National Cancer Medicines Advisory Group (NCMAG) Programme

NCMAG114 Raloxifene | Advice Document v1.0 |October 2024

The primary prevention of breast cancer in post-menopausal people at moderate or high risk who are not suitable for on-label alternatives [A]

NCMAG Decision | this off-label, off-patent use is **supported**

This advice acknowledges that widespread implementation will require development of pathways for breast cancer chemoprevention services in NHSScotland.

[A] NCMAG considers proposals submitted by clinicians for use of cancer medicines outwith SMC remit. For more detail on NCMAG remit please see our website.

Decision rationale

After consideration of all the available evidence, NCMAG Council acknowledged the likely high number needed to treat with raloxifene to prevent one breast cancer case and consequently the high uncertainty of its cost-effectiveness. The council considered that for the very small number of people who are not suitable for on-label breast cancer chemopreventive medicines, that off-label raloxifene should be supported as an option.

Governance arrangements

Each NHS board must ensure all internal governance arrangements are completed before medicines are prescribed. The benefits and risks of the use of a medicine should be clearly stated and discussed with the patient to allow informed consent.

Proposal Details	
Proposers	Scottish Cancer Genetics Group
Medicine Name	Raloxifene
Cancer type	Breast Cancer
Proposed off-label and off-patent use[A]	The primary prevention of breast cancer in post-menopausal people at moderate to high risk for whom anastrozole and tamoxifen are not suitable.
Medicine Details	Form: Film-coated tablets

	Dose: 60mg once daily, orally, for five years
Advice eligibility criteria	Eligible individuals must meet ALL the following criteria: • Moderate risk[B] OR high risk[C] of breast cancer • Not suitable for on-label alternatives • Post-menopausal • Have severe osteoporosis • Have a uterus • Do not have a history, or increased risk, of thromboembolic disease

[A] Raloxifene is on label (has marketing authorisation) for the treatment and prevention of osteoporosis in post-menopausal women.

[B] Moderate risk of breast cancer (lifetime risk of greater than 17% but less than 30% or an age range-specific risk between 3% and 8% between the ages of 40 and 50 years)

[C] High risk of breast cancer (lifetime risk of greater than 30% or an age range-specific risk greater than 8% between the ages of 40 and 50 years)

1. Current management context

Breast Cancer incidence, symptoms, prognosis and treatment

Breast Cancer is cancer that begins in the breast; symptoms include new lump, skin changes, nipple changes, and changes in breast size, shape, or feel. It is the most commonly diagnosed cancer in the UK with approximately 5,180 new cases in Scotland in 2021[1, 2]. Broadly, breast cancer is divided into three types: Oestrogen and or Progesterone receptor (ER) positive, Human Epidermal Receptor Positive 2 (HER2), and triple-negative (neither ER nor HER2 positive). Among these, ER positive breast cancer has the best prognosis, while triple-negative has the worst[3]. In Scotland, data are available for estimated 5-year breast cancer specific survival (BCSS) based on deprivation. For ER positive, BCSS is 88% in the least deprived and 81% in the most deprived areas. For HER2 positive, BCSS is 86% in the least deprived and 66% in the most deprived areas. For triple negative, BCSS is 75% in the least deprived and 70% in the most deprived areas[4]. Treatment typically includes surgery, radiotherapy, and systemic therapy, tailored to the patient's fitness, cancer stage, and type. ER-positive breast cancer treatment often involves chemotherapy followed by at least five years of endocrine therapy and, in some cases, targeted therapy. HER2-positive treatment usually includes chemotherapy and either trastuzumab or a pertuzumab, trastuzumab combination, followed by endocrine therapy if ER-positive. Triple-negative treatment usually includes chemotherapy and may also include immunotherapy.

Risk factors for breast cancer and chemoprevention guidelines

Breast cancer is a multifactorial disease, which may involve an interaction between environmental, lifestyle, hormonal and genetic factors. A family history of breast cancer is associated with an increased risk of the disease, which escalates with the number of affected relatives and their age at diagnosis.

National Institute for Health and Care Excellence (NICE) guidelines classify individuals with a family history of breast cancer into 3 groups: those whose risk of developing breast cancer over their lifetime is similar to the general population (less than 17%), those with moderate risk (17 to 29%), or high risk (30% or greater)[5].

Raloxifene is recommended by NICE, the National Comprehensive Cancer Network and the American Society of Clinical Oncology for chemoprevention[5-7]. It is licensed in the USA by the FDA, the Australian Therapeutics Goods Authority and the New Zealand Medicines and Medical Authority for the reduction in risk of invasive breast cancer in post-menopausal women at high risk for invasive breast cancer[8-10].

Chemoprevention is the use of medication to prevent cancer from occurring. Informed decision making is essential as patients must understand the absolute benefit of taking a medicine, with known side effects, to prevent a disease. Raloxifene has been proposed as an option for a subgroup of post-menopausal individuals with severe osteoporosis (where anastrozole is unsuitable), and with an intact uterus (where there are increased risks with tamoxifen use)[5].

Pharmacology of raloxifene

Raloxifene is a Selective Oestrogen Receptor Modulator (SERM) that inhibits the action of oestrogen in the breast, thereby reducing one of the main pathways for breast cancer growth. Unlike tamoxifen, it has an antagonistic effect in the endometrium.

2. Evidence review approach

A literature search to identify clinical and economic evidence was conducted on key electronic databases including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, major international health technology agencies, as well as a focused internet search. The search strategy comprised both Medical Subject Headings and keywords. The main search concepts were raloxifene, moderate- and high-risk and breast cancer prevention. Titles and abstracts were screened by one reviewer with a second opinion sought when required. The included key research study was critically appraised using the Cochrane risk of bias version 2.0 tool[11].

3. Clinical evidence review summary

Evidence overview

Three randomised controlled studies of raloxifene were identified as relevant to this proposal: the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 study, the Multiple Outcomes of Raloxifene Evaluation (MORE) study, and its extension study, the Continuing Outcomes Relevant to Evista (CORE) study[12-14]. The STAR P-2 study compared raloxifene with tamoxifen in post-menopausal people at increased risk of breast cancer. The MORE study population was selected by history of osteoporosis rather than risk of breast cancer. The CORE study treatment duration of 8 years does not align with the proposed treatment duration of 5 years. Therefore, both the MORE and CORE studies are considered as supportive studies for this evidence review.

Clinical Efficacy Evidence

Evidence comparing raloxifene with tamoxifen in study population at risk of breast cancer

The STAR P-2 study was a phase three, double blind, randomised controlled study comparing raloxifene (60mg daily) plus placebo with tamoxifen (20mg daily) plus placebo in post-menopausal people aged ≥35 years at an increased risk of developing breast cancer. People were eligible for participation if they had a five-year predicted breast cancer risk of ≥1.67% based on the Gail breast cancer risk model and were not taking tamoxifen[15, 16]. Patients were randomised using a biased coin minimisation method (to reduce treatment imbalances) with stratification for age, ethnicity, history of lobular carcinoma in situ and 5-year predicted risk of breast cancer to receive raloxifene (n=9,873) or tamoxifen (n=9,872) for five years. The mean age of participants was 58.5 years and approximately half of participants were aged between 50 and 59 years (54%). Approximately 52% of participants had undergone a hysterectomy and over 70% had a first-degree relative with a history of breast cancer. The primary outcome was the occurrence of invasive breast cancer. The secondary outcomes included non-invasive breast cancer, death, quality of life, endometrial

cancer, cardiovascular disease, thromboembolism, osteoporotic fractures and cataracts. This evidence review focuses on the results of the updated analysis of the STAR P-2 longer-term follow-up[16].

Summary of results from the STAR P-2 study

The median follow-up time was 81 months. The mean duration of treatment was 46.8 months for the raloxifene group and 43.5 months for the tamoxifen group. Overall compliance, as measured by tablet counts, was lower in the tamoxifen group with protocol medication drop-out rates reported as 39% compared to 27% in the raloxifene group. Results for the raloxifene group indicated a 24% relative risk increase (absolute risk 0.6%) of developing invasive breast cancer compared with the tamoxifen group (Table 1). Therefore, the study did not meet its primary outcome of demonstrating superiority of raloxifene over tamoxifen in terms of invasive breast cancer.

Table 1 | Results for the STAR P-2 study[16, 17]

Outcome	Events (n[%])		Rate per 1,000 Person-Years		Risk Ratio (95% CI)
	Raloxifene n=9,873	Tamoxifen n=9,872	Raloxifene	Tamoxifen	
Overall breast cancer	447 (4.5%)	358 (3.6%)	Not reported[a]	Not reported[a]	1.25 (1.09 to 1.43)[17]
Invasive breast cancer[b]	310 (3.1%)	247 (2.5%)	5.0	4.0	1.24 (1.05 to 1.47)
Non-invasive cancer[c]	137 (1.4%)	111 (1.1%)	2.2	1.8	1.22 (0.95 to 1.59)
All cause mortality	202 (2.0%)	236 (2.4%)	3.2	3.8	0.84 (0.70 to 1.02)
Breast cancer mortality	4 (0.04%)	11 (0.1%)	Not reported[a]	Not reported[a]	Not reported

a The study did not report person-years of follow-up, therefore, the event rates per 1,000 person years could not be calculated.
b Primary outcome for the study.
c Non-invasive cancer was categorised as ductal carcinoma in situ (DCIS), lobular carcinoma in situ or both.
CI: confidence interval
Notes: Analysis was reported as intention-to-treat. Number included in the primary analysis: raloxifene = 9,754 and tamoxifen = 9,736. RR>1 indicates that the raloxifene group is at increased risk and RR <1 indicates that the raloxifene group is at reduced risk in comparison to tamoxifen.

A post-hoc analysis using a percent retention approach (often used to determine non-inferiority) estimated that raloxifene is about 76% as effective as tamoxifen in reducing invasive breast cancer and 78% as effective as tamoxifen in reducing non-invasive breast cancer[16]. The researchers extrapolated by using data from a study which compared tamoxifen with placebo[18] and estimated that raloxifene reduces the risk of invasive breast cancer by 38% and non-invasive breast cancer by 39% compared to placebo.

Supportive evidence sources | Evidence comparing raloxifene with placebo in study population not selected based on risk of breast cancer

The MORE study was a double-blind, randomised, placebo-controlled study that assessed the use of raloxifene in participants aged 80 years or younger with osteoporosis and at least 2-years post-menopausal. Participants were randomised to receive placebo (n=2,576), raloxifene 60mg/day (n=2,557) (proposed dose for raloxifene) or raloxifene 120mg/day (n=2,572) for four years. The

primary outcomes for the MORE study were the occurrence of vertebral and nonvertebral fractures, and bone mineral density. The incidence of breast cancer was a secondary outcome, therefore the population sample size was not calculated based on expected breast cancer incidence. The study achieved its primary outcome indicating that raloxifene is superior to placebo in reducing the risk of vertebral fractures and increasing bone mineral density in post-menopausal women with osteoporosis.

The CORE study was a double-blind, non-randomised, placebo-controlled study designed to assess the effect of four additional years of raloxifene (overall treatment duration was eight years) on the incidence of invasive breast cancer from participants enrolled in the MORE cohorts. On entry to the CORE study (n=4,011), approximately 54% of patients in each treatment group were considered at high risk for invasive breast cancer defined as a 5-year predicted risk of ≥1.67% based on the Gail breast cancer risk model[14].

Summary of results from the MORE and CORE studies

The median follow-up was 47.4 months in the MORE study. Results for the raloxifene group (data for both doses were combined) indicated a 72% relative risk reduction (1.1% absolute risk reduction [ARR]) of developing invasive breast cancer and a 62% relative risk reduction (1.1% ARR) of developing overall breast cancer compared to the placebo group (Table 2)[13]. The results for the CORE study showed a similar relative risk reduction of invasive breast cancer, and for overall breast cancer[14].

In a subgroup analysis of the CORE data (during the four-year period), raloxifene showed a 67% relative risk reduction in invasive breast cancer incidence for participants with a 5-year predicted risk ≥1.67% and a 33% relative reduction in the group with a 5-year predicted risk of <1.67% compared to placebo (HR 0.33 95% CI [0.16 to 0.67] and HR 0.67 95% CI [0.23 to 1.92], respectively)[19].

Table 2 | Results for the MORE study[14]

Secondary outcome	Events (n[%])		Rate per 1,000 Person-Years		Relative risk (95% CI)
	Raloxifene[a] n=5,129	Placebo n=2,576	Raloxifene	Placebo	
Overall breast cancer	33 (0.6%)	44 (1.7%)	1.9	5.3	0.38 (0.24 to 0.58)
Invasive breast cancer	22 (0.4%)	39 (1.5%)	1.3	4.7	0.28 (0.17 to 0.46)
Non-invasive breast cancer[b]	9 (0.2%)	5 (0.2%)	0.5	0.6	0.90 (0.30 to 2.69)

[a] This includes patients who received raloxifene 60mg/day (proposed dose for raloxifene) or raloxifene 120mg/day.

[b] All non-invasive cases in the MORE study were ductal carcinoma in situ (DCIS). The invasiveness in two participants could not be determined.

CI: confidence intervals

Notes: Analysis was reported as intention-to-treat. RR>1 indicates that the raloxifene group is at increased risk and RR <1 indicates that the raloxifene group is at reduced risk in comparison to placebo. Where the study reported the number of events and person-years of follow-up, the event rates per 1,000 person years were calculated.

Participant-related outcomes

As part of the STAR P-2 study, data were collected on quality of life, depression and sexual functioning using the following instruments - Center for Epidemiological Studies, Medical Outcomes Study Short Form 36 and the Medical Outcomes Study Sexual Functioning Scale, respectively[20]. The questionnaires were administered before treatment and every 6 months for 5 years. There were no significant differences between groups for physical health, mental health and depression.

Safety evidence

Raloxifene has a marketing authorisation for the treatment and prevention of osteoporosis in post-menopausal women. Its safety profile for the on-label use in post-menopausal women is described in the summary of product characteristics[21]. Increased risk of venous thromboembolic events (VTE) and death due to stroke have been noted. Active or past history of VTE are contraindications to raloxifene. Additionally, raloxifene is primarily metabolised by the liver and is contraindicated in people with hepatic insufficiency. In the MORE study there was a higher rate of thromboembolic events reported in the raloxifene 60 mg group compared to the placebo group (1.1% versus 0.5%) but there was no difference in the incidence of endometrial cancer between groups[13].

Based on the updated analysis of the STAR P-2 study, there was a lower incidence of endometrial cancer and thromboembolic events reported in the raloxifene group compared with the tamoxifen group (RR 0.55 [95% CI 0.36 to 0.83] and RR 0.75 [95% CI 0.60 to 0.93]), respectively). Furthermore, there was a lower incidence of cataracts reported in the raloxifene group compared with the tamoxifen group (RR 0.80 [95% CI 0.72 to 0.89])[16]. Based on the initial analysis of the STAR P-2 study (median follow-up of 47 months), there was no evidence of a difference in cardiovascular events and fractures between the treatment groups[15, 16].

Quality assessment

The risk of bias for the STAR P-2 study was considered low. The STAR P-2 study was unblinded at the time of the initial report and participants still receiving tamoxifen were offered raloxifene. Only 9% of participants chose to cross-over so this was unlikely to bias the later results. The risk of attrition bias due to loss to follow-up is unclear (1.3% of the originally randomised population).

Clinical effectiveness considerations

Raloxifene may reduce the risk of breast cancer compared to no breast cancer preventative treatment, however there are some uncertainties

The most robust evidence for raloxifene comes from the STAR-P2 study, which compared raloxifene to tamoxifen. The STAR-P2 study was a superiority study that did not meet its primary endpoint. Extrapolation was used to determine the relative effectiveness of raloxifene at preventing breast cancer compared with a placebo arm of a different study, with tamoxifen as a common arm in both studies. The STAR-P2 study estimated raloxifene to be about 76% as effective as tamoxifen in reducing invasive breast cancer and 78% as effective in reducing non-invasive

breast cancer. Based on the results of STAR-P2 and (NSABP-1, first data cut-off), it was extrapolated that raloxifene reduced the risk of invasive breast cancer in comparison to placebo by approximately 38%, (no measure of variance, such as confidence intervals, reported). This is likely an overestimate of raloxifene's effect as it assumed tamoxifen reduced invasive cancer by 50%, based on an early data cut of the NSABP-1, however, in the more recent IBIS-I study tamoxifen is estimated to reduce the risk of invasive cancer by about 23% in the post-menopausal population[18, 22]. This extrapolation does not account for differences between studies such as baseline patient characteristics, study design, outcome assessment and follow-up times. This introduces uncertainty around this relative effect estimate of raloxifene compared to placebo.

Furthermore, the analyses to calculate retained efficacy and the relative effect of raloxifene compared with placebo do not appear to be pre-specified (protocol details not available).

The median follow-up of STAR P-2 was 81 months, which represents 60 months of treatment and an additional 21 months of follow-up. The difference in cumulative incidences for invasive breast cancer between raloxifene and tamoxifen widens as time from randomisation lengthens; with the effect of raloxifene appearing to decrease over time. The long-term benefit of tamoxifen has been demonstrated in the IBIS-I trial, but there is uncertainty regarding the long-term benefit of raloxifene in preventing invasive breast cancer when compared to no treatment.

There is less robust evidence from the placebo-controlled MORE and CORE studies, which may provide reassurance on the activity of raloxifene in preventing breast cancer.

The MORE study estimated that the number needed to treat with raloxifene for 4 years to prevent one case of invasive breast cancer was 93 people. This may be an underestimate of absolute benefit as only 12% of MORE study participants had a first degree relative with breast cancer. The MORE and CORE studies were not designed to demonstrate the effect of raloxifene on the incidence of invasive breast cancer; this was a secondary outcome in both studies. The CORE population was a subgroup of MORE study participants, who were not re-randomised, so results should be interpreted with some caution. There was a median treatment gap of 11 months between studies during which participants could have taken raloxifene, tamoxifen other SERMs, or no treatment.

Raloxifene has not been shown to reduce all-cause or breast cancer death

All-cause or breast cancer specific mortality were not primary outcomes in the studies, which were not designed to detect a mortality difference between raloxifene and the control groups. In the STAR-P2 trial, deaths were 2.0% (202/9873) in the raloxifene arm and 2.4% (236/9874) in the tamoxifen arm. More mature data may help understand the impact of raloxifene on breast cancer and all-cause mortality. The CORE study, which compared eight years of raloxifene to placebo, did not find a difference in all-cause mortality.

The benefits of raloxifene are primarily due to a reduction in development of oestrogen receptor-positive breast cancer, which has high survival rates.

The evidence may be generalisable to the Scottish population. However, there are some differences regarding patient populations, methods of risk assessment, and breast cancer screening between the studies and practice in Scotland.

There are differences in the criteria and methods for assessing people at increased risk of breast cancer in the STAR-P2 study, compared with the criteria in this proposal, which are based on NICE criteria. These differences in eligibility criteria, as well as the accuracy of risk assessment calculators, may reduce the generalisability of the results[23].

Breast cancer screening has evolved since the time of recruitment for the STAR-P2 trial, which used annual mammography. Current practice is for annual screening for high-risk individuals aged between 40 and 65 years. For moderate-risk individuals aged between 40- and 50-years annual screening is offered followed by three yearly screening from 50 years. These differences may reduce the generalisability of the results.

The patient demographics may be generalisable to the Scottish population with 93% of participants being white, however all were recruited from North America. The STAR-P2 eligibility criteria were not specific for patients who are unsuitable for anastrozole, while the MORE study included osteoporotic people, aligning with the proposed use of raloxifene in those for whom anastrozole is unsuitable.

In the MORE study raloxifene was administered for 4 years instead of five and comprised of two raloxifene treatment groups, one of which received a daily dose of 120mg which does not align with the proposed 60mg. In the MORE study 12% of participants had a first degree relative with breast cancer, which further reduces the generalisability of findings to the proposed population.

Adverse effects

Across the STAR-P2 and MORE studies approximately 13,000 post-menopausal people at increased risk of breast cancer were exposed to raloxifene, providing reassurance that the safety profile in this population has been well studied.

In the MORE study, raloxifene at 60mg per day increased the risk of thromboembolic events compared to placebo. In the STAR-P2 trial, there was a decrease in the relative risk of thromboembolic events in people receiving raloxifene compared to those receiving tamoxifen.

The results from the MORE and CORE studies did not show any increase in risk of endometrial cancer with raloxifene compared to placebo. Compared to tamoxifen, raloxifene decreased the risk of endometrial cancer.

Rates of gynaecological and vasomotor symptoms were higher compared to placebo in the MORE trial. Overall, there were no unexpected side effects from raloxifene in the STAR-P2 trial compared to its on-label indications.

4. Patient group summary

We received a patient group statement from Breast Cancer Now. A representative from Breast Cancer Now was present at the NCMAG council meeting. Breast Cancer Now is a registered charity and received 0.9% pharmaceutical company funding in the past two years. The key points from the submission are summarised below:

- People experience many emotions when dealing with the complexities around risk management. Living with the knowledge that you are at an increased risk of developing breast cancer will affect everyone differently, while some might not worry or think about the prospect, others have increased worry and anxiety at the possibility.
- Breast Cancer Now highlight that additional options will give individuals more choice, it may reduce anxiety in people as they would be taking a more active role in their risk reduction.
- Many complex factors affect individual choice when considering chemopreventive medicine including side effects, how taking a tablet every day for 5 years will fit into their lifestyle, the effectiveness at risk reduction and how each medicine compares to each other.
- Living with the knowledge of an increased risk of breast cancer is an individual experience, it is important that people are provided with information relating to all available options and potential risks so that they can make an informed choice that is right for them.

5. Benefit-risk balance

This is an off-label use of raloxifene for a specific group of individuals in whom on-label alternatives are not suitable. Raloxifene may reduce the risk of invasive, non-invasive and overall breast cancer but there is uncertainty on the relative treatment effect, mortality and long-term benefit of treatment. Compared to placebo, raloxifene increases the risk of thromboembolic events and less serious side effects like vasomotor and gynaecological symptoms.

6. Council review |Clinical benefit-risk balance evaluation

After consideration of all the available evidence regarding the clinical benefits and risks, the Council recognised the uncertainties in the data and acknowledged the likely high number needed to treat with raloxifene to prevent one breast cancer case. Despite these uncertainties, it was agreed that there is a small subgroup of post-menopausal people for whom it is important to have raloxifene available as an option. Council was satisfied that a case had been made for the clinical effectiveness of raloxifene in the sub-population of post-menopausal people who have severe osteoporosis and for whom both on-label alternatives of anastrozole and tamoxifen are not suitable.

7. Economic evidence review summary

Economic Overview

In accordance with the proposal, the economic review covers the use of raloxifene for the primary prevention of breast cancer in post-menopausal people over the age of 25 years who are at moderate or high risk. A literature review of economic evaluations on this topic screened 184 studies (details of search methodology in Section 2), of which two evaluated the cost-effectiveness of chemoprevention with raloxifene in the relevant setting. The economic evaluation presented in CG164 National Institute for Health and Care Excellence (NICE) guidance (2017 update) was preferred due to its applicability to the proposal. The NICE Centre for Guidelines shared the original models related to chemoprevention under academic confidentiality. The analysis investigated the costs and consequences of raloxifene compared to no chemoprevention[5].

Type of economic evaluation

A cost-consequences analysis (CCA) was adapted based on models provided by NICE and was deemed appropriate for comparing chemoprevention strategies in post-menopausal people. This revised model was used for the analysis. A lifetime time horizon was employed to calculate all costs and health outcomes related to the treatment. A discount rate of 3.5% per annum was applied to all costs incurred after the first year. The results are summarised as incremental cost per breast cancer case prevented. However, as the CCA analysis does not incorporate quality-adjusted life-year (QALY) gains, so for illustrative purposes, an estimate of the minimum QALY gain required per prevented breast cancer case for raloxifene to be considered cost-effective at a willingness-to-pay range of £20,000 to £30,000 per QALY is provided. Incremental adverse events and other consequences are also discussed.

Model Overview

The original model by NICE comprised of post-menopausal individuals separated into two separate models based on high risk and moderate risk of developing breast cancer[5]. Therefore, the model was adapted to incorporate costs and effects relevant to the proposed use in NHSScotland. Several changes were made to the model, which will be discussed sequentially.

The baseline age distribution of the cohort followed the proportion of participants in the IBIS-I study[22]. Therefore, the hypothetical cohort of 1,000 individuals were distributed into high and moderate risk profiles for their respective age groups. In addition, the weighted risk estimates were used to combine high and moderate risk original models into a combined model. The risk distribution was assumed to be 6.5% for high-risk population and 93.5% for moderate-risk population, based on expert opinion of clinicians in Scotland. This approach aligns with clinical data. The estimate of relative risk was sourced from STAR P-2 study, which found that tamoxifen is associated with a lower incidence of invasive breast cancer compared to raloxifene [RR (95%CI): 0.81 (0.66 to 0.99)][16, 17]. To estimate raloxifene's efficacy relative to placebo, we performed an in-house indirect comparison using the efficacy of tamoxifen relative to placebo from the IBIS-I trial

(second data cut). This resulted in a 5% estimated risk reduction of invasive breast cancer with raloxifene compared to placebo (RR: 0.95).

Annual cost of treatment with raloxifene (60mg/day) was derived from Scottish drug tariff [accessed 29 Jan 2024]. Revisions were made to include updated costs of breast cancer treatment to account for changes in the treatment landscape since 2017, building upon the costs presented in CG164 NICE guidance as a baseline[5]. Specifically, the costs of certain targeted therapies used in the treatment of early breast cancer (such as abemaciclib, trastuzumab, pertuzumab, trastuzumab emtansine, and pembrolizumab) were calculated using proportions derived from clinical expert opinion and NHSScotland confidential national contract prices for medicines. Currently, these medications are integrated into treatment pathways within NHSScotland. Where necessary, costs were adjusted to current prices using the health category Consumer Price Index (CPI) Index rates from the Office for National Statistics (accessed Jan 2024). Finally, age-specific mortality data for females were sourced from Office for National Statistics National Life Tables for Scotland 2020-22 (accessed Mar 2024).

Population, intervention, comparator, outcomes

As summarised above, the revised model considered moderate and high risk post-menopausal people with no personal history of breast cancer, who have no history or increased risk of thromboembolic disease or endometrial cancer, and who are eligible for chemoprevention with raloxifene. The post-menopausal group comprised people aged 50 years and above. This approach may not fully capture the complexity of menopause onset, which is influenced by multiple interlinked factors beyond age. The intervention was 60mg of raloxifene administered once daily over a five-year period, with no chemoprevention as the comparator. In line with assumption of the original model, 50% of people discontinued raloxifene after one year of treatment, with the remaining 50% continuing treatment for the full 5 years[5]. The primary outcome of the analysis was the cost per breast cancer prevented. Additionally, the minimum QALY gain required per prevented breast cancer case is provided for illustrative purposes.

Cost inputs

The costs of breast cancer treatment, costs of monitoring and managing adverse events resulting from chemoprevention with raloxifene are detailed in Tables 3 to 5. The model assumed that all people receiving chemoprevention would need two GP consultations per year while treatment was ongoing (Table 4).

Table 3 |Cost components of breast cancer treatment

Category	Surgery	Radiotherapy	Chemotherapy and targeted therapy[a]	Other drugs[b]	Total costs
Estimated cost	£ 3,506	£ 2,325	£ 16,198	£ 3,115	**£ 25,144**

[a] These include costs associated with chemotherapy drugs, chemotherapy delivery (8 cycles) and targeted therapy medicines (used in early breast cancer only) and was based on expert opinion and confidential medicine costs. Costs related to targeted therapy administration, follow-up appointments, and toxicity management are not included.

[b] These include - pegfilgrastim, dexamethasone, ondansetron, metoclopramide and weighted average of five endocrine therapies.

Table 4 | Monitoring costs from chemoprevention with raloxifene

Category	Cost per person per year on raloxifene
GP Visit	£ 94

GP = General Practitioner

Table 5 | Costs associated with potential adverse events of raloxifene

Adverse event		Unit costs	Source
Endometrial cancer		£ 5,815	CG164 NICE guidance (Uplifted)
Thromboembolic events[a]		£ 2,137	NHS National Cost Collection Tariff 2021/22 (Uplifted)
Fractures	Hip fracture (3.2%)	£ 21,275	CG164 NICE guidance (Uplifted)
	Wrist fracture (22.1%)	£ 830	
	Vertebral fracture (2.1%)	£ 849	
	Other fractures (72.6%)	£ 2,372	

[a] Assumed as costs for deep vein thrombosis (DVT).
Refer to Table 6 for incremental adverse events compared to no chemoprevention.

Key result

In the base case, raloxifene incurs an additional cost of £349,939 per 1,000 high and moderate risk post-menopausal individuals, compared to no chemoprevention. This additional cost is driven primarily by costs of chemoprevention and monitoring consultations with GPs. However, it is partially offset by a reduction in the cost of breast cancer treatment. The total cost to prevent a single case of breast cancer in this group was determined to be £141,427. To be cost-effective, chemoprevention with raloxifene in this group requires a minimum gain of 4.7 QALYs and 7.1 QALYs per breast cancer case prevented, for £30,000 and £20,000 per QALY willingness-to-pay threshold, respectively.

Table 6 | Base case result for 1,000 post-menopausal people who received raloxifene followed over a lifetime horizon

Cost consequences results (Raloxifene versus no chemoprevention)		
Incremental cost per 1,000 people		£349,939
Breast cancer cases prevented		3
Incremental thromboembolic events per 1,000 people		1
Incremental endometrial cancer cases per 1,000 people		0
Incremental fractures per 1,000 people		-7
Minimum QALY gain required per breast cancer case prevented to be cost-effective for respective ICER threshold[a]	£20,000 per QALY	7.1
	£30,000 per QALY	4.7
Cost per breast cancer case prevented		**£141,427**

[a] Minimum QALY gain provided for illustrative purposes. An incremental gain of 1.33 QALYs per breast cancer case prevented was estimated by comparing the utility of a 50-year-old individual with breast

cancer to that of an individual without breast cancer over a five-year period[24]. The calculated minimum QALY gain can be compared to this estimate to assess the likelihood of being cost-effective.

Key uncertainties

One-way sensitivity analysis (OWSA) revealed that the model is particularly sensitive to variations in the cost of breast cancer treatment and the effectiveness of chemoprevention. The cost of breast cancer treatment was adjusted by ±40%, considering a conservative cost estimate used in the base case. The base case relative risk of tamoxifen to raloxifene from STAR P-2 study was altered by ±5% to illustrate that the model is highly sensitive to the clinical efficacy estimate. For ease of interpretation, the sensitivity analysis results presented in Table 8 and 9 represent relative risk of raloxifene to placebo derived from indirect comparison with relative risk of breast cancer for tamoxifen to placebo from IBIS-I in post-menopausal population (RR: 0.77). This differs from the risk reduction derived from indirect comparison conducted in the STAR P-2 post-hoc analysis (Section 3), which are based on indirect comparison to relative risk of tamoxifen to placebo from the study by Fisher et al. (1998) (RR: 0.50).

Table 7 | OWSA for cost per breast cancer case prevented by change in cost of breast cancer treatment

	Total cost of breast cancer treatment	Cost per breast cancer case prevented (% change)
Sensitivity analysis 1	£15,000	£148,265 (+5%)
Base case	£25,144	£141,427
Sensitivity analysis 2	£35,000	£134,782 (-5%)

OWSA = one way sensitivity analysis

Table 8 | OWSA for cost per breast cancer case prevented by change in relative risk reduction of raloxifene (compared to no chemoprevention)

	Relative risk reduction (raloxifene compared to no chemoprevention)[a]	Cost per breast cancer case prevented (% change)
Sensitivity analysis 3	9.3%	£66,948 (-53%)
Base case	4.5%	£141,427
Sensitivity analysis 4	-0.3%	N/A[b]

OWSA = One-way sensitivity analysis

[a] Relative risk reduction of raloxifene to placebo is presented here using indirect comparison of relative risk of tamoxifen to raloxifene from STAR P-2 (RR: 0.81) and tamoxifen to placebo from IBIS-I trial in post-menopausal population (RR: 0.77).

[b] N/A – not applicable. The result is not meaningful due to no reduction in risk with raloxifene (i.e. RR<0).

Table 9 | OWSA for minimum QALY gain required per breast cancer case by change in relative risk reduction of raloxifene (compared to no chemoprevention)

	Relative risk reduction (raloxifene compared to no chemoprevention)[a]	Minimum QALY gain required per breast cancer case prevented to be cost-effective for respective ICER threshold[c] (% change)
For £20,000 per QALY		
Sensitivity analysis 5	9.3%	3.35 (-53%)
Base case	4.5%	7.07
Sensitivity analysis 6	-0.3%	N/A[b]
For £30,000 per QALY		
Sensitivity analysis 7	9.3%	2.23 (-53%)
Base case	4.5%	4.71
Sensitivity analysis 8	-0.3%	N/A[b]

[a] Relative risk reduction of raloxifene to placebo is presented here using indirect comparison of relative risk of tamoxifen to raloxifene from STAR P-2 (RR: 0.81) and tamoxifen to placebo from IBIS-I trial in post-menopausal population (RR: 0.77).
[b] N/A – not applicable. The result is not meaningful due to no reduction in risk with raloxifene (i.e. RR<0).
[c] Minimum QALY gain provided for illustrative purposes. An incremental gain of 1.33 QALYs per breast cancer case prevented was estimated by comparing the utility of a 50-year-old individual with breast cancer to that of an individual without breast cancer over a five-year period[24]. The calculated minimum QALY gain can be compared to this estimate to assess the likelihood of being cost-effective.

Cost-effectiveness considerations

Generalisability

NHSScotland prices were used when available to ensure results of greater relevance. For other costs, inflation adjustments using CPI Index rates specific to health category were used (accessed Jan 2024). Further adaptations to the model (outlined in Model overview sub-section) improved the external validity to NHSScotland. The actual annual discontinuation rate of chemoprevention with raloxifene is unknown; therefore, the analysis relied on expert estimates[5]. The pathways for individuals receiving breast cancer chemoprevention in NHSScotland have not yet been established. The revised model, which aligns with the original NICE model, assumes that individuals on chemoprevention will have two GP monitoring visits per year. However, it remains unclear whether this is how chemoprevention monitoring will be implemented in NHSScotland. A scenario analysis was performed by excluding GP monitoring costs, resulting in £36,660 cost per breast cancer case prevented, which represents a 74% reduction compared to base case. The overall analysis was deemed applicable with minor constraints.

Limitations of cost consequence analysis

The key limitation of a CCA is that it does not integrate costs and outcomes into a cost-per-QALY result. It provides a disaggregated summary of costs and outcomes. Consequently, decision-makers

must assess cost-effectiveness while considering treatment costs and outcomes separately. The cost per breast cancer prevented can be evaluated against a willingness-to-pay threshold. For illustrative purposes, we present an estimate of the minimum QALY gain required per prevented breast cancer case for raloxifene to be considered cost-effective within a willingness-to-pay range of £20,000 to £30,000 per QALY. In a separate analysis presented within the CG164, NICE estimated an incremental gain of 1.33 QALYs per breast cancer case prevented by modelling the utility of a 50-year-old individual with breast cancer to that of an individual without breast cancer over a five-year period[5]. The calculated minimum QALY gain can be compared to this estimate to assess the likelihood of being cost-effective. However, it is crucial to exercise caution when using this estimate due to its inherent limitations. Specifically, it was derived using mortality and utility estimates from studies conducted before 2010 and was only estimated over a five-year period.

In addition, the clinical efficacy of raloxifene in preventing breast cancer is grounded in evidence from the STAR P-2 study, which compares raloxifene to tamoxifen. This comparison necessitated an assumption that the impact of tamoxifen in the IBIS-I trial is similar to its impact in the STAR P-2 trial. This assumption may not necessarily be valid due to differences in study design, population, and other factors. Therefore, there is uncertainty regarding its actual relative efficacy when compared to a placebo (no chemoprevention). In addition, despite the STAR P-2 study having a median follow-up period of 81 months, the actual duration over which treatment effects persist remains uncertain. The model assumes that the benefits of chemoprevention last throughout an individual's lifetime. Furthermore, the model assumes uniform reduction in breast cancer risk across all cancer types, regardless of oestrogen receptor status. Some studies suggest potential differences, which the model does not account for. However, an estimated cost of early breast cancer treatment based on clinician opinion and weighted average methodology was used in the revised model, which considers receptor status and corresponding targeted therapy.

The model does not consider mortality rates following breast cancer or adverse events. This means that people with and without breast cancer, as well as those with treatment related adverse events, have equal mortality rates. This could potentially result in a slight overestimation of the number of adverse events in the treatment group.

Finally, it is important to note that breast cancer treatment costs can vary based on the stage of cancer. However, this analysis does not account for the costs associated with managing metastatic disease. Moreover, costs related to targeted therapy administration, follow-up appointments, and toxicity management are not included. As a result, we have used a conservative estimate for total cost of breast cancer treatment. It is important to note that this might lead to an underestimation of cost per breast cancer case prevented of raloxifene compared to no chemoprevention strategy, as indicated in the sensitivity analysis (Table 7).

Summary

In summary, the revised analysis, with changes to increase the relevance for NHS Scotland, was considered relevant for decision-making purposes.

8. Council review | Cost-effectiveness evaluation

After considering all the available evidence, the Council acknowledged that the case for cost effectiveness is very uncertain. The key uncertainties are the likely high number needed to treat to prevent a breast cancer case, the role and cost of GP monitoring of patients while on raloxifene and capturing the full cost of treating breast cancer.

9. Council review | Overall proposal evaluation

After consideration of all relevant information: clinical, economic, uncaptured benefits and non-health factors, Council made the decision to support this use in post-menopausal people for whom on-label alternatives anastrozole and tamoxifen are not suitable, as detailed in the advice eligibility criteria.

10. Service impact

There are currently no national pathways for the routine prescribing of breast cancer chemopreventive medicines. Implementation of the routine use of chemopreventive medicines will require development of these and it is likely to result in initial service challenges, with uncertainties surrounding the treatment pathway and medicine uptake. This challenge has been recognised and relevant stakeholders are considering approaches to the development of these pathways. A systematic review estimated that the uptake of breast cancer chemoprevention is 16%, based on published trials[25]. However, clinical experts estimate that the real-world uptake could be as low as 1.5%. Furthermore, raloxifene is expected to be a low percentage of the total prescribing of chemopreventive medicines.

11. Budget impact

The change in management would increase the net medicines budget impact of management for this group. The Scottish drug tariff price of raloxifene 60 mg (28 tablets) is £4.03, with a daily dose of 60 mg, and assumed 5 years of treatment with 100% adherence. The cost per person in year 1 is expected to be £52, with a national net medicines budget impact of approximately £1,467 (based on an estimated uptake of 28 in the post-menopausal population). The cost per person in year 2 is expected to be £52, with a national net medicines budget impact of approximately £1,519 (based on an estimated uptake of 29 in the post-menopausal population). These estimates are based on the Scottish drug tariff price (accessed Jan 2024) and annual uptake of 5%.

Separate information will be supplied to the boards to facilitate budget impact assessment.

12. Acknowledgements

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This advice represents the view of the NCMAG Council and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

Minor document amendments

Date	Previous version	Amendment	Updated version	Approved by