The Clinical Effectiveness and Cost Effectiveness of Prevention and Treatment of Osteoporosis.

A report from the NICE Decision Support Unit

Authors:
Dr Allan Wailoo, Lecturer, Sheffield Health Economics Group, University of Sheffield.
Dr Chris McCabe, Senior Lecturer, Sheffield Health Economics Group, University of Sheffield.

Accompanying documents:
Appendix 1 - Raloxifene Treatment for Osteoporosis: Comments on Company Submission. Professor Keith Abrams and Dr Alex Sutton.
Report Tables 1-6
Report Figures 1-16

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This work draws on the SHEMO model developed by Stevenson et al.[1] and reported in the Technology Appraisal Report. Dr Stevenson provided advice for the additional modelling described here. Dr Jon Karnon provided advice on the breast cancer modelling and provided expert review. Ms. Fiona Sampson provided access to the latest version of the ScHARR cardiovascular prevention cost effectiveness model.

1. Background to the project

This report is a supplement to the Technology Appraisal Report (TAR) produced by Stevenson et al.[1] SCHARR, University of Sheffield. In the TAR, the cost-effectiveness of alternative treatments for Osteoporosis was estimated by updating the Sheffield Health Economic Model for Osteoporosis[2] (SHEMO). However, one of the drugs under consideration – Raloxifene – was found to be associated with a substantial reduction in breast cancer risk and possible reduction in risk of Cardiovascular Disease (CVD), in addition to the impact on fracture risk. In some populations modelled, the benefits of breast cancer risk reduction accounted for 80% of total QALYs gained. The SHEMO model was developed as a model of osteoporosis and, although the costs and benefits associated with breast cancer and CVD events were included in the analysis the appraisal committee felt there would be value in having a more detailed analysis of the costs and outcomes associated with Raloxifene's effect on breast cancer.

The Decision Support Unit (DSU) was asked to undertake additional analyses around the SHEMO model, with appropriate costs and benefits to reflect the impact of Raloxifene on breast cancer risk and CVD events.

2.1 Risk of breast cancer and Raloxifene

The ScHARR model developed for this appraisal included the reduced relative risk of breast cancer associated with Raloxifene and this same figure has been used in the results presented in this report.

For Raloxifene, the probability of breast cancer is based on the relative risk of 0.38 (0.24 – 0.58) which is taken from the MORE study3. This mean figure, and the uncertainty around it, has also been used to calculate the results presented here following a review of this clinical trial evidence (see Appendix One).

2.2 Risk of CHD events and Raloxifene

The conventional approach to estimating the cost effectiveness of CVD prevention therapies is to characterise the baseline CVD event risk of the target population and then apply the relative risk reduction observed in the trial to estimate the number of events avoided, the life years gained and the quality of life gains associated with treatment[4]. The standard reference for estimating the baseline risk of CVD events is the Framingham Study[5]. The MORE study did not report data on the baseline risk profile of the study groups. Therefore we have used the trial event data reported by Barrett-Connor et al.[6] to estimate the annual risk of CVD events in the untreated population. These data are reported in Table 1.

Annual event rates were calculated on the basis of a constant distribution over the 4 years of MORE study follow-up. Data on the timing of CVD events was not reported.

3. Modelling of Breast Cancer.

In order to calculate the costs and benefits associated with breast cancer, an existing model, the Adjuvant Breast Cancer group (ABC) model, was adapted and updated. Full details of this model are reported in Karnon and Brown[7] (2002). The model was designed to assess the cost effectiveness of Tamoxifen and chemotherapy versus chemotherapy alone. The principal details of this model are described here along with description of updates that have been made in order to adapt the output for use alongside the SHEMO model.

The most substantial changes are those that relate to parameters used for particular chemotherapy regimens. Current NICE guidance[8] recommends the use of anthracycline based chemotherapy regimens for the treatment of early stage breast cancer. The ABC model incorporates values for a mixture of anthracycline and non-anthracycline based regimens and several values have therefore been altered.

Structure of the model

In brief, the updated ABC model operates as illustrated in Figure 1. Women that develop breast cancer that is detected at an early stage receive Tamoxifen in combination with six cycles of anthracycline-based chemotherapy. Patients then enter a disease-free interval (DFI) state from which they either die with no evidence of cancer or they may experience a relapse. A relapse may be of two forms: locoregional

relapse is followed by a period of remission that can be followed either by death without evidence of cancer or a further relapse to metastases states, or metastases can be experienced directly from exiting the DFI. The model describes three metastases states: soft tissue, bone and visceral metastases, which refer to the dominant site of the disease. Each of these metastases states is followed by death.

Breast cancer can be detected at later stages and therefore women may also enter the model directly at any of the relapse states.

Locoregional relapse is associated with short-term treatment costs (radiotherapy and chemotherapy). Therapy received by patients whilst in metastases states is dependent on prognosis on the basis of DFI.

Transitions are made on a monthly basis and the model is run for a maximum of 50 years. This is a probabilistic model and 1000 Monte Carlo simulations were run to estimate costs and outcomes in terms of QALYs.

Principal adaptations to the ABC model

The SHEMO model describes the costs and benefits associated with the use of Raloxifene for 5 years for a cohort of 100 women commencing treatment aged 50, 60, 70 and 80 years. The estimates used here are for two groups of women: those at the threshold for Osteoporosis (assumed to equate to a T-score of –2.5SD[9]) who have suffered a previous fracture (referred to from this point as the "single-risk" group) and average osteoporotic women with double the risk of fracture[10] that have suffered a previous fracture (referred to from this point as the "double risk" group).

The analysis assumes that Raloxifene reduces vertebral fractures only. The reduction in the number of expected breast cancers compared to no treatment with Raloxifene was estimated and the costs and benefits of breast cancer estimated for the age of the patient. It is assumed that women only develop breast cancer once. 1000 simulations using a normal distribution of the logger relative risk of breast cancer for Raloxifene were calculated.

These estimates were paired randomly with the outputs provided from running the original SHEMO model (excluding breast cancer risk). Confidence intervals and cost effectiveness acceptability curves based on the 1000 simulations were then calculated.

Proportion of women with breast cancer starting from late stage breast cancer – the ABC breast cancer model was designed to examine the cost effectiveness of breast cancer treatments for women diagnosed with early stage breast cancer. Data from the Thames Cancer registry[11] were used to calculate the stage distribution of breast cancers by age group. Table 2 shows the raw data. A large proportion of cases are registered as "not known" in this data and these were excluded. Metastases are recorded as a single category and an equal distribution between the three metastases states in the model (soft-tissue, bone and visceral) was therefore assumed.

Costs – The SHEMO model updated costs reported in Kanis et al.[12] to 2001/2 prices using inflation figures found in Netten and Curtis[13]. Where appropriate, prices quoted for the ABC model have also been updated using these data.

Costs of chemotherapy drugs – The ABC model estimated the cost of chemotherapy from ten separate estimates of the cost of a cycle of chemotherapy. Only four of these sources have been included here. Of those estimates where components were individually aggregated "CAF 1 clinic visit", and "CAF, literature-based estimate estimate of health professionals time" were included[14]. The remaining six sources are based on non-anthracycline based chemotherapy regimens and were therefore excluded.

Cost of Tamoxifen - was excluded from the original model since this was common to both comparisons. This has been included here using BNF 2002 prices (£8.71 per month).

Age of onset of breast cancer – The original ABC model simulates patients aged between 50 and 59yrs. Since the output from the SHEMO model identifies the age in years of women developing breast cancer, estimates of the costs and benefits of women that develop breast cancer were made for women aged 50-54, 60-64, 70-74

and 80-84, which corresponds to the starting age of the population cohorts followed for five years.

Toxicity – the toxicity associated with breast cancer treatment (specifically chemotherapy or chemotherapy and Tamoxifen) was incorporated into the ABC model over the first six months of treatment. These data were used to estimate costs and impact on QALYs. These data have not been updated to include only anthracycline based chemotherapy toxicities since this is not a crucial part of the model in its current form.

Timing of relapse – In the original ABC model, five studies were combined to calculate the rate of recurrence for tamoxifen plus chemotherapy. The maximum follow-up presented was 14 years but the rate of recurrence had declined to almost zero by that time. Only one of these studies, Gerard et al.[15], was based on anthracycline based chemotherapy regimens and only data from this study has been used in the updated model used here. Follow-up for this study was 4 years but the annual probability of the remaining cohort leaving the disease free interval had declined to 0.007 by this time, substantially lower than the probabilities observed in the four non-anthracycline based studies, see Table 3. Therefore, women who were disease free after 4 years (as opposed to 14 years in the ABC model) were assumed to be free of cancer and their overall survival was taken as that of the general population from that point onwards.

General population mortality rates were also updated using data from the Government Actuary Department[16].

Assumptions and limitations of breast cancer modelling

- Toxicity data has not been updated
- Literature on anthracycline-based therapies used in the model is limited to just one trial.
- The data sources on which the ABC model is primarily based do not tend to incorporate women over the age of 65 years. The results presented here are based on the assumption that these results can be applied to older age groups.

- The benefit of Raloxifene in reducing breast cancer risk (and CHD events in those models where this is included) is assumed to end once treatment with the drug ends, that is, after 5 years.
- The benefit of Raloxifene in reducing breast cancer risk (and CHD events) is assume to begin immediately on commencement of treatment

4. Modelling cardiovascular benefits of Raloxifene therapy.

The costs and benefits associated with avoided CVD events were estimated using an adapted model based upon that reported by Davey-Smith et al[17]. This is a simple annual life table model which compares the cost-effectiveness of statins and other treatments. The model operates on a yearly basis, where each year women may remain healthy, enter a cardiovascular event state, a cerebrovascular event state, a CVD death state or a non-CVD death state. The CVD and non-CVD death states are terminal states.

For the cardiovascular event and cerebrovascular event states, there are separate quality of life decrements and cost penalties. These states have a fixed duration of one year, after which the woman is assumed to return to full health for the start of the next year. All deaths are assumed to take place in the middle of the year, and therefore deaths contribute 0.5 QALYs in the year that they occur.

The model calculates the number of quality-adjusted life years lived by women treated with Raloxifene compared to those not treated. The analysis is run for five years for a cohort of 100 women. All transition probabilities were equal for each of the five years over which the model was run.

Since the MORE study did not report age specific event rates, the probability of CVD death and CVD events were assumed to be independent of the age cohort. The relative risk of CVD used was

The model incorporated a probability that any of the 100 women in each cohort were at high risk of CVD events, and the QALY gains and cost offsets were weighted by

this probability, to reflect the lack of evidence for Raloxifene having an effect on the cardiovascular event rate in the general osteoporotic population.

As the cost of Raloxifene is included in the SHEMO analysis, no additional cost for Raloxifene therapy was incorporated.

The model produced the difference costs and QALYs between the treated and the untreated cohort during the five years follow-up.

The cost of each cardiovascular event was £2,306 and the cost of a cerebrovascular event was £8,230, based on 2002/3 NHS Reference costs. The quality of life decrement was 0.1 for the cerebrovascular event and 0.05 for the cardiovascular event.

Four cohorts of 100 women, aged 50, 60, 70 and 80 years, were followed through the model for five years.

All cardiovascular events were assumed to be myocardial infarctions. This assumption was expected to favour Raloxifene as unstable angina and coronary ischaemia are less severe events than myocardial infarctions with a lower quality of life (qol) impact and smaller costs. The disaggregated cardiovascular event data were not reported and therefore is was not possible to ascribe separate qol weights and costs to each event. Similarly, all cerebrovascular events were assumed to be strokes, although Transient Ischaemic Attacks (TIAs) were also recorded in the total figure. Again this assumption was expected to favour Raloxifene as the cost and qol effect of TIAs is likely to be substantially less than that for stroke.

Discount rates

Costs have been discounted at 6% per annum and benefits at 1.5% per annum.

5. Results

5.1. Reduction in the incidence of breast cancer

The SHEMO model follows a cohort of 100 patients taking Raloxifene for a period of five years. As in the original TAR report, the incidence of breast cancer in a

population with osteoporosis is based on data from the Office of National Statistics[18] and the Cauley study[19]. These data are reproduced in Table 4.

The relative risk of breast cancer for Raloxifene of 0.38 (95% CI, 0.24 to 0.56) was used to calculate the reduction in the incidence of breast cancer in the model cohort for 1000 simulations. The mean of these simulations is shown below in Figure 2.

4.2 Breast Cancer costs and benefits.

The additional costs and reduction in Quality Adjusted Life Years were calculated for women that develop breast cancer aged 50-54yrs, 60-64yrs, 70-74yrs and 80-84yrs for use in conjunction with the SHEMO model. These figures are shown in Figures 3 and 4. Note that the original TAR incorporated breast cancer costs at £8541 for non-fatal cases and £10,981 for fatal cases.

4.3. Cost effectiveness results

Results are presented by age group for patients aged 50, 60, 70 and 80 years at the start of treatment with Raloxifene. The mean additional cost per additional QALY is presented for the SHEMO model assuming that Raloxifene has no impact on breast cancer risk, for the SHEMO model results combined with breast cancer reduction and for these results combined with CHD event reduction. These analyses are for:

a) An osteoporotic population at the threshold fracture risk but have experienced a previous fracture (single-risk group)

b) An average osteoporotic population that have experienced previous fracture (double-risk group).

These results indicate the costs and QALYs of treatment with Raloxifene compared to a no treatment option (intake of Calcium and Vitamin D assumed adequate). No incremental analyses comparing Raloxifene with other drugs have been undertaken.

4.3.1 “Single risk” group

Table 5 present the marginal costs, marginal QALYs, the cost per QALY and 90% confidence interval.

At the age of 50yrs, the cost-effectiveness of Raloxifene is in excess of £200,000 per QALY gained when breast cancer benefits are not included in the model. The inclusion of these benefits has a substantial impact on the results, lowering the cost effectiveness ratio to £26k (90% CI, £21k to £34k). The inclusion of breast cancer benefits associated with Raloxifene has a negligible impact on costs but a substantial impact on QALYs (89% of total benefits), as shown in Figure 5. When the model also includes the costs and benefits of reduced CHD events, the mean cost per QALY is in the region of £24k. Figure 6 shows the relative contribution each of the three components of benefit make to the total QALY gain.

The cost-effectiveness acceptability curves at age 50 yrs are shown in Figure 7. Including breast cancer benefits causes the cost-effectiveness acceptability curve to rise rapidly from a probability of 0.006 at £20,000 per QALY to 0.85 at £30,000 per QALY. The inclusion of CHD benefits shifts the cost-effectiveness acceptability curve slightly to the left, indicating a greater probability that Raloxifene is cost-effective at each value of a QALY.

At age 60, the mean cost per QALY is similar to that for patients aged 50yrs. The exclusion of breast cancer benefits generates a cost per QALY in excess of £200,000. The inclusion of breast cancer benefits reduces this figure to £34k(90% CI, £28k to £44k) with breast cancer benefits accounting for 83% of the overall benefit. The cost-effectiveness acceptability curve (Figure 8) shows that when breast cancer benefits are included, the probability rises rapidly between £25,000 (0.001) and £40,000 (0.88) per QALY. The inclusion of CHD benefits lowers the mean cost per QALY to £30,000 and the probability that Raloxifene is cost effective at this value is 0.59.

The mean cost per QALY in patients aged 70yrs is lower than at younger ages and this is more substantially driven by non-vertebral fracture reductions. The mean cost per QALY is £75K when breast cancer benefits are excluded and this reduces to £33k when breast cancer benefits are included. Breast cancer benefits account for 53% of the overall QALY gain in this model as shown in Figure 5. The cost-effectiveness acceptability curves shown in Figure 9 indicate that when breast cancer benefits are included in the model, the probability that Raloxifene is cost-effective rises from

0.004 at £25,000 per QALY to over 0.7 at £35,000 per QALY. The inclusion of CHD benefits lowers the cost-effectiveness further to a mean of approximately £29K.

Figure 5 shows that in patients aged 80yrs, breast cancer benefits comprise a relatively small proportion of overall benefit (45%). When breast cancer benefits are excluded the mean cost per QALY is approximately £130k and the inclusion of those benefits lowers this mean to approximately £67k. When the benefits of reducing CHD events are also included in these results, the mean cost per QALY is lowered to £51k. Figure 10 shows the cost-effectiveness acceptability curves. There is only a very low probability that Raloxifene is cost effective in any of the three sets of results at values below £40,000 per QALY gained. Even with the inclusion of CVD benefits, this probability only rises to 0.5 at a value of £50,000 per QALY gained.

4.3.2 "Double-risk" group

The mean cost per QALY and 90% confidence intervals for this population are shown in table 6.

At the age of 50yrs, the mean cost per QALY when benefits of Raloxifene are restricted to those derived from reduced vertebral fractures is in excess of £100k. The inclusion of breast cancer benefits has a substantial effect, lowering the mean to £23k (90% CI, £18k to £29k) and £21k when CVD benefits are also included. Figures 11 and 12 indicate that the greatest component of benefit associated with Raloxifene in these models is breast cancer (77% and 72% respectively). The cost-effectiveness acceptability curves for Raloxifene in the "double-risk" population aged 50yrs are shown in figure 13. At £30,000 per QALY the probability that Raloxifene is cost-effective is over 90% if breast cancer benefits are included but fracture benefits account for only a small part of this figure.

At the age of 60yrs the cost per QALY is similar to those aged 50yrs at £107k when fractures alone are assessed. The inclusion of additional benefits lowers the cost per QALY substantially. When breast cancer benefits are included the mean lowers to £29k per QALY gained and £26k per QALY gained when CVD benefits are also included. Note that in both cases the upper bound of the 90% confidence interval is in

excess of £30k per QALY gained. When breast cancer benefits are included the probability that Raloxifene is cost-effective rises from 0.16 at £25,000 per QALY gained to over 0.9 at values over £35,000 per QALY gained. When CVD benefits are also included then the probability of 0.9 is reached at a value of £30,000 per QALY gained, as shown in figure 14.

Raloxifene generates a lower cost per QALY in those aged 70yrs than in younger women, even in the absence of benefits other than vertebral fractures. The mean cost per QALY is £35k, £21k and £19k in the vertebral fracture model, breast cancer model and CVD models respectively. Figure 15 shows the cost-effectiveness acceptability curve for this age group. At £30,000 per QALY the probability that Raloxifene is cost effective is 0.32, 0.97 and 0.99 in each of the three models. Interestingly, it is the benefit of reduced fracture risk that generate the majority of total benefits in these models (approximately 60%).

Finally, table 6 indicates that in those aged 80yrs, the lowest mean cost per QALY is generated in the version of the model that includes CVD benefits and this is over £32k (90% CI, £25k to £43k). Raloxifene generates a mean cost per QALY that is approximately £40k when only breast cancer and fracture benefits are included in the model. For both scenarios that included the breast cancer benefits, the lower bound of the 90% confidence interval is below £30k. Figure 16 shows the cost-effectiveness acceptability curves for this population. When breast cancer benefits are included the probability that Raloxifene is cost-effective is 0.07, 0.33 and 0.62 at £30k, £35k and £40k respectively. When CVD benefits are also included probabilities for the equivalent thresholds are 0.39, 0.74 and 0.90.

5. Discussion

This analysis supplements and updates the work described in the Technology Appraisal report[20]. Specifically, a model of the costs and benefits of breast cancer treatment has been adapted in order to estimate the cost-effectiveness of Raloxifene. Additionally, cost-effectiveness has been re-estimated to reflect the possible benefits associated with Raloxifene on cardiovascular events.

In comparing Raloxifene with no treatment the following summary points may be made:

- In a population aged 50, Raloxifene appears relatively cost-effective only with the inclusion of breast cancer benefits. This is the case in both the "single" and "double" risk populations.
- Breast cancer benefits account for over 75% of QALYs generated in this population.
- In a population aged 60, breast cancer benefits also account for a substantial proportion of overall benefit in both "single" and "double" risk populations.
- In the "single-risk" population, the mean cost per QALY is approximately £30,000 when CVD benefits are included.
- In a population aged 70, Raloxifene is unlikely to be cost-effective at a threshold of £30,000 per QALY gained if there is no benefit from breast cancer risk reduction.
- The inclusion of breast cancer and CHD benefits lowers the mean cost per QALY to £21k and £19k respectively in the "double-risk" population and £33k and £29k in the "single-risk" population.
- Breast cancer benefits do not comprise such a substantial component of overall benefit in the 70yr and 80yr old age groups.
- In a population-aged 80yrs, none of the scenarios assessed generate a cost per QALY that would usually be considered cost-effective (the lowest mean estimate is £51k) in the "single-risk" populations.
- The inclusion of CHD benefits produces a cost per QALY of £32k in the "double-risk" population.

These results should be considered in conjunction with Appendix 1, which provides an overview of the clinical evidence that underlies this additional modelling of breast cancer and CVD benefits.

Several factors should be recognised as potential limitations to the analysis.

None of the models presented here have included the impact of thromboembolic disease, which is a potentially serious adverse event associated with Raloxifene (see

Appendix 1). The figures presented in Appendix 1 indicate a relative risk of thromboembolic disease at a dose of 60mg Raloxifene of 2.35 [95% CI: 1.20 to 4.62, P=0.01]. Based entirely on the number of cases observed within the trial, in a population of 100 women an additional 0.63 cases would be expected. Given that the marginal QALY gain from reduced fractures alone in the single risk group ranges from 0.6 to 1.8 (depending on age) then this could be an important omission.

The analysis assumes simple additivity of fracture, breast cancer and CVD benefits for Raloxifene. If for example, there is an inverse relationship between the risk of breast cancer and the risk of CVD (as suggested in Appendix 1) then the results presented may be biased, that is, patients would not experience both CVD and breast cancer benefits as the model assumes. The extent to which this potential bias is important varies between patient populations but since, in general, breast cancer benefits are substantially greater than CVD benefits, this may not be an important issue.

Normal treatment forms the comparator in each of the scenarios explored. However, this may not be appropriate in all situations. In those age groups where alternative treatments are considered for use, for example bisphosphonates, these treatments may constitute a meaningful comparison to Raloxifene. An additional estimate that might be realistic is the comparison between bisphosphonates and bisphosphonates plus Raloxifene.

Where favourable cost-effectiveness results are generated predominantly due to the impact of Raloxifene on breast cancer risk, rather than from reductions in fracture risk, it may be the case that other breast cancer specific comparators are relevant e.g. prophylactic Tamoxifen. However, given that the baseline risk of breast cancer for women with osteoporosis is lower than that of the general female population, such comparisons may also then be relevant in the general population.

In considering the evidence for the effectiveness of Raloxifene on the incidence of breast cancer, it is important to note the caveats reported in Appendix 1. The MORE study was designed to assess the effect of Raloxifene on vertebral fractures and therefore, despite the statistical significance of the results in respect of breast cancer,

further follow up is desirable to verify the findings. Whilst the results of the MORE study support the expectation that Raloxifene has an impact on breast cancer, as the trial was designed to examine the impact on fracture rates, the estimate of the magnitude of the breast cancer effect provided by this study must be treated with great caution. Two trials are currently in progress and are expected to report in the next few years.

In the meantime however, it should be noted that the MORE study reports the effectiveness of Raloxifene in an osteoporotic population. Generalising this effectiveness to a sub-population such as those at high risk of cardiovascular disease or breast cancer, would represent a departure from the evidence for effectiveness, and should therefore be treated with great caution.

Finally, the MORE study used a relatively crude risk scoring system in the analysis of CVD benefits. A statistically significant reduction in CVD events was observed in those classified as high-risk but the classification system combines heterogeneous patient groups into this category. Therefore, there is some doubt as to whether high-risk patients could be identified in clinical practice.

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