

Cost-effectiveness model for Sweden

Background document

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1 Background

The purpose of a reference model is to serve as a tool for assessing the cost-effectiveness of the treatment and prevention of osteoporosis. In particular the model is intended to be used for validating existing and new models and may also be used instead of developing new models. This cost-effectiveness model is based on previous modelling experience developed over almost 15 years [1-6], and meets the properties of good decision analytic modelling [7, 8]. The model has also been described in a recent position paper of the International Osteoporosis Foundation (IOF) written by Zethraeus *et al.*[9].

2 Introduction

2.1 The ICER

The incremental cost-effectiveness ratio (ICER) is defined as

$$ICER = \frac{\Delta C}{\Delta E} = \frac{C_1 - C_0}{E_1 - E_0} \quad (1)$$

where ΔC is the difference in total cost between intervention and no intervention, and ΔE is the difference in effectiveness between intervention and no intervention.

Costs can be divided into two different categories: direct and indirect costs. Direct costs consist of medical costs, which are costs directly attributed to health care interventions e.g. hospitalisations, outpatient visits and drugs etc, and non-medical costs that can be associated with provision of medical services, e.g. transportation, home help and informal care etc. Indirect costs are costs related to lost productivity due to illness or treatment.

In this model two effectiveness measures were included: life years gained and quality adjusted life years (QALYs) gained. The QALY outcome measure is the most relevant in a health-policy perspective, since by using a common denominator it allows for comparisons of the value of interventions across disease states.

2.2 A brief introduction to Markov models

Markov models are a specific type of discrete state-transition simulation models. The simulated cohort of patients is divided into a finite number of states based on, for example, the current health status of the patient. The states are mutually exclusive and collectively exhaustive. The most important assumption of the Markov model is that future events only depend on the current state that the patient is in, and not on prior events [10]. This is called the **Markovian property**, and means that all patients within each state are treated the same irrespectively of their (medical) history.

Time is handled as discrete periods of the same length (cycles). Let s_t^i denote the health state of patient i at time t , where $s_t^i = (1..S)$ and S is the number of states in the model. The **transition probability** from state a to state b at time t can be written $T(a,b,t) = P(s_t = b | s_{t-1} = a)$. The Markovian property requires that the transition probability be independent of s_{t-i} for all $i > 1$.

Markov models are a commonly used tool in medical decision analysis. The model is especially appropriate to use when the disease in focus is characterised by recurrence of certain events and when these are based on continuous risk over time [11].

2.2.1 Half cycle correction

In the Markov model the state transitions occur at the end of the cycle. In reality fractures occur continuously over time. If the membership is counted at the end of the cycle the survival will be overestimated. Therefore the method of half-cycle correction is used. By adding one extra cycle and assuming that the first and last cycle in the model is half as long as the cycles in between, the overestimation will be corrected.

2.2.2 Cohort simulations

The use of a cohort simulation approach is the most frequently used method in Markov model analyses. The cohort simulation considers a hypothetical cohort of persons which all begin the process with some determined distribution among the states. In the following cycle the cohort will be divided among the states according to transition probabilities, which yields a new distribution of the cohort among the states. This will continue in the subsequent cycles until the process has reached its cycle limit.

The *cycle sum* which is the utility or cost¹ accrued in each cycle can be calculated by the formula:

$$\text{Cycle sum} = \sum_{s=1}^S f_s * U_s \quad (2)$$

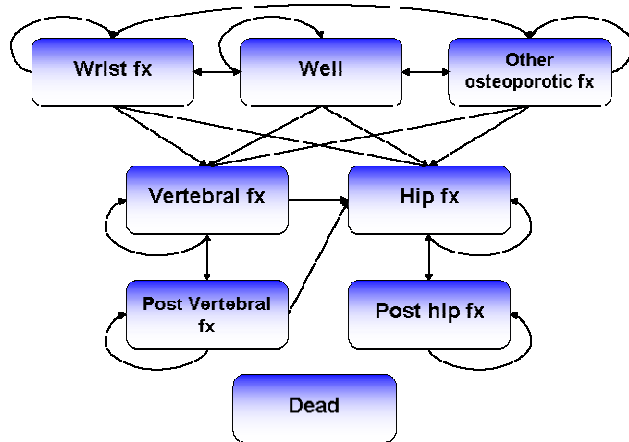
Where S is the number of states, f_s is the fraction of the cohort in state s and U_s is the utility of state s .

¹ Formula in the case of costs: $\text{Cycle sum} = \sum_{s=1}^S f_s * C_s$

3 The model

The model presented here is a further development of a Markov cohort model earlier used to estimate the cost-effectiveness of osteoporotic therapies in Sweden [12, 13], Denmark [14] Spain, Belgium, Finland [1], USA, Japan, Australia, Germany [15] and the UK [2]. The model investigates the cost-effectiveness of treatment alternatives for osteoporosis. The structure of the model is shown in the state transition diagram in *Figure 3*. A new feature of the model version used in this model is the introduction of a new health state that represents other osteoporotic fracture types than the “classical” hip, vertebral and wrist (although not implemented in the present model) fracture types. Fracture types to be included in this new health state depend on the scenario that is analysed and data availability.

Figure 1 Structure of the Markov cohort simulation model



The cycle length is one year and all patients are followed through the model from the age at the start of treatment until they are 100 years old or dead. There is always a probability of remaining in the same state or to die. All the patients begin in the *well* health state. Each year a patient has a probability of having a fracture, remaining healthy or to die. If a patient dies, she will move to the *dead* health state and remain there for the rest of the simulation (arrows to the *dead* health state are excluded to simplify the figure). If the patient incurs a fracture, she will move, depending on fracture type, to the *hip fracture*, *spine fracture*, *wrist fracture* or *other osteoporotic fracture* health state. After one year in one of these states the patient can have a new fracture, move to the *post hip fracture* state, *post vertebral fracture* state or die. Wrist fracture and other osteoporotic fracture are assumed to have an impact on costs and morbidity only in the first year after fracture, therefore after one year in these health states patients move, if not fractured once more, back to the *well* health state. Patients in the *post vertebral fracture* state can stay in this state, have a vertebral fracture, hip fracture or die. From the *post hip* state it is only possible to stay in the *post hip* state, have another hip fracture or to die. Consequently, patients who have had a hip fracture cannot experience any future wrist, vertebral or other osteoporotic fractures, and patients in the vertebral and *post vertebral* states cannot have a wrist fracture. The probability of having a vertebral or a wrist fracture after a hip fracture is low, and the consequences on mortality and quality of life after having experienced multiple, different fractures has been poorly investigated. Therefore the conservative approach of only looking at the isolated effects of the most severe fracture type is used. It leads to a slight underestimation of the number of spine and wrist fractures, which will have negligible impact on the cost-effectiveness.

3.1 Target patient groups

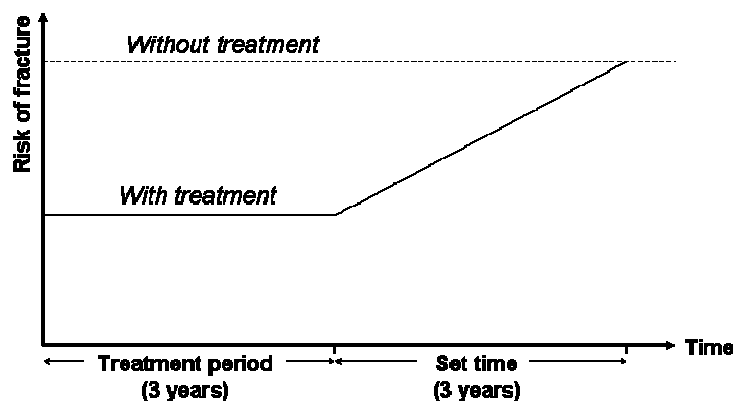
The model allows a wide range of theoretical female Swedish populations to be simulated. Starting age of treatment can be varied from 50 to 99 years and the relative risk of fracture from 1 to 20.

3.2 Modelling the intervention

3.2.1 Intervention length and offset-time

The model allows interventions lengths and offset times to be changed freely. During the “offset time” the fracture risk reduction declines linearly to zero. In all, an intervention will have an effect for $\text{Years}_{\text{intervention}} + \text{Years}_{\text{offset}}$ years which is illustrated with an example of 3+3 years in *Figure 2*.

Figure 2 Effect of intervention



3.2.2 Treatment cost and treatment effect on fractures and quality of life

Treatment effect can be varied independently for hip, vertebral and wrist fractures. Also, it is possible to model the effects of therapy on quality of life (as in the case of hormone replacement therapy or an unwanted side-effect) independently of any fracture reducing effect. In the case of bone-specific agents that affects only fracture risk, all gained QALYs will come from avoiding fractures and their associated mortality. The cost of an intervention can also be changed freely.

4 Data in the model

4.1 Risk of fracture

The age-specific risks of hip and wrist fracture for Swedish females used in the model were taken from a population based study from Malmö [16] (*Table 1*). The population risks in the model can be modified by using different relative risks.

4.2 Costs

4.2.1 Discounting

All costs are in year 2004 values and given in Swedish kronor (SEK). When needed the costs were inflated using the Consumer Price Index from *Statistics Sweden* [17]. Discount rates for both costs and effects can be varied freely.

4.2.2 Cost of fractures

Costs of a fracture can be divided into acute costs, which occur the first year following the fracture, and long-term costs, which can persist several years after fracture or even for the remainder of the lifetime of the patient.

Direct and indirect fracture costs in Sweden during the first year after a hip, clinical vertebral and wrist fracture was derived from Zethraeus et al. [18, 19].

Hip fracture costs the second and following years were based on the age differentiated proportion of patients, that come from home before fracture, that reside in nursing home 1 year after fracture [20]. These patients were assumed to remain in nursing home for the rest of their lives [4] at a daily cost of SEK 1 605 [21]. Vertebral and wrist fracture was assumed to incur costs the first year after fracture only.

All fracture costs used in the model are summarised in *Table 2* and *Table 3*

4.2.3 Costs in added life years

It has been argued that difference between consumption and production for the patients, commonly referred to as cost in added life years, should be included when conducting a cost-effectiveness analysis [22]. Estimates on the costs in added life years are available for Sweden [23] (*Table 4*). Cost in added life years can be switched on and off in the reference model

4.3 Quality of life

Estimates of the reduction in quality of life the year after osteoporotic fractures were derived from a study based on patients recruited at the orthopaedic department at the Malmö University Hospital in the south of Sweden [19]. Since the quality of life status before the fracture was not collected in the Malmö study social tariff values [24] were used to calculate the disutility associated with each fracture type. By multiplying this number with age differentiated population values [25], fracture specific quality of life weights were obtained (*Table 5*) [26].

The quality of life in subsequent years after a hip fracture was assumed to be 90% of that of a healthy individual.[4] Wrist fractures are not assumed to be associated with any utility loss after the first year.

A UK case control study of patients enrolled in the MORE showed that the quality of life was reduced by approximately 9% when the clinical vertebral fracture may have occurred at a previously unknown time [27]. Based on these findings, we conservatively assumed that the loss of utility the second and following years for a clinical vertebral fracture is 0.05, which gives a multiplier of 0.929.

The user can also in add the model a quality of life change caused by the treatment itself rather than by avoided fractures. Quality of life effects from fractures can not be altered.

4.4 Mortality

The age-specific annual mortality rates for the general population in Sweden are based on the years 1998-2001 (*Table 7*) [17].

Patients with fractures have a higher mortality compared to the normal population. In a study by Odén et al. [28] age differentiated mortality the first and following years after a hip fracture was calculated. (*Table 8* and *Table 9*).

There are studies showing that persons with osteoporosis have a higher degree of frailty compared to the population, which suggests that excess mortality among fracture cases is not entirely attributed to the fracture event, but to co-existing morbidity [29, 30]. Along with previous findings, we assumed that 30% of the excess mortality (compared to normal mortality) after a hip fracture was associated with the hip fracture event.

A clinical vertebral fracture is also associated with an increase in mortality [31-33]. Even when the mortality is adjusted for BMD and co-morbid conditions, patients with osteoporotic vertebral fractures have been shown to have a significantly higher mortality compared to osteoporotic patients without fracture [34, 35]. Age differentiated mortality risks (first and following years) after clinical vertebral fractures was taken from Johnell et al.[36] (*Table 10* and *Table 11*). Again it was assumed that only 30% of the excess mortality was related to the fracture event. Wrist fracture was assumed not to be associated with any excess mortality [31, 32].

Note: The mortalities in tables Table 7-Table 11 are absolute values and are not adjusted for any co-morbidity.

5 Tables

Table 1 Incidence of female osteoporotic fractures in Sweden, per 1000

	Hip	Vertebral	wrist		Hip	Vertebral	wrist
50	0.634	1.622	4.014	76	11.568	10.444	10.064
51	0.622	1.616	4.092	77	13.080	11.110	10.320
52	0.610	1.610	4.17	78	14.778	11.214	10.672
53	0.598	1.604	4.248	79	16.476	11.318	11.024
54	0.586	1.598	4.326	80	18.174	11.422	11.376
55	0.574	1.592	4.404	81	19.872	11.526	11.728
56	0.562	1.586	4.482	82	21.570	11.630	12.080
57	0.550	1.580	4.56	83	24.654	12.586	12.438
58	0.828	1.870	4.784	84	27.738	13.542	12.796
59	1.106	2.160	5.008	85	30.822	14.498	13.154
60	1.384	2.450	5.232	86	33.906	15.454	13.512
61	1.662	2.740	5.456	87	36.990	16.410	13.870
62	1.940	3.030	5.68	88	40.074	17.366	14.228
63	2.174	3.302	5.926	89	43.158	18.322	14.586
64	2.408	3.574	6.172	90	46.242	19.278	14.944
65	2.642	3.846	6.418	91	49.326	20.234	15.302
66	2.876	4.118	6.664	92	52.410	21.190	15.660
67	3.110	4.390	6.91	93	55.494	22.146	16.018
68	3.592	5.068	7.336	94	58.578	23.102	16.376
69	4.074	5.746	7.762	95	61.662	24.058	16.734
70	4.556	6.424	8.188	96	64.746	25.014	17.092
71	5.038	7.102	8.614	97	67.830	25.970	17.450
72	5.520	7.780	9.040	98	70.914	26.926	17.808
73	7.032	8.446	9.296	99	73.998	27.882	18.166
74	8.544	9.112	9.552	100	77.082	28.838	18.524
75	10.056	9.778	9.808				

Source: [16]

Table 2 Annual direct cost of fractures in different age groups (SEK)

	50-64	65-74	75-84	85-
1st year				
<i>Hip fracture¹</i>	86 087	93 722	165 513	231 344
<i>Clinical vertebral fracture²</i>	32 633	32 633	32 633	32 633
<i>Wrist fracture²</i>	20 736	20 736	20 736	20 736
	50-59	60-69	70-79	80-89
2nd year and following				
<i>Hip fracture³</i>	39 250	38 079	59 754	86 116

Source: 1. [18]

2. [19]

3. Based on the proportion of patients that have moved to nursing home one year after hip fracture [20].

Table 3 Annual indirect cost of fractures in different age groups (SEK)

50-64	
1st year	
<i>Clinical vertebral fracture</i>	33 512
<i>Wrist fracture</i>	3 533

Source: [19]

Table 4 Costs in added life years (SEK)

Age	Production-consumption
50-64	70 065
65-74	-163 469
75-84	-191 855
85-	-302 751

Source: [23]

Table 5 Calculation of the disutility of a fracture

Multiplier¹	
1st year	
<i>Hip</i>	0.792
<i>Clinical vertebral fracture</i>	0.626
<i>Wrist</i>	0.977
<i>Morphometric vertebral fracture</i>	0.816
2nd year and following	
<i>Hip</i>	0.90
<i>Clinical vertebral fracture</i>	0.929

1. Source: [19, 25]

Table 6 Female population utility scores

Age	General population utility
50-59	0.82
60-69	0.78
70-79	0.78
80-	0.74

1. Source: [25]

Table 7 Normal mortality for women in Sweden (per 1000)

50	2.69	60	6.63	70	17.18	80	53.00	90	155.63	100	348.51
51	2.85	61	7.29	71	19.48	81	58.78	91	170.39		
52	3.13	62	7.83	72	22.08	82	65.46	92	187.82		
53	3.33	63	8.51	73	24.80	83	72.61	93	210.30		
54	3.69	64	9.46	74	27.51	84	81.21	94	224.54		
55	4.04	65	10.43	75	31.16	85	93.67	95	245.13		
56	4.41	66	11.36	76	34.49	86	102.98	96	263.90		
57	4.84	67	12.71	77	38.26	87	115.10	97	282.43		
58	5.25	68	14.02	78	42.46	88	126.77	98	303.06		
59	5.91	69	15.63	79	47.28	89	141.76	99	319.35		

Source: [17]

Table 8 Risk of mortality the year after hip fracture (per 1000)

50	35.4	60	52.7	70	91.6	80	168.2	90	293.7	100	530.6
51	37.7	61	53.0	71	97.4	81	178.8	91	298.7		
52	38.1	62	52.7	72	108.0	82	190.1	92	322.0		
53	38.4	63	55.9	73	115.1	83	197.8	93	353.1		
54	41.1	64	59.2	74	121.6	84	210.3	94	369.9		
55	42.3	65	59.9	75	134.5	85	225.8	95	397.0		
56	41.8	66	62.5	76	140.1	86	235.2	96	420.8		
57	42.9	67	75.4	77	147.8	87	248.2	97	444.1		
58	44.3	68	77.7	78	158.8	88	259.2	98	470.7		
59	48.5	69	84.3	79	162.8	89	273.8	99	490.7		

Source: [28]

Table 9 Risk of mortality the following years after hip fracture (per 1000)

50	16.1	60	24.1	70	46.3	80	86.9	90	158.5	100	348.5
51	17.1	61	24.3	71	49.4	81	92.7	91	170.4		
52	17.3	62	24.3	72	54.8	82	98.8	92	187.8		
53	17.5	63	26.4	73	58.5	83	103.2	93	210.3		
54	18.8	64	29.0	74	62.0	84	110.2	94	224.5		
55	19.3	65	30.1	75	68.7	85	118.7	95	245.1		
56	19.1	66	31.4	76	71.6	86	124.3	96	263.9		
57	19.6	67	38.0	77	75.8	87	131.8	97	282.4		
58	20.3	68	39.2	78	81.6	88	138.3	98	303.1		
59	22.2	69	42.6	79	83.9	89	146.9	99	319.4		

Source: [28]

Table 10 Risk of mortality the year after a clinical vertebral fracture (per 1000)

50	39.9	60	67.8	70	107.7	80	152.5	90	215.1	100	348.5
51	43.0	61	69.0	71	111.5	81	158.3	91	215.1		
52	44.1	62	69.6	72	120.3	82	164.4	92	228.2		
53	45.1	63	74.9	73	124.8	83	167.2	93	246.6		
54	48.8	64	80.2	74	128.4	84	173.8	94	254.7		
55	50.9	65	81.0	75	138.4	85	182.5	95	269.7		
56	51.0	66	82.2	76	140.4	86	186.1	96	282.4		
57	53.0	67	96.3	77	144.5	87	192.4	97	294.6		
58	55.5	68	96.5	78	151.2	88	197.0	98	309.0		
59	61.5	69	101.9	79	151.3	89	204.2	99	319.4		

Source: [36]

Table 11 Risk of mortality the following years after a clinical vertebral fracture (per 1000)

50	26.2	60	44.5	70	70.8	80	100.2	90	155.6	100	348.5
51	28.3	61	45.4	71	73.3	81	104.0	91	170.4		
52	29.0	62	45.7	72	79.1	82	108.0	92	187.8		
53	29.6	63	49.2	73	82.0	83	109.9	93	210.3		
54	32.1	64	52.7	74	84.4	84	114.2	94	224.5		
55	33.4	65	53.2	75	91.0	85	120.0	95	245.1		
56	33.5	66	54.0	76	92.3	86	122.3	96	263.9		
57	34.9	67	63.3	77	95.0	87	126.5	97	282.4		
58	36.5	68	63.5	78	99.4	88	129.5	98	303.1		
59	40.4	69	67.0	79	99.5	89	141.8	99	319.4		

Source: [36]

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