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The cost-effectiveness of raloxifene therapy for postmenopausal women in the UK

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Summary

OBJECTIVE: To estimate the cost-effectiveness of drug therapy for postmenopausal women in the UK. Two options are considered: hormone replacement therapy (HRT) and raloxifene, each for a duration of 2, 5 and 10 years.

METHODS: Cost-effectiveness is measured in terms of cost per life year gained, where effects are estimated using a disease risk model to forecast disease incidence, survival and life expectancy with and without therapy. Probabilities of disease incidence and survival curves are first calculated using mean population-based data and then recalculated incorporating drug therapy effects on risk of breast cancer, hip fracture and coronary heart disease. Compliance rates and the effect of therapy on the disease risk were identified through review of published and unpublished clinical trial reports. Costs are estimated in 1998 UK£ and comprise drug costs, monitoring costs, treatment costs for averted disease events, and costs from additional years of life. In the sensitivity analysis, quality of life data are incorporated and a cost-utility analysis is conducted. The sensitivity of results to other model parameters is also tested.

RESULTS: The cost per life year gained relative to no therapy for HRT ranges from £15,158-£51,428 depending on age at initiation of therapy and duration of therapy. For raloxifene the corresponding figures are £25,647-£56,255. In the sensitivity analysis for HRT the incremental cost per life year gained ranges from £9,355-£150,199, depending on age at initiation of therapy, duration of therapy and parameter values used. For raloxifene, the corresponding range is £14,882-£88,279. The cost-utility analysis indicates that under the assumption that drug therapy has no effect on quality of life with no disease the incremental costs per QALY gained for HRT and raloxifene relative to no therapy range from £18,451-£61,629 and £31,502-£66,056, respectively, depending on age at initiation of therapy and duration of therapy.

CONCLUSIONS: The range of baseline cost-effectiveness values for both therapies are broadly similar, though this disguises the fact that their effects on disease risk and their drug costs are somewhat different. Specifically, the lower drug cost of HRT to raloxifene is counteracted by the much more favourable impact of raloxifene on breast cancer risk.

Introduction

Evidence suggests that hormone replacement therapy (HRT) has a positive role in the prevention of osteoporosis and coronary heart disease (CHD) for postmenopausal women. Against these potential benefits is the possibility that HRT is associated with an increased risk of breast cancer and endometrial cancer. Recent evidence suggests that raloxifene, a new non-steroidal benzothiopene licensed in the UK as therapy for postmenopausal women, has, like HRT, a preventative effect on the risk of osteoporotic fracture and CHD (Delmas et al., 1997). However, unlike HRT, raloxifene is thought to substantially reduce the risk of breast cancer without having an effect on endometrial tissue.

Despite the potentially superior clinical benefits of raloxifene over HRT, the drug cost of raloxifene is higher. Consequently, the issue of cost-effectiveness becomes relevant as a means of identifying the patient group most appropriate for raloxifene therapy.

Methods

The aim of this study is to estimate the cost-effectiveness of drug therapy for postmenopausal women in the UK. The perspective taken is that of the NHS. Two options are considered: HRT; and, raloxifene; each for a duration of 2, 5 and 10 years. Cost-effectiveness is considered for women receiving therapy at age 55 and 60. Earlier ages are not considered because raloxifene is licensed in the UK as therapy for postmenopausal women. Effects are measured in terms of life-years gained and the form of economic evaluation is therefore cost-effectiveness analysis. In the sensitivity analysis, quality of life data are incorporated and a cost-utility analysis is conducted.

Measuring effectiveness

A disease risk model is used to forecast disease incidence, survival and life expectancy with and without therapy. Life expectancy is calculated by estimating the area under the survival curve from age at initiation of therapy to age 85, where the height of the survival curve at a particular age is the cumulative probability of surviving from the age at initiation of therapy to that age. The cumulative probability of survival is calculated by using age-related disease

incidence and mortality data to assess the one year probability of survival. Probabilities of disease incidence are first calculated using mean population-based data and then recalculated incorporating drug therapy effects on risk of breast cancer, hip fracture and CHD. Life-years gained from therapy are calculated by subtracting baseline life expectancy from the life expectancy calculated incorporating drug therapy effects.

The mathematical formulation of the effectiveness model is presented in the Technical Appendix. There are two important implications of the model structure. The first is that the disease effects are treated as being additive and are separable. This assumes there are no comorbidities across the diseases of interest. The second implication is that disease incidence at age i is mapped on to disease mortality at age i using average population data. On the one hand this is likely to overestimate mortality given disease at age i [e.g. $P(die/CHD_i)$, etc.], since individuals may die from disease at age i contracted in earlier years. On the other hand this is likely to underestimate mortality given disease at age i since individuals may contract disease at age i and die from it in later years.

Data sources

Data on the incidence of CHD was obtained from CHD risk equations derived from the Framingham Heart Study (Martens and Guibert, 1994; Martens et al., 1993), incorporating baseline epidemiological data for the UK population. Epidemiological data on CHD risk factors were obtained from sources used previously in a UK-based economic evaluation (Drummond et al., 1993). Data on the incidence of hip fracture was taken from Bacon et al. (1996) and Boyce and Vessey (1985). Data on the incidence of breast cancer was taken from national morbidity statistics (1994). Mortality data for CHD, breast cancer and all other causes was taken from national mortality statistics (1997). Since national statistics are thought to underestimate true mortality associated with hip fractures (Daly et al., 1993), an overall mortality rate from hip fracture of 25% is used. The data sources and values employed are consistent with previous analyses (Daly et al., 1993; Col et al., 1997).

Effect of therapy on disease risk

Compliance rates and the effect of therapy on the risk of breast cancer, CHD and hip fracture were identified through review of published and unpublished clinical trial reports. Assumptions and data sources are presented in Table 1. Data from on-going clinical trials for raloxifene

were used when appropriate (e.g. "data on file"). Where such data were used, reference is made to appropriate clinical opinion.

The major costs of osteoporosis (some 87%) are associated with fracture of the hip rather than vertebral or Colles fracture (Dolan and Torgerson, 1998). The effects of raloxifene on hip fracture risk are not yet known. An indirect approach of assessing its potential impact is to examine its effects on bone mineral density (BMD). This suggests that raloxifene has approximately 75% of the efficacy of HRT on BMD of the hip (Data on file [Eli Lilly & Co.]). If HRT decreases hip fracture by 50% (Cauley et al., 1995) then, assuming that the major effect on risk is mediated through changes in BMD, raloxifene might be expected to decrease hip fracture by 37%.

The increased risk of breast cancer associated with HRT is taken from The Collaborative Group on Hormonal Factors in Breast (1997) which found a relative risk of breast cancer of 1.35 (range 1.21 to 1.49) for women who had taken HRT for more than five years. We have used these values for the model. The increase in risk has been assumed to be the same for all types of HRT at all doses. It has also been assumed that there is no increased risk of breast cancer for women who have been taking HRT for less than five years. Combined results from studies of over 12,000 women treated with raloxifene for at least 2.5 years have shown a mean reduction of 54% in newly diagnosed cases of breast cancer versus placebo (Data on file [Eli Lilly & Co.]; Jordan et al., 1998).

Both raloxifene and HRT have an effect on surrogate markers of cardiovascular disease. For modelling scenarios, we have applied a risk reduction of 35% to HRT. For the sensitivity analysis, we are modelling a risk reduction range of 20% to 50% (Stampfer et al., 1991; Falkeborg et al., 1992; Grodstein et al., 1997; The Writing Group for the PEPI Trial, 1995). Raloxifene produces a significant reduction in total cholesterol (3% to 6%) and low density lipoprotein cholesterol (4% to 10%, mean 7%). High density lipoprotein cholesterol and triglyceride concentrations do not change significantly (Data on file [Eli Lilly & Co.]). On the basis of these clinical data, a conservative value of 16% reduction in cardiovascular episodes has been modelled.

Start delay is the time prior to when drug therapy affects disease risk. Rise time is the time it takes from the end of the start delay until the maximum risk reduction is achieved. Stop delay and set time are defined analogously to start delay and rise time, respectively.

Measuring costs

Costs are estimated in 1998 UK£ and comprise: drug costs; monitoring costs; NHS treatment costs for breast cancer, CHD and hip fracture averted; and, NHS costs from additional years of life.

28-day drug therapy costs for HRT and raloxifene are £8.00 and £19.76, respectively. There are many HRT preparations available. We have used a monthly cost that is illustrative of prescriptions being initiated now for postmenopausal women and have varied this in the sensitivity analysis. The cost of raloxifene used is that for the recommended dose.

It is assumed that patients receiving therapy make two additional visits to see their GP during each year of therapy to monitor the effects, at a cost of £9.10 per visit (Hughes, 1991).

Expected treatment costs for CHD, breast cancer and hip fracture are £2,247, £2,845 and £3,254, respectively. These estimates are derived from a range of comprehensive UK-based cost analyses (Piercy and Phillips, 1995; Drummond et al., 1993; Daly et al., 1993).

Counterbalanced against the savings in health care costs due to the prevention of disease from therapy are higher costs of health care for other diseases which are incurred over additional years of expected life. An annual cost of £808 is used, based on updated average per capita health care expenditure (OHE, 1998).

The mathematical formulation of the cost model is presented in the Technical Appendix.

Measuring cost-effectiveness

Cost-effectiveness is calculated as the ratio of the net change in costs from therapy to the net change in life expectancy, or $(D+M-\Delta C+\Delta N)/\Delta L$, where D is the cost of drug therapy, M is the cost of monitoring therapy, ΔC denotes the expected savings in treatment costs from a reduced incidence of disease due to therapy, ΔN is the expected increase in NHS expenditure required during the additional years of life arising from therapy, and ΔL is the expected increase in life expectancy from therapy. Future costs and changes in life expectancy are initially discounted to present values at an annual rate of 6%. This is varied in the sensitivity analysis.

Sensitivity analysis

A univariate sensitivity analysis is conducted to assess the sensitivity of results to changes in: compliance rates; effect of therapy on disease risk; HRT costs; and, discount rates. The range of values used are presented in Table 2. A sensitivity analysis is also conducted on the cost-effectiveness of therapy in postmenopausal women at increased risk of hip fracture. The relative risk of hip fracture in this higher-risk group is 2.6 compared to the age-specific risks in the general population (Marshall et al., 1996).

A further sensitivity analysis is conducted on the consequence of incorporating quality of life effects. Quality of life gains are added to the life years gained from drug therapy in order to calculate the incremental cost per quality-adjusted life year (QALY) gained from drug therapy. The quality of life weights used are presented in Table 3. Since the study population comprises postmenopausal women, therapy has no effect on menopausal symptoms. QALYs gained from therapy therefore arise from increased life expectancy and reduced incidence of non-fatal disease events. Two hypothetical scenarios are examined where drug therapy produces modest increases in quality of life throughout the duration of therapy.

Results

Baseline results

Baseline results are presented in Table 4. HRT and raloxifene both increase the life expectancy of postmenopausal women though a positive incremental cost is incurred for this

improvement. The incremental cost per life year gained relative to no therapy for HRT ranges from £15,158-£51,428 depending on age at initiation of therapy and duration of therapy. For raloxifene the corresponding figures are £25,647-£56,255.

Sensitivity analysis

Results of the sensitivity analysis are presented in Table 5. For HRT, the incremental cost per life year gained ranges from £9,355-£150,199, depending on age at initiation of therapy, duration of therapy and parameter values used. For raloxifene, the incremental cost per life year gained in the sensitivity analysis ranges from £14,882-£88,279.

The results of the cost-utility analysis are presented in Table 6. Under the assumption that drug therapy has no effect on quality of life with no disease the incremental costs per QALY gained for HRT and raloxifene relative to no therapy range from £18,451-£61,629 and £31,502-£66,056, respectively, depending on age at initiation of therapy and duration of therapy. Introducing hypothetical assumptions that drug therapy causes modest increases in quality of life throughout the duration of therapy produces dramatic reductions in the incremental cost per QALY gained.

Discussion

This paper presents an economic evaluation of HRT and raloxifene for postmenopausal women in the UK. Whilst the range of baseline cost-effectiveness values for both therapies are broadly similar, this disguises the fact that their predicted effects on risk of breast cancer, CHD and hip fracture and their drug costs are somewhat different. The lower drug cost of HRT to raloxifene (£8.00 versus £19.76 for 28 days of therapy) is counteracted by the more favourable impact of raloxifene on breast cancer risk (risk *reduction* of 54%-77% depending on age versus risk *increase* of 0%-35% depending on duration of therapy). Both therapies are more cost-effective if the patient is older at initiation of therapy and therefore at a higher risk of disease. HRT is more cost-effective with a shorter duration of therapy (2 years) since the effect of therapy on breast cancer risk over this time is assumed to be zero. After 5 years of therapy HRT is assumed to increase breast cancer risk so therapy becomes less cost-effective.

For raloxifene, therapy is more cost-effective when the duration of therapy is longer so that a longer period of risk reduction is achieved.

The sensitivity analysis indicates that the effect of therapy on disease risk may affect cost-effectiveness. However, whilst some uncertainty may exist concerning the true effect of therapy on risk of breast cancer, CHD and hip fracture there is little that health care providers can do to increase cost-effectiveness by improving these effects. One factor that providers may be able to have an effect on which does affect cost-effectiveness is compliance. Clearly this is an important factor in the cost-effectiveness of therapy for postmenopausal women and to improve the value for money of such therapy, health care providers may wish to pursue strategies aimed at improving compliance.

The baseline scenarios model for postmenopausal women at normal risk of hip fracture. Women with osteopenia are at increased risk of hip fracture compared with the normal population of postmenopausal women. Therapy was more cost-effective in this group (see Table 5). Thus to improve cost-effectiveness health care providers may wish to target therapy at this higher-risk group.

In the cost-utility analysis, the incremental costs per QALY gained for both therapies are initially slightly higher than the incremental costs per life year gained. Quality of life is the same for individuals with no disease receiving drug therapy as for individuals with no disease not receiving drug therapy. QALYs gained from therapy arise solely from increased life expectancy and reduced incidence of non-fatal disease, and there are no QALY gains from improvements in quality of life over the duration of therapy. When it is hypothetically assumed that drug therapy produces modest increases in quality of life throughout the duration of therapy, this produces dramatic reductions in the incremental cost per QALY gained.

Some possible limitations of this study should be noted. First, this economic evaluation is based on a computer-generated disease risk model, and potential problems associated with using economic models to assess the cost-effectiveness of health care programmes are well documented (Sheldon, 1996; Glick et al., 1993, Rittenhouse 1996). Particularly, the use of CHD risk equations derived from the Framingham Heart Study to estimate incidence of CHD have been criticised (Sheldon, 1996; Glick et al., 1993). However, doubts surrounding the

ability of Framingham Heart Study data to predict CHD incidence have been at least partly dispelled by Morris (1997) and Schulte and Assman (1991) who demonstrate that CHD risk equations derived from the Framingham Heart Study are able to predict the incidence of CHD obtained in a number of major clinical trials. Nevertheless, doubts surrounding models of this kind remain.

Second, estimation of cost-effectiveness in the baseline analysis requires selection of best point estimates of the impact of drug therapy on breast cancer, CHD and hip fracture. For raloxifene, the estimates used were based on data generated from a relatively small number of ongoing clinical trials. As further data become available from these trials any uncertainty surrounding the true impact of therapy is likely to be reduced.

Third, life expectancy is calculated by estimating the area under the survival curve from age at initiation of therapy to age 85. Calculation to an older age is not possible due to a lack of annual age-specific data on disease incidence and mortality for the UK population. Failure to estimate survival curves beyond age 85 has the effect of assuming that there is no difference in mortality after this age between women receiving therapy and those not receiving therapy. This is probably a realistic assumption in this study given that we consider therapy initiated at age 55 and 60 years of up to 10 years duration.

Despite these potential limitations, this economic evaluation is notable for two reasons. First, because it is the first economic evaluation of drug therapy for postmenopausal women in the UK; second, because it is the first UK-based economic evaluation of raloxifene.

Issues for discussion

We would particularly welcome comments on the following:

1. Is it appropriate to assume to treat disease effects as being additive in the model?
2. Is it appropriate to map disease incidence at age i on to disease mortality at age i, given that it may underestimate or overestimate disease mortality?

3. Using economic modelling techniques there is a usually trade-off between accuracy and simplicity. Is modelling of the kind used here appropriate (particularly where there is an absence of clinical trial data)?
4. Is raloxifene cost-effective? Put another way, what is or what should be the critical cost-effective ratio?

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Technical appendix

Measuring effectiveness

Initially, we assume the probability of dying at age i from CHD, breast cancer and hip fracture is calculated as follows

$$P(\text{diefromCHD}_i) = P(\text{CHD}_i)*P(\text{die/CHD}_i) \quad [1a]$$

$$P(\text{diefrombreastcancer}_i) = P(\text{breastcancer}_i)*P(\text{die/breastcancer}_i) \quad [1b]$$

$$P(\text{diefromhipfracture}_i) = P(\text{hipfracture}_i)*P(\text{die/hipfracture}_i) \quad [1c]$$

Obtaining incidence data [$P(\text{CHD}_i)$, $P(\text{breastcancer}_i)$ and $P(\text{hipfracture}_i)$] and mortality data [$P(\text{diefromCHD}_i)$, $P(\text{diefrombreastcancer}_i)$ and $P(\text{diefromhipfracture}_i)$] from the sources listed in the text we calculate $P(\text{die/CHD}_i)$, $P(\text{die/breastcancer}_i)$ and $P(\text{die/hipfracture}_i)$ using equations [1a]-[1c]. We then estimate the probability of surviving age i, $P(\text{survive}_i)$

$$P(\text{survive}_i) = 1 - [P(\text{diefromCHD}_i) + P(\text{diefrombreastcancer}_i) + P(\text{diefromhipfracture}_i) + P(\text{diefromallothercauses}_i)] \quad [2]$$

The discounted cumulative probability of surviving to age j, $\text{CumP}(\text{survive}_j)$, is then calculated as follows

$$\text{CumP}(\text{survive}_j) = \prod_{i=Y}^{j} \frac{P(\text{survive}_i)}{(1+r)^{i-Y}}, \qquad [3]$$

where Y is the age at initiation of therapy and r is the discount rate. Discounted life expectancy, L, is then calculated as follows

$$L = \sum_{j=Y}^{85} \text{CumP}(\text{survive}_j) \qquad [4]$$

L is calculated initially assuming no therapy, L_{nt}. The effects of drug therapy are included via their modification of $P(CHD_i)$, $P(\text{breastcancer}_i)$ and $P(\text{hipfracture}_i)$ in equations [1a]-[1c]. $P(\text{die/CHD}_i)$, $P(\text{die/breastcancer}_i)$ and $P(\text{die/hipfracture}_i)$ are assumed to remain constant and $P(\text{diefromCHD}_i)$, $P(\text{diefrombreastcancer}_i)$ and $P(\text{diefromhipfracture}_i)$ are recalculated. From equations [2]-[4] L is then recalculated using these adjusted values, L_{dt}, assuming that $P(\text{diefromallothercauses}_i)$ remains constant in equation [2]. Expected increases in life expectancy resulting from drug therapy, ΔL, are thus calculated as follows

$$\Delta L = L_{nt} - L_{dt} \qquad [5]$$

Measuring costs

Total discounted drug costs, D, and total discounted monitoring costs, M, are calculated as follows

$$D = \sum_{i=Y}^{Y+U} \frac{d_i}{(1+r)^{i-Y}} \qquad [6]$$

$$M = \sum_{i=Y}^{Y+U} \frac{m_i}{(1+r)^{i-Y}} \qquad [7]$$

where d_i is the annual drug cost at age i, m_i is the annual monitoring cost at age i, and U is the duration of therapy.

NHS treatment costs for breast cancer, CHD and hip fracture are estimated by first calculating the expected cost of disease at age k, $E[\text{Cost}((.)_k)]$, as follows

$$E[\text{Cost}(CHD_k)] = \{\prod_{i=Y}^{k-1} P(\text{survive}_i) * [1 - P(CHD_i)]\} * P(CHD_k) * \text{Cost}(CHD_k) \qquad [8a]$$

$$E[\text{Cost}(\text{breastcancer}_k)] = \{\prod_{i=Y}^{k-1} P(\text{survive}_i) * [1 - P(\text{breastcancer}_i)]\} * P(\text{breastcancer}_k) * \text{Cost}(\text{breastcancer}_k) \qquad [8b]$$

$$E[Cost(hipfracture_k)] = \{\prod_{i=Y}^{k-1} P(survive_i) * [1 - P(hipfracture_i)]\} * P(hipfracture_k) * Cost(hipfracture_k) \quad [8c]$$

where $Cost((.)_k)$ is the cost of treatment at age k. NHS treatment costs for breast cancer, CHD and hip fracture, C, are then calculated as follows

$$C = \sum_{k=Y}^{85} \frac{E[Cost(CHD_k)] + E[Cost(breastcancer_k)] + E[Cost(hipfracture_k)]}{(1+r)^{k-Y}} \quad [9]$$

C is calculated initially assuming no therapy, C_{nt}. Effects of drug therapy are then included via their modification of $P(CHD_i)$, $P(breastcancer_i)$ and $P(hipfracture_i)$ which, from equations [1a]-[1c] and [2] affects the expected cost of disease via equations [8a]-[8c]. C is then recalculated using these adjusted values, C_{dt}. Expected savings in lifetime disease treatment costs from a reduced incidence of breast cancer, CHD and hip fracture, ΔC, are then calculated as follows

$$\Delta C = C_{nt} - C_{dt} \quad [10]$$

NHS costs from additional years of life are calculated by first estimating NHS expenditure on illnesses other than CHD, breast cancer and hip fracture in year k, n_k, as follows

$$n_k = [\prod_{i=Y}^{k-1} P(survive_i)] * (AE_k - \{E[Cost(CHD_k)] + E[Cost(breastcancer_k)] + E[Cost(hipfracture_k)]\}) \quad [11]$$

where AE_k is the average NHS expenditure per person at age k. Lifetime NHS expenditure on illnesses other than CHD, breast cancer and hip fracture, N, is then calculated as follows

$$N = \sum_{k=Y}^{85} \frac{n_k}{(1+r)^{k-Y}} \quad [12]$$

N is calculated initially assuming no therapy, N_{nt}. Effects of drug therapy are then included via their modification of $P(CHD_i)$, $P(breastcancer_i)$ and $P(hipfracture_i)$ which affects lifetime NHS expenditure on illnesses other than CHD, breast cancer and hip fracture in equation [12] via equations [1a]-[1c], [2] and [8a]-[8c]. N is then recalculated using these adjusted values, N_{dt}. Expected increase in NHS expenditure required during the additional years of life arising from therapy, ΔN, are then calculated as follows

$$\Delta N = N_{nt} - N_{dt} \quad [13]$$

Table 1. Assumptions and data sources for compliance with drug therapy and effect of drug therapy on risk of breast cancer, CHD and hip fracture

	HRT	Raloxifene
Breast cancer		
Start delay (years)	5	1
Rise time (years)	0	0
Risk change (%)	0 (2 years therapy) +35 [1] (5,10 years therapy)	-54 [2] (age 55-65) -77 [3] (age 66+)
Stop delay (years)	5	0
Set time (years)	0	0
CHD		
Start delay (years)	0	0
Rise time (years)	1	1
Risk change (%)	-35 [4-7]	-16 [8-9]
Stop delay (years)	0	0
Set time (years)	1	1
Hip fracture		
Start delay (years)	0	0
Rise time (years)	0	0
Risk change (%)	-50 [10]	-37 [11]
Stop delay (years)	0	0
Set time (years)	5	5
Compliance (%) [12]	72	80

Sources

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11. Data on file (Eli Lilly & Co.) and expert opinion. Clinical trial data suggest that raloxifene has 75% of the impact of HRT at the hip.
12. Data on file (Eli Lilly & Co.). Compliance levels based on pill counts from clinical trial data)

Table 2. Assumptions and data sources used in sensitivity analysis

		HRT	Raloxifene
Compliance (%)	best	100	100
	worst	50	50
Breast cancer risk (%)	best	+21	-72 (age 55-65) -90 (age 66+)
	intermediate	+35 (2 years therapy only)	-
	worst	+49	-25 (age 55-65) -51 (age 66+)
CHD risk (%)	best	-50	-20
	worst	-20	-12
Hip fracture risk (%)	best	-60	-45
	worst	-40	-30
HRT drug costs	best	£6	n/a
	worst	£10	n/a
Discount rate (costs, benefits [%])	case 1	0, 0	0, 0
	case 2	6, 1.5	6, 1.5

Table 3. Quality of life weights for specific health states

Age	Myocardial infarction [1]	Angina [2]	Coronary insufficiency [3]	Hip fracture [4]	Breast cancer [5]	No disease, without drug therapy [6-7]	No disease, with drug therapy		
							No increase [8]	+0.02 increase [9]	+0.05 increase [10]
First year									
50-64	0.63	0.80	0.80	0.66	0.51	0.82	0.82	0.84	0.87
65-74	0.59	0.75	0.75	0.62	0.48	0.77	0.77	0.79	0.82
75-84	0.55	0.70	0.70	0.58	0.45	0.72	0.72	0.74	0.77
Second year and following									
50-64	0.71	0.80	0.80	0.74	0.51	0.82	0.82	0.84	0.87
65-74	0.66	0.75	0.75	0.69	0.48	0.77	0.77	0.79	0.82
75-84	0.62	0.70	0.70	0.65	0.45	0.72	0.72	0.74	0.77

Sources

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8. Since no statistically significant differences in QoL were observed between HRT and raloxifene (Data on file [Eli Lilly & Co.]), UK general population values used as baseline are also used unchanged for both interventions.
9. Hypothetical scenario assuming +0.02 increase on quality of life scores with no disease with drug therapy
10. Hypothetical scenario assuming +0.05 increase on quality of life scores with no disease with drug therapy

Table 4. Results of baseline analysis by age at initiation of therapy and duration of therapy

	Age at initiation of therapy 55 years			Age at initiation of therapy 60 years		
	2 years	5 years	10 years	2 years	5 years	10 years
Cost-effectiveness of HRT relative to no therapy						
Life years gained	0.0067	0.0091	0.0233	0.0135	0.0240	0.0521
Incremental cost (£)	205	470	824	205	472	831
Incremental cost per life year gained (£)	30,724	51,428	35,432	15,158	19,635	15,970
Cost-effectiveness of raloxifene relative to no therapy						
Life years gained	0.0083	0.0256	0.0513	0.0127	0.0350	0.0732
Incremental cost (£)	467	1,073	1,876	466	1072	1,877
Incremental cost per life year gained (£)	56,255	41,879	36,586	36,679	30,677	25,647

Table 5. Results of sensitivity analysis: incremental cost per life year gained (£ [% difference from baseline]) relative to no therapy by age at initiation of therapy and duration of therapy

		Age at initiation of therapy 55 years			Age at initiation of therapy 60 years		
		2 years	5 years	10 years	2 years	5 years	10 years
HRT baseline		30,724	51,428	35,432	15,158	19,635	15,970
Compliance	best	22,220 (-28)	39,918 (-22)	26,012 (-27)	10,909 (-28)	14,566 (-26)	11,755 (-26)
	worst	43,683 (+42)	66,205 (+29)	49,243 (+39)	21,715 (+43)	26,903 (+37)	22,168 (+39)
Breast cancer risk	best	46,559 (+52)	37,758 (-27)	28,473 (-20)	18,211 (+20)	17,300 (-12)	14,479 (-9)
	intermediate	71,040 (+131)	-	-	21,046 (+39)	-	-
	worst	150,199 (+389)	80,690 (+57)	46,914 (+32)	24,940 (+65)	22,705 (+16)	17,806 (+11)
CHD risk	best	24,094 (-22)	33,370 (-35)	23,348 (-34)	11,796 (-22)	13,991 (-29)	11,427 (-28)
	worst	42,153 (+37)	110,158 (+114)	72,418 (+104)	21,110 (+39)	32,726 (+67)	26,480 (+66)
Hip fracture risk	best	28,770 (-6)	47,725 (-7)	33,203 (-6)	14,212 (-6)	18,560 (-5)	15,212 (-5)
	worst	32,960 (+7)	55,751 (+8)	37,979 (+7)	16,237 (+7)	20,840 (+6)	16,805 (+5)
HRT drug costs	best	24,141 (-21)	40,377 (-21)	27,837 (-21)	11,911 (-21)	15,431 (-21)	12,577 (-21)
	worst	37,307 (+21)	62,479 (+21)	43,027 (+21)	18,406 (+21)	23,840 (+21)	19,364 (+21)
Discount rate	case 1	17,295 (-44)	32,923 (-36)	21,909 (-38)	9,558 (-37)	13,103 (-33)	10,735 (-33)
	case 2	18,762 (-39)	32,673 (-36)	19,738 (-44)	9,930 (-34)	12,685 (-35)	9,355 (-41)
Increased risk of hip fracture (osteopenic population, RR=2.6)		19,070 (-38)	24,707 (-52)	20,927 (-41)	9,648 (-36)	11,747 (-40)	10,302 (-35)
Raloxifene baseline		56,255	41,879	36,586	36,679	30,677	25,647
Compliance	best	45,284 (-20)	34,182 (-18)	29,500 (-19)	29,472 (-20)	24,963 (-19)	20,774 (-19)
	worst	88,279 (+57)	63,194 (+51)	57,116 (+56)	57,842 (+58)	46,668 (+52)	39,526 (+54)
Breast cancer risk	best	48,408 (-14)	35,317 (-16)	30,855 (-16)	32,998 (-10)	26,869 (-12)	22,930 (-11)
	worst	76,188 (+35)	59,825 (+43)	52,232 (+43)	44,729 (+22)	39,766 (+30)	32,243 (+26)
CHD risk	best	52,849 (-6)	39,616 (-5)	34,214 (-6)	33,694 (-8)	28,359 (-8)	23,661 (-8)
	worst	60,123 (+7)	44,411 (+6)	39,305 (+7)	40,239 (+10)	33,404 (+9)	27,996 (+9)
Hip fracture risk	best	53,654 (-5)	40,871 (-2)	35,619 (-3)	34,527 (-6)	29,633 (-3)	24,870 (-3)
	worst	58,746 (+4)	42,803 (+2)	37,475 (+2)	38,793 (+6)	31,652 (+3)	26,367 (+3)
Discount rate	case 1	31,611 (-44)	24,114 (-42)	21,865 (-40)	22,757 (-38)	19,520 (-36)	16,824 (-34)
	case 2	34,641 (-38)	24,567 (-41)	19,914 (-46)	24,140 (-34)	19,276 (-37)	14,882 (-42)
Increased risk of hip fracture (osteopenic population, RR=2.6)		39,798 (-29)	31,097 (-26)	28,779 (-21)	24,395 (-33)	21,867 (-29)	19,168 (-25)

Table 6. Incremental cost per QALY gained of drug therapy relative to no therapy by age at initiation of therapy and duration of therapy

	Age at initiation of therapy 55 years			Age at initiation of therapy 60 years		
	2 years	5 years	10 years	2 years	5 years	10 years
HRT						
Assuming no increase in quality of life with drug therapy [1]						
QALYs gained	0.0057	0.0076	0.0189	0.0111	0.0194	0.0412
Incremental cost (£)	205	470	824	205	472	831
Incremental cost per QALY gained (£)	36,205	61,629	43,527	18,451	24,336	20,198
Assuming +0.02 increase in quality of life with drug therapy [2]						
QALYs gained	0.0439	0.0948	0.1686	0.0489	0.1053	0.1872
Incremental cost (£)	205	470	824	205	472	831
Incremental cost per QALY gained (£)	4,680	4,962	4,887	4,196	4,485	4,440
Assuming +0.05 increase in quality of life with drug therapy [3]						
QALYs gained	0.1012	0.2256	0.3932	0.1057	0.2341	0.4064
Incremental cost (£)	205	470	824	205	472	831
Incremental cost per QALY gained (£)	2,030	2,086	2,096	1,944	2,017	2,046
Raloxifene						
Assuming no increase in quality of life with drug therapy [1]						
QALYs gained	0.0071	0.0217	0.0430	0.0106	0.0289	0.0546
Incremental cost (£)	467	1,073	1,876	466	1072	1,877
Incremental cost per QALY gained (£)	66,056	49,376	43,618	44,094	37,107	31,502
Assuming +0.02 increase in quality of life with drug therapy [2]						
QALYs gained	0.0453	0.1089	0.1929	0.0484	0.1148	0.2058
Incremental cost (£)	467	1,073	1,876	466	1072	1,877
Incremental cost per QALY gained (£)	10,311	9,850	9,725	9,637	9,343	9,122
Assuming +0.05 increase in quality of life with drug therapy [3]						
QALYs gained	0.1026	0.2398	0.4177	0.1051	0.2436	0.4251
Incremental cost (£)	467	1,073	1,876	466	1072	1,877
Incremental cost per QALY gained (£)	4,551	4,476	4,491	4,437	4,402	4,416

Notes

1. Since no statistically significant differences in QoL were observed between HRT and raloxifene (Data on file [Eli Lilly & Co.]), UK general population values used as baseline are also used unchanged for both interventions.
2. Hypothetical scenario assuming +0.02 increase on quality of life scores with no disease with drug therapy
3. Hypothetical scenario assuming +0.05 increase on quality of life scores with no disease with drug therapy