures only
Population studied in base case : Women aged 70 years with low spine BMD and a prevalent vertebral fracture
Underlying Fracture Incidence : Hip and spine fracture incidence was taken from 1999 German Hospital discharge statistics (Statistisches Bundesamt, 2000)
Methodological weaknesses compared to SHEMO:

- Only hip and spine fractures considered.
- Breast cancer effect excluded for raloxifene.

Cost Data taken from Pientka and Friedrich. Z Gerontol Geriat (1999)

- The cost per hip fracture is assumed to be $17,326 in the year of the fracture.
- The cost per spine fracture is assumed to be $5,355 in the year of fracture.
- No costs in subsequent years were assumed.

Utility Data
taken from Jonsson et al Osteoporosis (1998)

- Reduction in utility of 0.2 and 0.1 in the year following a hip fracture and subsequent years respectively.
- Reduction in utility of 0.1and 0.09 in the year following a spine fracture and subsequent years respectively.

Mortality Data
The paper reports that mortality associated with a fracture was possible, but the values assumed were not reported.

Overview.

The results produced in this paper will be more favourable to the intervention that that in SHEMO due to the higher assumed cost of fracture. However the exclusion of other fractures than those at the hip and spine will mean that the results are less favourable than those produced by SHEMO. It is unclear whether the assumed incidence is greater or smaller than that used in SHEMO.

10. Kanis et al. Bone (2005)

Funding: None listed.
Intervention : Hypothetical drug.
Model Structure : Markov cohort model
Fracture Sites considered : All osteoporotic fractures
Population studied in base case : Hypothetical women at varying risk
Underlying Fracture Incidence : UK epidemiological study for hip and wrist (Singer et al. J Bone Joint Surg, 1998), relative ratios of hip to other from Sweden to obtain other fracture incidence（Kanis et al. Ost Int, 2000)
Methodological weaknesses compared to SHEMO:
The costs of osteoporotic fractures are assumed proportional to utility decrement with hip used as the reference case. The costs are US based, and may not be applicable to the UK. Additionally the hypothesis of costs being proportional to disutility was derived with assumed small disutility for peripheral fractures. Newer data on disutility has shown the disutility to be much higher, resulted in the known costs also being transformed by a similar proportion. In SHEMO the disutility from hip and spine fractures are broadly similar, but there is a marked difference in price. In this paper the costs associated with hip and spinal fractures would be assumed to be similar. [Particularly as the costs for hip fracture are already high due to the assumed proportion of patients (25%) entering a nursing home following ahip fracture.
Cost Data

- Hip fracture first year costs taken from Kanis et al. Health Tech Assess, 2002)
- $12,488 between 50 and 64 years rising to $15,579 for women aged 85 years or over. These assume that 25% of women enter a nursing home at all ages.
- $1,997 costs assumed in subsequent years.
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Utility Data:
Hip and Spine fractures taken from Jonsson et al. Ost Int (1999)

- A multiplier of 0.79 in the year following a hip fracture.
- A multiplier of 0.90 in subsequent years following hip fracture.
- A multiplier of 0.63 in the year following a spine fracture.
- A multiplier of 0.93 in subsequent years following a spine fracture.

Other fractures taken from estimates from the National Osteoporosis Foundation (Ost Int , 1998) with minor modifications (Kanis et al. Ost Int , 2004)
Detailed data not provided.
Mortality Data
In the year following a hip fracture, excess mortality was varied from 1.3 to > 9.0 dependent on age as reported in Oden et al (Ost Int, 1998)

In the year following a spine fracture, excess mortality was 2.5 in the initial year and 1.3 in subsequent dependent on age as reported in Johnell et al (Ost Int, 2004)
No other fractures were associated with mortality
The attributable rate of mortality due to fracture was set at 23% for both hip and spine fractures

Overview.
Assuming that costs are proportional to disutility results in the costs associated with peripheral fractures being greatly increased. This has most effect in the younger patients where peripheral fractures are relatively more common and is significantly favourable to the drug. Furthermore the assumption of 25% of patients entering nursing home at all ages, compared with the 0% at 50 – 59 years in SHEMO, is greatly favourable to the drug as hip fracture costs are elevated, and the ratio between hip fracture costs and disutility is used in conjunction with disutility at other fracture sites to calculate the estimated cost. The use of a hypothetical drug with a 35% reduction in all fracture sites means that the results are not directly comparable with those in the technical appraisal.