Health Technology Assessment 2007; Vol. 11: No. 26

Hormonal therapies for early breast cancer: systematic review and economic evaluation

D Hind, S Ward, E De Nigris, E Simpson,
C Carroll and L Wyld

July 2007

Health Technology Assessment
NHS R&D HTA Programme
www.hta.ac.uk

How to obtain copies of this and other HTA Programme reports.
An electronic version of this publication, in Adobe Acrobat format, is available for downloading free of charge for personal use from the HTA website (http://www.hta.ac.uk). A fully searchable CD-ROM is also available (see below).

Printed copies of HTA monographs cost £20 each (post and packing free in the UK) to both public **and** private sector purchasers from our Despatch Agents.

Non-UK purchasers will have to pay a small fee for post and packing. For European countries the cost is £2 per monograph and for the rest of the world £3 per monograph.

You can order HTA monographs from our Despatch Agents:

– fax (with **credit card** or **official purchase order**)
– post (with **credit card** or **official purchase order** or **cheque**)
– phone during office hours (**credit card** only).

Additionally the HTA website allows you **either** to pay securely by credit card **or** to print out your order and then post or fax it.

Contact details are as follows:

HTA Despatch
c/o Direct Mail Works Ltd
4 Oakwood Business Centre
Downley, HAVANT PO9 2NP, UK

Email: orders@hta.ac.uk
Tel: 02392 492 000
Fax: 02392 478 555
Fax from outside the UK: +44 2392 478 555

NHS libraries can subscribe free of charge. Public libraries can subscribe at a very reduced cost of £100 for each volume (normally comprising 30–40 titles). The commercial subscription rate is £300 per volume. Please see our website for details. Subscriptions can only be purchased for the current or forthcoming volume.

Payment methods

Paying by cheque
If you pay by cheque, the cheque must be in **pounds sterling**, made payable to *Direct Mail Works Ltd* and drawn on a bank with a UK address.

Paying by credit card
The following cards are accepted by phone, fax, post or via the website ordering pages: Delta, Eurocard, Mastercard, Solo, Switch and Visa. We advise against sending credit card details in a plain email.

Paying by official purchase order
You can post or fax these, but they must be from public bodies (i.e. NHS or universities) within the UK. We cannot at present accept purchase orders from commercial companies or from outside the UK.

How do I get a copy of *HTA on CD*?

Please use the form on the HTA website (www.hta.ac.uk/htacd.htm). Or contact Direct Mail Works (see contact details above) by email, post, fax or phone. *HTA on CD* is currently free of charge worldwide.

The website also provides information about the HTA Programme and lists the membership of the various committees.

Hormonal therapies for early breast cancer: systematic review and economic evaluation

D Hind,[1*] S Ward,[1] E De Nigris,[1] E Simpson,[1] C Carroll[1] and L Wyld[2]

[1] The School of Health and Related Research (ScHARR), University of Sheffield, UK

[2] Surgical Oncology, University of Sheffield, UK

* Corresponding author

Declared competing interests of authors: none

Published July 2007

This report should be referenced as follows:

Hind D, Ward S, De Nigris E, Simpson E, Carroll C, Wyld L. Hormonal therapies for early breast cancer: systematic review and economic evaluation. *Health Technol Assess* 2007;**11**(26).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE and *Science Citation Index Expanded (SciSearch®)* and *Current Contents®*/Clinical Medicine.

NIHR Health Technology Assessment Programme

The Health Technology Assessment (HTA) Programme, now part of the National Institute for Health Research (NIHR), was set up in 1993. It produces high-quality research information on the costs, effectiveness and broader impact of health technologies for those who use, manage and provide care in the NHS. 'Health technologies' are broadly defined to include all interventions used to promote health, prevent and treat disease, and improve rehabilitation and long-term care, rather than settings of care.

The research findings from the HTA Programme directly influence decision-making bodies such as the National Institute for Health and Clinical Excellence (NICE) and the National Screening Committee (NSC). HTA findings also help to improve the quality of clinical practice in the NHS indirectly in that they form a key component of the 'National Knowledge Service'.

The HTA Programme is needs-led in that it fills gaps in the evidence needed by the NHS. There are three routes to the start of projects.

First is the commissioned route. Suggestions for research are actively sought from people working in the NHS, the public and consumer groups and professional bodies such as royal colleges and NHS trusts. These suggestions are carefully prioritised by panels of independent experts (including NHS service users). The HTA Programme then commissions the research by competitive tender.

Secondly, the HTA Programme provides grants for clinical trials for researchers who identify research questions. These are assessed for importance to patients and the NHS, and scientific rigour.

Thirdly, through its Technology Assessment Report (TAR) call-off contract, the HTA Programme commissions bespoke reports, principally for NICE, but also for other policy-makers. TARs bring together evidence on the value of specific technologies.

Some HTA research projects, including TARs, may take only months, others need several years. They can cost from as little as £40,000 to over £1 million, and may involve synthesising existing evidence, undertaking a trial, or other research collecting new data to answer a research problem.

The final reports from HTA projects are peer-reviewed by a number of independent expert referees before publication in the widely read monograph series *Health Technology Assessment*.

Criteria for inclusion in the HTA monograph series

Reports are published in the HTA monograph series if (1) they have resulted from work for the HTA Programme, and (2) they are of a sufficiently high scientific quality as assessed by the referees and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search, appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

The research reported in this monograph was commissioned and funded by the HTA Programme on behalf of NICE as project number 03/20/01. The protocol was agreed in June 2005. The assessment report began editorial review in July 2006 and was accepted for publication in October 2006. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

The views expressed in this publication are those of the authors and not necessarily those of the HTA Programme or the Department of Health.

ISSN 1366-5278

Published by Gray Publishing, Tunbridge Wells, Kent, on behalf of NCCHTA.
Printed on acid-free paper in the UK by St Edmundsbury Press Ltd, Bury St Edmunds, Suffolk.

T

Abstract

Hormonal therapies for early breast cancer: systematic review and economic evaluation

D Hind,[1*] S Ward,[1] E De Nigris,[1] E Simpson,[1] C Carroll[1] and L Wyld[2]

[1] The School of Health and Related Research (ScHARR), University of Sheffield, UK

[2] Surgical Oncology, University of Sheffield, UK

* Corresponding author

Objectives: To establish the clinical and cost-effectiveness of aromatase inhibitors (AIs) anastrozole, letrozole and exemestane compared with tamoxifen in the adjuvant treatment of early oestrogen receptor-positive breast cancer in postmenopausal women.

Data sources: Major electronic databases and three trials registers were searched from May to June 2005. Three conference abstract databases were searched in December 2005. Industry submissions.

Review methods: Studies evaluating the clinical effectiveness of AIs against 5 years' tamoxifen treatment were included and critically appraised. The review of the health economics of AIs in early breast cancer in comparison with standard therapies included a review of existing economic evaluations of the relevant therapies, a critique of each of the economic evaluations submitted to the National Institute for Health and Clinical Excellence (NICE) by pharmaceutical manufacturers and a detailed explanation of the methodologies and results of the authors' economic model. The three treatment strategies (primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy) were considered separately within the authors' economic analysis.

Results: A meta-analysis of three trials found a significant difference in overall survival when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Significant improvements in overall survival are yet to be demonstrated in other strategies. Compared with 5 years' tamoxifen, disease-free survival (disease recurrence or death from any cause) was significantly improved in the primary adjuvant setting with anastrozole and letrozole, and with an exemestane switching strategy. Other trials did not report this outcome. Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole and letrozole, anastrozole switching, extended adjuvant anastrozole or letrozole. The AIs and tamoxifen have different side-effect profiles, with tamoxifen responsible for small but statistically significant increases in endometrial cancer and, sometimes, thromboembolic events and stroke. AIs show a trend towards increases in osteoporosis, the statistical significance of which increases with follow-up time. The absence of tamoxifen treatment also increases the risk of hypercholesterolaemia and cardiac events in postmenopausal women. There was no significant difference in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies. The cost-effectiveness results for AIs compared with tamoxifen in the primary adjuvant setting, are estimated to be between £21,000 and £32,000 per quality-adjusted life-year (QALY) based on an analysis over 35 years. There is currently no trial evidence for exemestane in this setting. The cost-effectiveness results for anastrozole and exemestane, compared with tamoxifen in the unplanned switching setting, are estimated to be £23,200 and £19,200 per QALY, respectively, based on an analysis over 35 years. There is currently no trial evidence for letrozole in this setting. In the extended adjuvant setting, the cost per QALY for letrozole compared with placebo is estimated to be £9800, based on an analysis over 35 years. All these results are considered to be conservative. In the base case it is assumed that the benefits of AIs over tamoxifen or placebo seen during the therapy period are gradually lost during the following 10 years. An alternative scenario, the 'benefits maintained' scenario, is tested in sensitivity analysis. Here it is assumed that following the treatment period the annual rate of recurrence in both arms is the same. This reduces the cost-effectiveness ratio by over 50%, to around £10,000–12,000, £5000 and £3000 in the primary adjuvant, unplanned switching and extended adjuvant setting, respectively. The limited

evidence to date of benefits after the therapy period suggests that the 'benefits maintained' scenario may be realistic. The results from the economic analyses within the industry submissions are generally lower than the results from the authors' model and are close to or below £12,000 in all three settings. The authors' analyses generally produce a lower estimate of QALY gain for the aromatase inhibitors, due to the more conservative assumption regarding benefits, along with differences in the utility values used in the their analysis.
Conclusions: On the basis of the current data and within their licensed indications, AIs can be considered clinically effective compared with standard tamoxifen treatment. However, their long-term effects, in terms of both benefits and harms, remain unclear. Under the conservative assumption that benefits gained by AIs during the treatment period are gradually lost over the following 10 years, the cost per QALY for AIs compared with tamoxifen is estimated to be between £21,000 and £32,000 in the primary adjuvant setting and around £20,000 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £10,000. Under the less conservative assumption that rates of recurrence are the same in both arms after the therapy period is complete, the incremental cost-effectiveness ratios are typically at least 50% lower, suggesting that AIs are likely to be considered cost-effective in all three settings. Understanding of the long-term treatment effects on cost-effectiveness is, however, incomplete. Data on the impact of AIs on survival are awaited from the majority of the trials to confirm whether or not the benefits seen in disease-free survival and recurrence rates are translated into overall survival benefit in the medium to long-term.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Angioedema A vascular reaction involving the deep dermis or subcutaneous/submucal tissues. Excessive fluid in the subcutaneous tissues caused by dilatation and increased permeability of the capillaries and characterised by development of giant wheals.

Anaphylaxis Acute, inflammatory reaction caused by immune response.

Anorexia Uncontrolled lack or loss of the appetite for food.

Arthralgia Pain in a joint.

Arthritis An inflammatory condition that affects joints.

Arthrosis A disease of a joint.

Asthenia Weakness; lack of energy or strength.

Osteoporosis A reduction in the amount of bone mass, leading to fractures.

Pharyngitis Inflammation of the pharynx.

Stevens–Johnson syndrome A severe form of allergic reaction that most often results from a medication. The rash can be generalised and even appear on the palms of the hands and soles of the feet.

List of abbreviations

ABCSG	Austrian Breast and Colorectal Cancer Study Group
AE	adverse event
AI	aromatase inhibitor
ARNO	Arimidex®–Nolvadex®
ARR	absolute risk reduction
ASCO	American Society of Clinical Oncology
ATAC	'Arimidex', Tamoxifen, Alone or in Combination
BIG	Breast International Group
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CHD	coronary heart disease
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CSR	Clinical Study Report
CT	computed tomography
CTG	Clinical Trials Group
CVA	cardiovascular accident

continued

List of abbreviations *continued*

CVD	cardiovascular disease
DCIS	ductal carcinoma *in situ*
DFS	disease-free survival
DR	distant recurrence
DSU	Decision Support Unit
DVT	deep vein thromboembolic
ECOG	Eastern Cooperative Oncology Group
ER	oestrogen ('estrogen') receptor (status)
ES	Endocrine Subscale
ESMO	European Society for Medical Oncology
FACT-B	Functional Assessment of Cancer Chemotherapy for Breast Cancer
FDA	Food and Drug Administration
FEMTA	Femara R-Tamoxifen
GABG	German Adjuvant Breast Cancer Group
HR	hazard ratio
HRT	hormone replacement therapy
ICER	incremental cost-effectiveness ratio
IES	Intergroup Exemestane Study
IPD	individual patient data
ITA	Italian Tamoxifen Arimidex
ITT	intention-to-treat
LRR	loco-regional recurrence
LYG	life-year gained
MCS	mental component score
MENQOL	Menopause Specific Quality of Life
NCIC	National Cancer Institute of Canada
NICE	National Institute for Health and Clinical Excellence
NNT	number-needed-to-treat
NNTB	number-needed-to-treat (benefit)
NNTH	number-needed-to-treat (harm)
NSASBC	National Surgical Adjuvant Study of Breast Cancer
NSABP	National Surgical Adjuvant Breast and Bowel Project
ONS	Office for National Statistics
PCS	physical component score
PE	pulmonary embolism
PR	progesterone receptor (status)
PSA	probability sensitivity analysis
QALY	quality-adjusted life-year
QUOROM	Quality of Reporting of Meta-analyses
RCT	randomised controlled trial
SABCS	San Antonio Breast Cancer Symposium
SF-36	Short Form with 36 Items
SIGN	Scottish Intercollegiate Guidelines Network
TEAM	Tamoxifen Exemestane Adjuvant Multinational
TIA	transient ischaemic attack
TNM	tumour node metastases
UICC	Union Internationale Contre le Cancer
WCISU	Welsh Cancer Intelligence and Surveillance Unit
WMCIU	West Midlands Cancer Intelligence Unit

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Description of proposed service

Aromatase inhibitors (AIs) are proposed for the adjuvant treatment of oestrogen receptor-positive early breast cancer in postmenopausal women in three different indications: (1) instead of the current anti-oestrogen treatment, tamoxifen, for 5 years ('primary adjuvant'); (2) instead of tamoxifen for 2–3 years of an adjuvant programme, implemented opportunistically after a woman survives disease free for a period on tamoxifen ('unplanned switching strategy'), or planned from the time of surgery ('planned sequence strategy'); (3) for 3–5 years in women who are disease free following 5 years of tamoxifen: this is known as an 'extended adjuvant' strategy. The three AIs and their licensed indications are (1) anastrozole (primary adjuvant), (2) letrozole (primary adjuvant, extended adjuvant) and, (3) exemestane (unplanned switching).

Epidemiology and background

Around 23,000 postmenopausal women will be diagnosed with oestrogen receptor-positive early breast cancer every year. Treated with tamoxifen, disease will have recurred in about one-quarter after 5 years with recurrences continuing up to 20 years after surgery.

Objectives of the review

The objectives of this review were to establish the clinical and cost-effectiveness of aromatase inhibitors (AIs) anastrozole, letrozole and exemestane compared with tamoxifen in the adjuvant treatment of early oestrogen receptor-positive breast cancer in postmenopausal women with oestrogen receptor-positive early-stage breast cancer.

Methods

Fourteen electronic bibliographic databases and three trials registers were searched from May to June 2005. Three conference abstract databases were searched in December 2005. Studies evaluating the clinical effectiveness of AIs against 5 years' tamoxifen treatment were included and critically appraised on the adequacy of allocation concealment, randomisation, double blinding and intention-to-treat analysis. Critical appraisal and data extraction into standardised forms were performed independently, unblinded, by two researchers.

Three strategies for the proposed use of AIs were considered. First, primary adjuvant therapy, comparing AIs with tamoxifen in treatment of patients randomised at zero years after surgery. Second, unplanned switch therapy, patients randomised following 2–3 years of tamoxifen to either continue on tamoxifen for the remainder of the 5-year adjuvant treatment period or switch to an AI. Third, extended/sequential adjuvant therapy, patients randomised after 5 years of tamoxifen to receive 5 years of further treatment on an AI or placebo.

The three treatment strategies were considered separately within the economic analysis. Trials with strategies that randomised patients half-way through or at the end of the standard 5-year adjuvant treatment period with a strategy which randomised patients immediately after surgery were not compared directly.

The independent economic analysis used a state transition (Markov) approach to simulate the disease outcomes of patients up to a time horizon of 35 years post-surgery for early breast cancer. The primary outcome of interest was the cost per quality-adjusted life-year (QALY) gained, associated with AIs versus tamoxifen (or placebo, in the case of the extended adjuvant setting).

HRs from the trials were applied to the tamoxifen event rates to estimate event rates in the aromatase inhibitor arm.

Costs of health states were based on a review of published evidence to obtain the most recent and appropriate costs. Where published data were not identified, clinical opinion was sought. First-year costs and subsequent-year costs are assigned for each of the different health states modelled. Costs of managing adverse events are modelled.

The utility of the disease-free population was adjusted for age, based on data from Kind and Dolan. A literature review was undertaken in order to identify utility estimates for health states within the model. These were used as multipliers to adjust the age-related utility of the general population following an event. It is assumed that there is no disutility for patients on AIs or tamoxifen.

Results

Number and quality of studies and direction of evidence

Seven Phase III randomised controlled trials of varying methodological quality were found. Meta-analysis of studies was prohibited by the heterogeneity of trial designs. As most of the study populations had a relatively good prognosis and events are rare, hazard ratios (HRs) with 95% confidence intervals (CIs) and absolute risk reductions (ARRs) are presented.

A meta-analysis of three trials found a significant difference in overall survival when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen (details academic-in-confidence). Significant improvements in overall survival are yet to be demonstrated in other strategies. Compared with 5 years' tamoxifen, disease-free survival (disease recurrence or death from any cause) was significantly improved: in the primary adjuvant setting with anastrozole (68 months' follow-up: HR 0.87, 95% CI 0.78 to 0.97; ARR 0.024) and letrozole (26 months' follow-up: HR 0.83, 95% CI 0.73 to 0.94; ARR 0.019), and with an exemestane switching strategy (31 months' follow-up: HR 0.68, 95% CI 0.56 to 0.82; ARR 0.035). Other trials did not report this outcome. Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole (68 months' follow-up: HR 0.79, 95% CI 0.70 to 0.90; ARR 0.031) and letrozole (26 months' follow-up: HR 0.74, 95% CI 0.64 to 0.87; ARR 0.021), anastrozole switching (28 months' follow-up: HR 0.59, 95% CI 0.44 to 0.81; ARR 0.027): extended adjuvant anastrozole (60 months' follow-up: HR 0.64, 95% CI 0.41 to 0.99; ARR 0.042) or letrozole (30 months' follow-up: HR 0.58, 95% CI 0.45 to 0.76; ARR 0.024). The AIs and tamoxifen have different side-effect profiles, with tamoxifen responsible for small but statistically significant increases in endometrial cancer and, sometimes, thromboembolic events and stroke. AIs show a trend towards increases in osteoporosis, the statistical significance of which increases with follow-up time. The absence of tamoxifen treatment also increases the risk of hypercholesterolaemia and cardiac events in women of this age. There was no significant difference in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies.

Cost-effectiveness results

The cost-effectiveness results for anastrozole and letrozole, compared with tamoxifen in the primary adjuvant setting, were estimated to be £32,000 and £21,600 per QALY, respectively, based on an analysis over 35 years. There is, however, greater uncertainty around the results for letrozole, as the hazard ratio is based on an average follow-up of 26 months, compared with 68 months for anastrozole. There is currently no trial evidence for exemestane in this setting.

The cost-effectiveness results in the unplanned switching setting for anastrozole and exemestane, compared with tamoxifen, were estimated to be £23,200 and £19,200 per QALY, respectively, based on an analysis over 35 years. There is currently no trial evidence for letrozole in this setting.

In the extended adjuvant setting, the cost per QALY for letrozole compared with placebo was estimated to be £9800, based on an analysis over 35 years.

All these results were considered to be conservative. In the base case it was assumed that the benefits of AIs over tamoxifen or placebo seen during the therapy period were gradually lost during the following 10 years. In other words, the rate of recurrence for AIs after the trial period was assumed to be higher than that for tamoxifen between 5 and 15 years post-surgery, to the extent that by year 15 the number of patients in a disease-free state was the same in both arms. An alternative scenario, the 'benefits maintained' scenario, was tested in sensitivity analysis. In this scenario, it was assumed that following the treatment period the annual rate of recurrence in both arms would be the same. This reduced the cost-effectiveness ratio by over 50%, to around £10,000–12,000, £5000 and £3000 in the primary adjuvant, unplanned switching and extended adjuvant setting, respectively. The limited evidence to date of benefits after the therapy period suggested that the 'benefits maintained' scenario may be realistic.

One-way and probabilistic sensitivity analysis suggested that these results were generally robust to changes in the key model parameters. Understanding of the long-term treatment effects is, however, incomplete. The economic model considered costs and benefits over the lifetime of a patient, requiring extrapolation of these costs and benefits well beyond the timeframe of the reported trial outcomes to date. Data on the impact of AIs on survival are awaited from the majority of the trials to confirm whether or not the benefits seen in disease-free survival and recurrence rates are translated into overall survival benefit in the medium to long term. The largest uncertainty in terms of adverse events relates to the future risk of fracture in the period following adjuvant therapy, as the treated population gets older

The results from the economic analyses within the industry submissions were generally lower than the results from the authors' model and were close to or below £12,000 in all three settings. The authors' analyses generally produced a lower estimate of QALY gain for the aromatase inhibitors, due to the more conservative assumption regarding benefits, along with differences in the utility values used in the economic model.

Conclusions

Clinical effectiveness

No individual study reported a difference in overall survival between any AI and tamoxifen (or placebo in the extended adjuvant setting). An unpublished meta-analysis of individual patient data from three trials did find a significant difference in overall survival when unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Compared with 5 years' tamoxifen, DFS (absence of disease recurrence or death from any cause) was significantly increased in the primary adjuvant setting (using anastrozole or letrozole) and the unplanned switching strategy (using anastrozole or exemestane). Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole or letrozole, an anastrozole or exemestane unplanned switching strategy and an extended adjuvant anastrozole or letrozole strategy. There is no evidence that AIs confer any advantage in overall health-related quality of life. On the basis of the current data and within their licensed indications, AIs can be considered clinically effective compared with standard tamoxifen treatment. However, their long-term effects, in terms of both benefits and harms, remain unclear.

Cost-effectiveness

Three treatment strategies for AIs – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – were considered separately within the economic analysis. Under the conservative assumption that benefits gained by AIs during the treatment period are gradually lost over the following 10 years, the cost per QALY for AIs compared with tamoxifen is estimated to be between £21,000 and £32,000 in the primary adjuvant setting and around £20,000 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £10,000. Under the less conservative assumption that rates of recurrence are the same in both arms after the therapy period is complete, the incremental cost-effectiveness ratios are typically at least 50% lower, suggesting that AIs are likely to be considered cost-effective in all three settings. However, understanding of the long-term treatment effects on cost-effectiveness is incomplete.

Need for further research

Randomisation of populations at any point other than the start of treatment programmes should be strongly discouraged in future trials as it limits the utility of the resulting dataset. In the present case, this means randomising at the start of, not half way through or at the end of, the adjuvant period, because the objective is the same from successful surgery until relapse or death.

Data on the impact of AIs on survival are awaited from the majority of the trials to confirm whether or not the benefits seen in disease-free survival and recurrence rates are translated into overall survival benefit in the medium to long term.

Long-term follow-up data on major adverse events, including cholesterol levels, cardiovascular events and fracture rates, are awaited. Evidence to date suggests that the impact of these adverse events does not unduly impact on the cost-effectiveness ratios. The long-term implications for the costs and benefits of AIs and tamoxifen will need to be reviewed as and when new information becomes available.

Chapter 1

Aim of the review

This review addresses the following question, in order to assist the production of guidance to NHS commissioners in England and Wales:
"*Are the aromatase inhibitors anastrozole, letrozole and exemestane clinically and cost-effective compared with tamoxifen in the adjuvant treatment of early oestrogen receptor-positive breast cancer in postmenopausal women with oestrogen receptor-positive early-stage breast cancer?*"

Chapter 2
Background

Description of underlying health problem

Epidemiology

Breast cancer is the most common cancer amongst women in England and Wales: 38,651 women were diagnosed as having breast cancer in 2003 (*Table 1*). The European age-standardised rate per 100,000 was 143.5 in England and 112.9 in Wales.[1,2] The lifetime risk is almost 11%: one in nine women will develop breast cancer at some point in their life. The most common age at diagnosis was between 55 and 59 years, although the median age was between 60 and 64 years. One-third of new breast cancer cases are aged 70 years or over. The likelihood of diagnosis increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically. Four in five new cases are diagnosed in women aged 50 years and over, with the peak in the 50–64 years age group; a recent increase in age-standardised incidence has been attributed to earlier detection through the breast screening programme set up in 1988.[3]

Taking age 50 years or over as a proxy for 'postmenopausal', there were 31,558 new cases of breast cancer recorded in 2003 (29,567 in England and 1991 in Wales) that are relevant to this review.

Aetiology

The causes of breast cancer are complex. It has been suggested that up to 10% of patients may have an inherited predisposition to the disease;[4] this can arise from mutations in particular genes.[5,6] A genetic disposition can be inherited from either parent, both of whom can transmit susceptibility without developing the disease themselves. Reported risk factors for breast cancer also include older age, early onset of menstruation, late menopause and greater age at first completed pregnancy.[7] In addition, increased risk is often associated with some forms of benign breast disease and with exposure of developing breast tissue to radiation.[4] Women who use products which contain oestrogen and progesterone – either oral contraceptives or hormone replacement therapy (HRT) – are thought to be at increased risk, but the effects are not large and disappear within a decade of giving up hormone use.[8] Ten years' use of HRT appears to lead to six extra breast cancers per 1000 women, increasing the individual risk over 20 years (age 50–70 years) from one in 22 to one in 19.[9]

There is some evidence that the risk of breast cancer is affected by lifestyle. Obesity is associated with a two-fold increase in risk among postmenopausal women; this has been linked with high intake of meat and dairy fat, but the precise nature of these relationships is still unclear.[10] Regular alcohol consumption (two or more drinks per day) is thought to increase risk by about 40%.[11] As with many other forms of cancer, eating more vegetables can reduce risk.[12] Physical activity also seems to reduce risk (in premenopausal women, at least), and more intensive activity may produce greater benefits, although this is not yet certain.[13] It seems, therefore, that there is scope for primary prevention, and intervention studies are in progress.

Pathology

Cancer is the uncontrolled division of cells leading to abnormal growth of tissue. Breast cancer is the abnormal uncontrolled proliferation of breast

TABLE 1 *Breast cancer: incidence (2003)*

	Age (years)					
	0–49	**50–59**	**60–69**	**70–79**	**80+**	**All cases**
England	6,942	9,346	8,093	6,578	5,550	36,509
Wales	364	602	518	439	432	2,355
All	7,306	9,948	8,611	7,017	5,982	38,864

Sources: Office for National Statistics[1] and Welsh Cancer Intelligence and Surveillance Unit.[2]

ductal or lobular epithelial cells. This process may be termed non-invasive, precancerous or 'ductal carcinoma *in situ*' (DCIS), if the abnormal cells are confined to the breast ductules. Once the cells acquire the ability to spread outside the basement membrane of the breast ducts, it is termed invasive cancer and can spread, both within the breast tissue and through the lymphatic system and the bloodstream to other parts of the body. Invasive cancer that is confined to the breast only is potentially curable. Once breast cancer cells spread into the bloodstream, metastatic disease may develop, which is incurable and almost always fatal. The cancer that is growing where it started in the body (in this case the breast) is called the 'primary cancer'. Other places to which it spreads and grows are called 'secondary cancers' or 'metastases'.

For most cases, diagnosis is by triple assessment (clinical assessment, mammography and/or ultrasound imaging, and fine needle aspiration or core biopsy). Invasive cancers are classified on the basis of the nature of the cancerous cells (histological type and grade) and the size and spread of the tumour. Assessment of the lymph nodes in the armpit (axilla) is crucial to staging and prognosis; this usually requires surgical excision of some or all of the axillary lymph nodes.[14]

After diagnosis of an invasive breast cancer, the extent of the disease is assessed and the tumour staged. The structure of the Union Internationale Contre le Cancer (UICC) tumour node metastases (TNM) staging system for breast cancer reflects how, when left untreated, cancer cells can spread locally to the breast tissue and the lymph glands in the armpit (Stages I–III) and through the bloodstream and lymphatic system to other parts of the body (Stage IV). UICC Stages I and II are known as 'early breast cancer' (*Table 2*).[15]

Prognosis

Prognosis in breast cancer depends on the stage of the disease at presentation (*Table 3*). A poor prognosis tumour is one where the chance of micro-metastases (metastases that are too small to be identified by conventional means) is high. Where visible metastases are absent, nodal status has been shown to be the single most important predictor of recurrence and survival, in both the short and long term.[17–20] Tumour size is also important, and other factors, such as menopausal status and oestrogen receptor status [see the section 'Current service provision' (p. 5)], appear to be significant factors in the first 3 years but not thereafter.[19]

TABLE 2 *UICC TNM clinical staging system*

TNM stage	Simplified explanation
0	DCIS
I	Small tumour <2 cm, lymph nodes negative, no detectable distant metastases
II	Tumour 2–5 cm but lymph nodes negative; or tumour <5 cm, lymph nodes positive; no detectable distant metastases
III	Large tumour >5 cm; or tumour of any size with invasion of skin or chest wall; or positive lymph nodes in the supraclavicular region but no detectable distant metastases
IV	Tumour of any size, lymph nodes positive or negative, distant metastases

TABLE 3 *5-year survival according to UICC stage of disease at diagnosis*

	I	II	III	IV
5-year survival (%)[16]	84	71	48	18

The risk of breast cancer recurrence is not stable over time, with the risk rising sharply in the second year after surgery and, for the most part, gradually declining thereafter (*Figure 1*).[21] However, breast cancer recurrence remains a long-term problem and, even 20 years after surgery, survival is lower in women who have had breast cancer relative to those who have never had breast cancer (*Table 4*).[22]

Significance in terms of ill-health (burden of disease)

Breast cancer is a significant cause of mortality in England and Wales. Around 10,500 women died from breast cancer in England in 2003, a rate of 29 deaths per 100,000 women. It is the most common cause of cancer death in women. A decline in mortality from a peak in 1988 has been linked to better treatment, including the use of tamoxifen, but also to screening.[23,24] Nevertheless, in 2001, the most recent year for which all-cause mortality data are available, only stroke, myocardial infarction and pneumonia killed more women.[25] Although, compared with other cancers, the chances of curing breast cancer are high when diagnosed early, about 80% of the disease burden in England and Wales is mortality rather than morbidity related.[26]

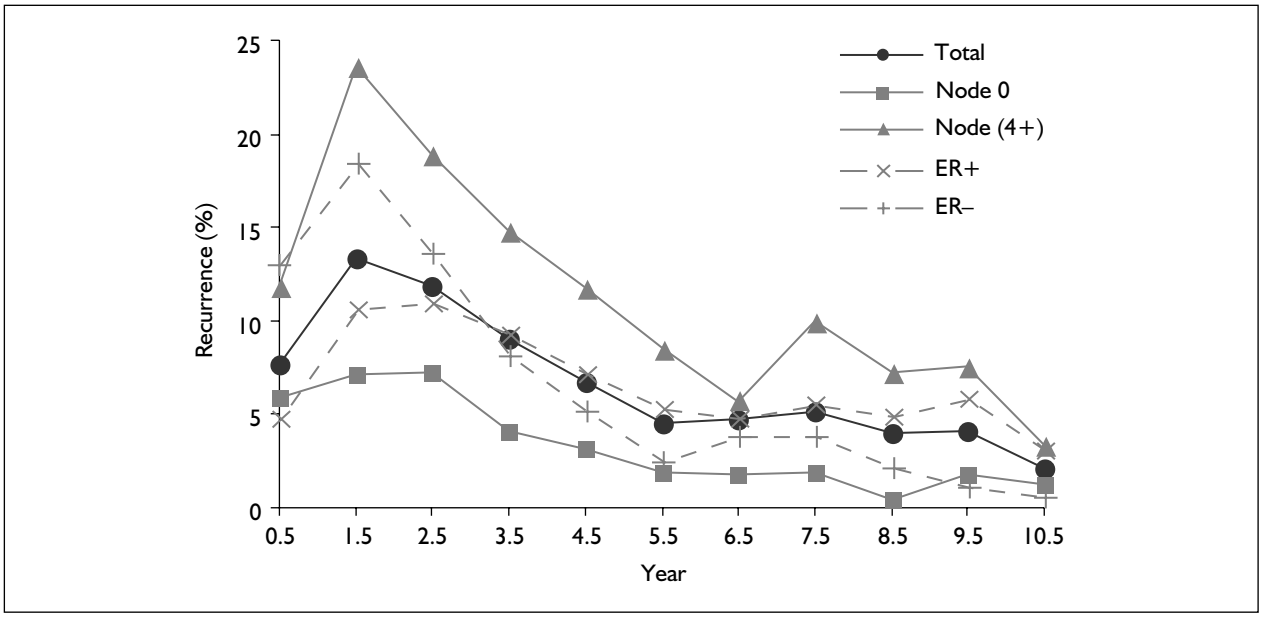

FIGURE 1 *Annual hazard of recurrence. Source: 3585 participants from seven Eastern Cooperative Oncology Group (ECOG) coordinated studies of postoperative adjuvant therapy for breast cancer.[21] The annual hazard rate is the probability (expressed here as a percentage) that a person's disease recurs during that year given that the person's disease has not recurred prior to the beginning of that year. Note that, compared with this review, the populations were diverse in terms of age and prognostic factors, and that only 57% of the population received this review's comparator, tamoxifen.*

TABLE 4 *Long-term relative survival*

Time (years)	Relative survival[a] (%) (95% CI)
1	94.0 (93.7 to 94.2)
5	80.3 (79.9 to 80.6)
10	71.7 (71.2 to 72.3)
15	67.5 (66.6 to 68.4)
20	64.5 (63.1 to 65.9)

[a] Predicted long-term relative survival (%) from breast cancer for female patients (aged 15–99 years), 2001–3, England and Wales; all ages (15–99 years), age-standardised. Source: Office for National Statistics.[22]

Current service provision

Current service provision

In 2002, the National Institute for Health and Clinical Excellence's (NICE's) guidance document *Improving Outcomes in Breast Cancer*[14] summarised contemporary service provision for diagnosis, treatment and follow-up of patients with early breast cancer. It states that "the treatment of primary breast cancer usually involves surgery, either breast conservation (wide local excision) or mastectomy". The purpose of surgery is to (1) control the disease locally (within the breast) or loco-regionally (within the breast and axillary lymph nodes) and (2) to determine the prognostic features of the primary cancer (see the section 'Prognosis', p. 4).

The biological features and stage of a woman's cancer will determine whether a patient has micro-metastases at the time of surgery. Because surgery is limited to the area around the breast, women with early breast cancer are considered for adjuvant systemic therapy to eradicate the micrometastases that cause relapses. This may involve endocrine (or 'hormone') therapy, chemotherapy or, more recently, molecular targeted therapies such as trastuzumab (Herceptin®), after surgery, depending on the prognostic features of the primary cancer. Choice of adjuvant treatment is determined by the risk of recurrence, oestrogen receptor (ER) status of the primary tumour and menopausal status.[27] *Improving Outcomes in Breast Cancer* states that "All women with hormone receptor-positive tumours should be offered hormone treatment for 5 years after primary therapy".[14]

Tamoxifen, a drug which blocks some of the actions of oestrogens and stimulates others, is the most commonly used form of hormonal treatment. It is generally well tolerated and requires no special precautions or facilities for use. However, tamoxifen can have short- and long-term side-effects including, most seriously, endometrial cancer.

A recent case–control study (n = 1169) found that the risk of endometrial cancer increased with longer duration of tamoxifen use ($p < 0.001$). Endometrial cancers of Stage III and IV occurred twice as frequently in long-term tamoxifen users (up to 2 years) than in non-users (17.4 versus 5.4%, $p = 0.006$). Long-term users were more likely than non-users to have had poor prognosis disease and poor endometrial cancer-specific survival (76% for up to 5 years, 85% for 2–5 years versus 94% for non-users, $p = 0.02$).[28] Conversely, tamoxifen also has beneficial side-effects. A randomised study (n = 4175) identified that 5 versus 2 years' tamoxifen significantly reduced 10-year mortality from coronary heart disease [hazard ratio (HR) = 0.67, 95% confidence interval (CI) 0.47 to 0.94, $p = 0.022$].[29] A number of previous clinical trials have pointed to the beneficial effects of tamoxifen (compared with placebo) in lowering cholesterol ($p < 0.001$)[30–32] and preventing cardiovascular events (HR = 0.68, 95% CI 0.48 to 0.97; $p = 0.03$).[33] Comparative studies, including one clinical trial, have also confirmed that tamoxifen increases bone mineral density whereas the latter decreases on placebo ($p < 0.001$).[34]

The benefits of tamoxifen, in respect of breast cancer, are greatest when the primary tumour is ER rich.[14] The majority of breast cancers have ERs but the percentage does vary with age (*Table 5*). Older patients are much more likely to have cancers with ERs.[35,36]

Treatment with tamoxifen prevents or delays the growth of metastases and increases a woman's chances of survival. Very strong evidence for the effectiveness of tamoxifen in the treatment of early breast cancer is derived from a systematic review of randomised controlled trials (RCTs) involving 30,000 women. For ER-positive disease only, allocation to 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31%, largely irrespective of the use of chemotherapy and of age, progesterone receptor status or other tumour characteristics. Tamoxifen also reduces the risk of developing cancer in the other breast ('contralateral breast cancer'). Treatment for 5 years is significantly more effective than for just 1–2 years.[37]

TABLE 5 *Receptor status by age (%)*

	Age (years)			
	50–59	**60–69**	**70–79**	**80+**
ER–/PR–	26	18	15	11
ER–/PR+	6	5	4	2
ER+/PR+	52	61	64	68
ER+/PR–	16	16	17	18

Source: Witliff and colleagues.[35,36]

Current service cost

The NHS spent £3.5 million on tamoxifen in England during 2004 (prescribing costs are not available for Wales).[38] However, the population of interest is only a subset (albeit a majority) of all women taking tamoxifen, which is also indicated for the treatment of premenopausal women with early breast cancer and some women with loco-regional and metastatic disease.[27] This section provides an indicative estimate of the cost for treating all cases of early breast cancer in England and Wales, based on routine and published data. Numbers and percentages may be rounded. The algorithm is presented in *Figure 2*. There are two broad questions: (1) how many postmenopausal women are eligible for adjuvant tamoxifen and (2) how much tamoxifen are they likely to consume?

Number of women eligible

The number of women eligible for surgery followed by adjuvant tamoxifen will vary according to assumptions about: (1) the incidence of breast cancer; (2) menopausal status; (3) stage at presentation and (4) hormone receptor status. There will also be decisions made by clinicians and patients on whether the following groups are treated under this indication: (5) women with ER-negative, progesterone receptor (PR)-positive tumours; (6) older women; (7) women with an 'excellent prognosis' under the Nottingham Prognostic Index. There is considerable uncertainty surrounding some of these variables: in this review the terms 'conservative' are used to indicate estimates that will result in more women being eligible for adjuvant tamoxifen and 'optimistic' to indicate that fewer women will be eligible.

Incidence of breast cancer

The most recent year for which age-adjusted incidence data are available for both England and Wales is 2003, when there were 38,864 registrations of new breast cancers (note: ICD-10 category C50 excludes DCIS). Taking English[41] and Welsh[42] incidence data back to 1998, the 5-year average annual increase in new breast cancer registrations is 2.3%. Assuming that this average annual increase is stable, the incidence will be 41,557 in 2006 and 45,551 in 2010 (*Table 6*).

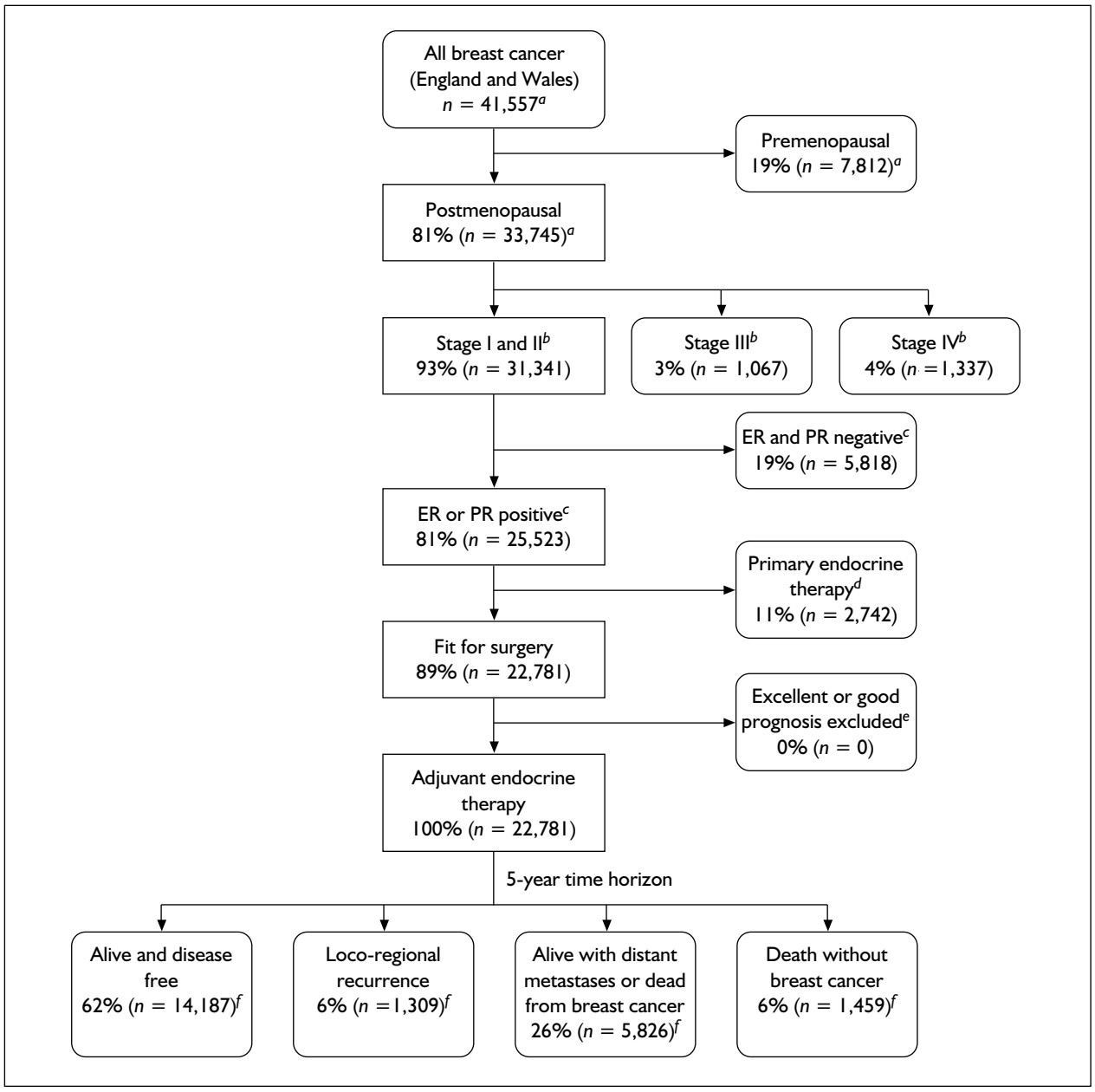

FIGURE 2 *Budget impact algorithm (projected 2006).* [a] *From 2003 figures (Office for National Statistics,*[1] *Welsh Cancer Intelligence and Surveillance Unit (WCISU)*[2]*).* [b] *Audit of 377 women from North Trent in 2002.*[39] [c] *Age-weighted data from 471 US biopsies.*[36] [d] *Proportions based on UK audit.*[40] [e] *No exclusion of women with excellent prognosis (see the section 'Number of women eligible', p. 6).* [f] *Data from West Midlands Cancer Intelligence Unit (WMCIU) on ER status of 9515 women (2002–4) and recurrence and mortality data for 6823 women (1996–7).*

Menopausal status

The 2003 datasets suggest that 81.2% of those presenting with new breast cancers will be aged 50 years or over, our proxy for the post-menopausal population. It is assumed that this value is stable over time.

Stage at presentation

The indication under examination only concerns women presenting with TNM Stage I and II disease. Information on TNM stage at presentation (see the section 'Pathology', p. 3) is not available from routine sources, but is provided by published audits (*Table 7*). In these datasets, the proportion of women with Stage I and II tumours ranges from 83%[43] (at the optimistic end) to 92%[39] (at the conservative end) of all those with invasive tumours of known stage. The audit with the largest sample size estimated the figure at 87%.[44] A more conservative scenario would involve a greater proportion of women with Stage I and II tumours and a more optimistic scenario fewer

TABLE 6 *Projected breast cancer population*

Year	England	Wales	Total	Annual increase	5-year average annual increase	Total (projected)
1998	32,908	1,917	34,825	–	–	–
1999	34,176	2,257	36,433	1.046	–	–
2000	33,829	2,079	35,908	0.986	–	–
2001	34,347	2,058	36,405	1.014	–	–
2002	34,319	2,211	36,530	1.003	–	–
2003	36,509	2,355	38,864	1.064	1.023	–
2004	–	–	–	–	–	39,742
2005	–	–	–	–	–	40,639
2006	–	–	–	–	–	41,557
2007	–	–	–	–	–	42,496
2008	–	–	–	–	–	43,456
2009	–	–	–	–	–	44,437
2010	–	–	–	–	–	45,441

TABLE 7 *Stage at presentation*

	Period	Sample size[a]	TNM I and II	TNM III	TNM IV
Golledge *et al.*[43]	1993–6	428	83	5	12
NYCRIS[44]	1998–9	7688	87	7	6
Wyld *et al.*[39] 55–69 years	2002	196	96	2	2
Wyld *et al.*[39] 70+ years	2002	164	88	5	1

[a] Excludes unknown receptor status and DCIS.

such women. We have opted to use the most conservative dataset[39] in the illustrated scenario because (1) it includes only women aged over 50 years – age and stage being dependent variables (because younger women are not screened in the UK and screening detects proportionately more early cancers);[45] and (2) it indicates something about the age distribution within the postmenopausal population which, in turn, informs other variables.

Hormone receptor status

Large biopsy studies have shown that the proportions of different ER and PR status are correlated by age groups.[35,36] For all scenarios, the data in *Table 5* were used to assess the likely proportions of women with different receptor status. The recording of ER status is now a mandatory quality measure for all UK breast units and ER unknowns should be very rare as a result: the calculations assume that ER status is known for all women.

ER-negative, PR-positive women

The original scope for this review defines the population of interest as women with ER-positive tumours. Some UK breast units also check PR status and give tamoxifen to women with ER-negative, PR-positive tumours (although not to women with ER-negative, PR-negative tumours). The evidence that this is beneficial is not consistent;[46] the phenotype constitutes a small sample size (about 5% of all tumours) and there is even debate over whether it exists at all (some consider the presence of ERs to be a prerequisite for PR positivity[47]). Nevertheless, a large meta-analysis has suggested that these women derive more benefit than those who are ER-negative, PR-negative,[37] but not as much as the remainder. An optimistic scenario would assume that only women with ER-positive tumours are treated; a conservative scenario would assume that those with ER-negative, PR-positive tumours are treated (the assumption in our illustrated scenario).

Older women

Two recent audits of UK practice confirmed that the use of 'primary endocrine therapy' (tamoxifen, without surgery, as the main treatment) is widespread, with 42% of all women with early breast cancer aged over 70 years being treated in this way[39] and 55% of those over the age of 80 years.[40] The usual premise for this action is that older patients are less likely to be fit for

surgery,[48] although it has a low complication rate[49] and is considered optimal treatment for most older women.[50,51] The relevance for the budget impact is that, without surgery, those women fall out of the adjuvant and into the neo-adjuvant indication (although there is no surgical intent, neither is primary endocrine therapy a licensed indication: neo-adjuvant therapy is considered the nearest analogue). An optimistic scenario would involve higher numbers of older women being treated with primary adjuvant therapy. A conservative estimate would assume all of these women are treated under the adjuvant indication. The illustrated scenario uses moderately conservative data and assumes that only 55% of those over the age of 80 years will receive primary endocrine therapy.[40]

NPI excellent prognosis

Anecdotally, it is understood that, whereas some centres give endocrine therapy to every hormone receptor-positive patient, others would not treat very low- and low-risk women in this way (Robertson J, University of Nottingham: personal communication, 2005). An annual audit shows the relative 5-year survival of women by different prognostic groups in the Nottingham Prognostic Index, a combined score of tumour size, grade and nodal status of invasive cancers. The 5-year relative survival rate for cancers in the excellent prognostic group is 100% and, for cancers in the good prognostic group, 98.7%.[52] For these women (16 and 21%, respectively, of all early breast cancer; Robertson J, University of Nottingham: personal communication, 2005) the benefit of tamoxifen is marginal. According to Robertson, adjuvant tamoxifen treatment would be the subject of discussion between consultant and service user with many choosing not to take it. An optimistic scenario would assume that many excellent and good prognosis women do not receive adjuvant tamoxifen; a conservative scenario would assume that they receive treatment under this indication (the assumption in the illustrated scenario).

Four scenarios

1. Scenario 1 (illustrated scenario) is moderately conservative. It uses Wyld and colleagues' staging data[39] (conservative) and includes: women with ER-negative and PR-positive tumours (conservative); all but 55% of those aged 80 years or more (moderately conservative); and excellent prognosis patients (conservative). Of all women with invasive breast cancer, 54.8% would be relevant to this appraisal.
2. Scenario 2 is moderately optimistic. It is the same as Scenario 1 except that it uses the NYCRIS data (more optimistic) on stage at diagnosis.[44] Of all women with invasive breast cancer, 51.2% would be relevant to this appraisal.
3. Scenario 3 is highly optimistic. It uses Golledge and colleagues' staging data[43] (optimistic) and excludes: women with ER-negative and PR-positive tumours (optimistic); 42% of those aged 70 years or more (optimistic); and excellent prognosis patients (optimistic). Of all women with invasive breast cancer, 35.4% would be relevant to this appraisal.
4. Scenario 4 is highly conservative. It uses Wyld and colleagues' staging data[39] (conservative) and includes: women with ER-negative and PR-positive tumours (conservative); all women of any age (very conservative); and excellent prognosis patients (conservative). Adjuvant tamoxifen would be indicated for 54.8% of all women with invasive breast cancer. Of all women with invasive breast cancer, 61.4% would be relevant to this appraisal.

Quantity of tamoxifen

The amount of tamoxifen consumed depends primarily on the relapse and mortality rates. Five-year mortality and recurrence data for 6823 invasive breast cancers diagnosed in the West Midlands in 1996 and 1997 (WMCIU data on file) suggest that around 62% of women will survive disease free and, if 100% compliance is assumed, take tamoxifen throughout this period (1825 days). Of the remainder, it is assumed that deaths without recurrence (6%) are evenly distributed over the 5-year period and that women keep taking tamoxifen until they die. Finally, it is assumed that all women who relapse (31%) stop taking tamoxifen and that they relapse with the same relative frequency as in the ER-positive subgroup of the ECOG study[21] (*Figure 1*). This is to recognise that relapse on tamoxifen is not evenly distributed over time. By convention, we assume that women who die or relapse during any year are on treatment for only half of that year (182.5 days).

A 30-tablet packet of non-proprietary tamoxifen (20 mg) costs £2.24.[27] However, routine data show that over 4% of the 20-mg formula tamoxifen dispensed in 2004 was AstraZeneca's proprietary tamoxifen, Nolvadex, the cost of a 30-tablet packet of which is £8.71. The result is that the average cost of a 30-tablet pack of tamoxifen (20 mg) is £2.51, and 4% of 20-mg tamoxifen formulation dispensed accounts for 17% of the total cost. Our calculations use this average cost, which works out as £0.0836 per woman per day.

TABLE 8 *Budget impact estimate (Scenario 1)*

	Alive, disease free (*n*)	Cost per year (*n* × 365 × £0.0837) (£)	Dead, no disease (*n*)	Cost per year (*n* × 182.5 × £0.0837) (£)	Relapse (*n*)	Cost per year (*n* × 182.5 × £0.0837) (£)	Total (£)
Baseline	22,889		0		0		
Year 1	21,797	665,655.76	293	4,476.90	798	12,190.88	682,323.54
Year 2	19,724	602,350.96	293	4,476.90	1,780	27,175.49	634,003.36
Year 3	17,602	537,522.31	293	4,476.90	1,830	27,937.42	569,936.64
Year 4	15,761	481,328.85	293	4,476.90	1,547	23,619.82	509,425.58
Year 5	14,254	435,294.46	293	4,476.90	1,214	18,540.29	458,311.66
Total		2,722,152.35		22,384.52		109,463.91	2,854,000.78

On the basis of these assumptions, costs are presented in *Table 8*.

These calculations indicate that, in Scenario 1 (relatively conservative), the NHS might spend around £2.9 million during 2006 on adjuvant tamoxifen treatment for postmenopausal women diagnosed with TNM Stage I and II breast cancer. In Scenario 2 (relatively optimistic) the figure would be £2.7 million, in Scenario 3 (highly optimistic) £1.8 million and in Scenario 4 (highly conservative), the figure would be £3.2 million.

Variation in services

Because all women with hormone receptor-positive tumours should be offered hormone treatment for 5 years after primary therapy,[14] and tamoxifen costs about £0.08 per day, it is thought that most eligible women currently receive it, except those who are intolerant (anecdotally, about 5%). Additionally, two recent audits of UK practice confirmed that the use of primary endocrine therapy (tamoxifen, without surgery, as the main treatment) is widespread, with 42% of all women aged over 70 years being treated in this way[39] and 55% of women with early-stage breast cancer over the age of 80 years.[40]

Description of new intervention

Identification of patients and important subgroups

Aromatase inhibitors (AIs) are indicated for the adjuvant treatment of postmenopausal women with hormone receptor-positive early-stage breast cancer. The effectiveness of three technologies from this pharmaceutical class is considered in this report; the licences for each differ slightly and are discussed fully below (see *Table 9* on p. 12).

Criteria for treatment

All women with early-stage breast cancer should be considered for adjuvant hormonal therapy following surgical removal of the tumour (see the section 'Current service provision', p. 5).

Intervention: aromatase inhibitors

The goal of hormone therapy in breast cancer is to deprive tumour cells of oestrogens, which are implicated in the development or progression of tumours. AIs do this by blocking the conversion of androgens to oestrogens in breast cancers, the breast and peripheral tissues.[53,54]

Anastrozole

Anastrozole (AstraZeneca UK Limited: ZD1033; Arimidex®) is a reversible (Type II), non-steroidal AI.[55] It is licensed for

- the treatment of advanced breast cancer in postmenopausal women
- the adjuvant treatment of postmenopausal women with hormone receptor-positive early invasive breast cancer.

Anastrozole is contraindicated in: premenopausal women; pregnant or lactating women; people with severe renal disease; people with moderate or severe hepatic disease; people with known hypersensitivity to anastrozole or to any of its excipients (see marketing authorisation for further details); and people receiving concomitant oestrogen-containing therapies.

Recommended dosage and administration

Anastrozole (one 1-mg tablet) is administered orally once per day. In the adjuvant setting, the marketing authorisation currently recommends that treatment is given for 5 years (a 'primary adjuvant' strategy), or 2–3 years in women who have received 2–3 years of adjuvant tamoxifen.

Side-effects
Hot flushes are very common (experienced by more than 10% of women). The following are common (experienced by between 1 and 10% of women): asthenia; joint pain/stiffness; vaginal dryness; hair thinning, mainly mild or moderate in nature; rash; nausea; diarrhoea; headache. The following are uncommon (experienced by between 0.1 and 1% of women): vaginal bleeding; anorexia; hypercholesterolaemia; vomiting; somnolence. The following are very rare (experienced by less than 0.01% of women); erythema multiforme; Stevens–Johnson syndrome; allergic reactions, including angioedema, urticaria and anaphylaxis.

The following warnings have been issued with regard to anastrozole.

Bone mineral density
Oestrogen-lowering agents cause a reduction in bone mineral density. Joint problems and fractures may occur with long-term therapy. Women with osteoporosis, or at risk of osteoporosis, should have their bone mineral density formally assessed by bone densitometry, for instance DEXA scanning at the commencement of treatment and at regular intervals thereafter. Treatment or prophylaxis for osteoporosis should be initiated according to local clinical practice and carefully monitored. Adequate data to show the effect of bisphosphonates on bone mineral density loss caused by anastrozole, or their utility when used prophylactically, are not currently published.

Plasma lipids
Under experimental conditions, patients were reported to have elevated serum cholesterol. Lipid levels should be checked on a regular basis.

Drug interactions
Results from a clinical trial suggest that tamoxifen should not be co-administered with anastrozole due to a reduction in anastrozole plasma concentrations.

Cost
A 28-tablet packet of Arimidex® (AstraZeneca's proprietary name for anastrozole) costs £68.56 net (or £2.45 per day).

Letrozole
Letrozole (Novartis Pharmaceuticals UK Limited: CGS 20267; Femara®) is a reversible (Type II), non-steroidal AI.[56] It is licensed for:

- adjuvant treatment of postmenopausal women with hormone receptor-positive invasive early breast cancer.
- the treatment of early invasive breast cancer in postmenopausal women who have received prior standard adjuvant tamoxifen therapy
- first-line treatment in postmenopausal women with advanced breast cancer
- advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed
- preoperative therapy in postmenopausal women with localised hormone receptor-positive breast cancer, to allow subsequent breast-conserving surgery in women not originally considered candidates for breast-conserving surgery.

In addition, a licence variation has just been accepted for 'early adjuvant treatment' of early hormone receptor-positive breast cancer in postmenopausal women. The precise indication is not clear at the time of writing.

Letrozole is contraindicated in: premenopausal women; hormone receptor status negative or unknown women (preoperative use only); pregnant or lactating women; people with moderate or severe hepatic or renal impairment; and people with hypersensitivity to the active substance or to any of its excipients (see marketing authorisation for further details).

Recommended dosage and administration
Letrozole (one 2.5-mg tablet) is administered orally once per day. The marketing authorisation currently recommends: (1) "in the [primary] adjuvant setting, treatment with [letrozole] should continue for 5 years or until tumour relapse occurs, whichever comes first"; (2) "following standard [5 years] adjuvant tamoxifen therapy, treatment with [letrozole] should continue for 3 years or until tumour relapse occurs, whichever comes first" (an 'extended adjuvant' strategy).

Side-effects
Hot flushes are very common. The following are common: anorexia; appetite increase; headache; dizziness; nausea; vomiting; dyspepsia; constipation; diarrhoea; alopecia; increased sweating; rash; myalgia; bone pain; arthralgia; arthritis; fatigue; peripheral oedema. The following are uncommon: urinary tract infection; tumour pain; leucopenia; hypercholesterolaemia; general oedema; depression; anxiety; somnolence; insomnia; memory impairment; dysaesthesia; taste disturbance; cataract; eye irritation; blurred vision; palpitations; tachycardia; thrombophlebitis; hypertension; dyspnoea; abdominal pain; stomatitis; dry mouth; increased hepatic enzymes;

pruritus; dry skin; urticaria; increased urinary frequency; vaginal bleeding; vaginal discharge; vaginal dryness; breast pain; pyrexia; mucosal dryness; and thirst. The following are rare (0.01–0.1% of women): cerebrovascular accident; pulmonary embolism; arterial thrombosis; cerebrovascular infarction.

The same warning concerning bone mineral density as for anastrozole (see the section 'Bone mineral density', p. 11) has also been issued for letrozole.

Drug interactions
None reported.

Cost
A 28-tablet packet of Femara® (Novartis's proprietary name for letrozole) costs £83.16 net (or £2.97 per day).

Exemestane

Exemestane (Pfizer Limited, UK: PNU 155971; Aromasin®) is a steroidal, irreversible AI.[57] It is licensed for:

- the adjuvant treatment of postmenopausal women with ER-positive invasive early breast cancer, following 2–3 years of initial adjuvant tamoxifen therapy
- the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy. Efficacy has not been demonstrated in patients with ER-negative status.

Exemestane is contraindicated in premenopausal, pregnant or lactating women and people with a known hypersensitivity to the active substance or to any of the excipients.

Recommended dosage and administration
Exemestane (one 25-mg tablet) is administered orally once per day. In the adjuvant setting, the marketing authorisation currently recommends that treatment is given following 2–3 years of initial adjuvant tamoxifen therapy for the remainder of the 5-year adjuvant period (an 'unplanned switching' strategy).

Side-effects
The following are very common: insomnia; headache; hot flushes; nausea; increased sweating; fatigue. The following are common: anorexia; depression; dizziness; carpal tunnel syndrome; abdominal pain; vomiting; constipation; dyspepsia; diarrhoea; rash; alopecia; pain; peripheral oedema. Somnolence and asthenia are uncommon. Thrombocytopenia and leucopenia are rare.

The following warnings have been issued with regard to exemestane: exemestane should not be administered to patients with rare hereditary problems of fructose intolerance, glucose–galactose malabsorption or sucrase–isomaltase insufficiency; exemestane contains methyl *p*-hydroxybenzoate, which may cause allergic reactions (possibly delayed).

The same warning concerning bone mineral density as for anastrozole (see the section 'Bone mineral density', p. 11) has also been issued for exemestane.

Drug interactions
The co-administration of drugs such as rifampicin, anticonvulsants (e.g. phenytoin and carbamazepine) and herbal preparations containing hypericum perforatum (St John's wort) known to induce CYP3A4 may reduce the efficacy of exemestane.

Aromasin® should not be co-administered with oestrogen-containing medicines.

Cost
A 90-tablet packet of Aromasin® (Pfizer's proprietary name for exemestane) costs £266.40 net (the equivalent of £82.88 for 28 tablets, or £2.96 per day).

Summary

The use of three AIs is proposed for the adjuvant treatment of early breast cancer. *Table 9* summarises the current licensed indications.

TABLE 9 *Licensed indications for aromatase inhibitors*

	Primary adjuvant	Planned sequence	Unplanned switch	Extended Adjuvant
Anastrozole[55]	✓	×	✓	×
Letrozole[56]	✓	×	×	✓
Exemestane[57]	×	×	✓	×

Personnel involved
AIs are taken orally and their administration does not require intervention of health service personnel additional to outpatient visits following surgery and pharmacy visits.

Setting
AIs are self-administered.

Equipment required
None.

Length of treatment
Three strategies have been proposed for the use of AIs. The first is 'primary adjuvant' treatment, used in place of the anti-oestrogen tamoxifen for 5 years. The second is used for the final 2–3 years of an adjuvant programme, following 2–3 years of tamoxifen treatment. This is known as an 'unplanned switching strategy' if it is implemented opportunistically after a woman survives disease free for a period on tamoxifen, or a 'planned sequence strategy' if it is planned from the time of surgery. The last strategy involves giving an aromatase inhibitor for 3–5 years following 5 years of tamoxifen; this is known as an 'extended adjuvant' strategy.

Follow-up required
NICE's *Improving Outcomes in Breast Cancer* guidance[14] states that: at the end of primary treatment, the patient and specialist should agree a written care plan; GPs should take responsibility for looking after women on long-term treatment with tamoxifen or other hormone-modifying drugs; that women should have continuing access to a breast care nurse, who should provide a telephone advice service and arrange appointments at a breast clinic if there seems to be cause for concern.

Anecdotally, it is understood that breast cancer units generally follow up women annually until 5 years after surgery. Hospital follow-up will be essential with long-term AI treatment because women will require (1) regular bone density monitoring and mammography and (2) discussion with experts on the pros and cons of different treatment options.

Degree of diffusion
The extent of uptake will depend on the approval that NICE gives to the different strategies mentioned in the section 'Length of treatment' above. However, it will also be influenced by the perceived risks presented by the adverse event profile: widespread concerns about bone health issues may mean that surgeons will not recommend 5 years of primary adjuvant treatment even were it approved.

Anticipated costs
Replacing the daily price of tamoxifen (£0.08/day) in *Table 8* with the price of anastrozole (£2.45/day) in the 2006 budget impact estimate for a primary adjuvant strategy (see the section 'Current service cost', p. 6) increases the cost from £2.9 million to £83 million (Scenario 1), £77 million (Scenario 2), £52 million (Scenario 3) or £93 million (Scenario 4). For letrozole (£2.97/day) and exemestane (£2.96/day), the cost would rise to £100 million (Scenario 1), £93 million (Scenario 2), £63 million (Scenario 3) or £113 million (Scenario 4).

This is a crude indicator of the upfront costs, which are likely to be underestimates: assuming that the new technologies reduce the hazard of relapse, the average woman will remain on an AI for longer than she would on tamoxifen. The economic model in Chapter 4 takes this and also the costs of long-term benefits and harms into account.

It is probable that unplanned switching or planned sequencing strategies would cost less, although the cost could vary depending on whether an AI or tamoxifen was given first. If we assume that women are given tamoxifen for the first 2 years and an AI for the next 3 years, the budget impact for Scenario 1 decreases to £52 million for an anastrozole and £62 million for letrozole or exemestane.

The cost of extended adjuvant treatment is also likely to be less than that of primary adjuvant treatment if, as in the trials, the AI were offered only to women who had survived disease free for 5 years (predicted to be about 60%: see *Figure 2*).

Chapter 3

Effectiveness

This systematic review was carried out according to the recommendations of the Quality of Reporting of Meta-analyses (QUOROM) statement.[58] A checklist can be found in Appendix 1.

Methods for reviewing effectiveness

Search strategy

The search aimed to identify all studies relating to anastrozole, letrozole and exemestane for the treatment of early-stage breast cancer. The following databases were searched: MEDLINE, EMBASE, CINAHL, BIOSIS, the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register, the Science Citation Index and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA) and OHE HEED. PreMEDLINE was also searched to identify any studies not yet indexed on MEDLINE. Current research was identified through searching the National Research Register, the Current Controlled Trials Register, the Medical Research Council Clinical Trials Register, the Proceedings of the American Society for Clinical Oncology (ASCO), the European Society for Medical Oncology (ESMO) and the San Antonio Breast Cancer Symposium (SABCS). Any industry submissions, and also any relevant systematic reviews, were handsearched in order to identify any further clinical trials. Searches were not restricted by language, date or publication type. The MEDLINE search strategy is presented in Appendix 2.

Inclusion and exclusion criteria

Systematic reviews and Phase III RCTs were included. Reviews of primary studies were not included in the analysis. Studies which were considered methodologically unsound were excluded from the review.

Studies randomising only the following population groups were included: postmenopausal women who have had surgery for early-stage breast cancer [Stages I and II of the American Joint Committee on Cancer (AJCC) system], whose tumours are ER-positive and: (a) who are hormonal therapy-naive; (b) who have survived disease free after 2–3 years of tamoxifen; or (c) who have survived disease free after 5 years of adjuvant tamoxifen. Studies designed to evaluate the experimental interventions in the following population groups were excluded: men, premenopausal women and women with DCIS, advanced stage breast cancer or ER-negative tumours.

Studies randomising only to the following experimental interventions were included: any one of the AIs anastrozole, letrozole or exemestane, administered adjuvant to surgical resection. This review considers any treatment strategy containing one of the above AIs, regardless of the point of randomisation in the study or the length and structure of the treatment programme. Studies randomising to the following interventions were excluded: AIs administered as neoadjuvant treatment; AIs administered in the adjuvant setting where the women in the comparator arm are not offered the current standard treatment of 5 years' single-agent tamoxifen (regardless of the point of randomisation).

Studies randomising only to the following comparators were included: tamoxifen alone, where trials randomise women who are hormonal therapy-naive or have survived disease free after 2–3 years of tamoxifen; placebo, where trials randomise women who have survived disease free after 5 years of adjuvant tamoxifen. Studies randomising to other comparators were excluded.

Studies designed to assess the following outcomes were included: overall survival (the review's primary outcome), defined as the hazard of death from any cause after any follow-up, or the time to death from any cause expressed in months; disease-free survival, however defined; recurrence, however defined; adverse events and toxicity, however defined; and health-related quality of life, however defined.

Where outcome data were available, the following subgroups were analysed separately: node-positive versus node-negative tumours; expression of other molecular markers where available.

Validity assessment

Published papers were assessed according to the accepted hierarchy of evidence, whereby meta-analyses of RCTs are taken to be the most authoritative forms of evidence, with uncontrolled observational studies the least authoritative.

Two researchers (DH and ES) assessed papers, unblinded, for four generic dimensions of methodological quality associated with estimates of treatment effects in controlled trials, described by Schulz and colleagues: (1) allocation concealment; (2) randomisation method; (3) intention-to-treat (ITT) analysis; and (4) double blinding.[59] The quality of reporting in studies assessing quality of life end-points was also critically appraised using methods described by Gill and Feinstein,[60] Sanders and colleagues[61] and Naito and colleagues.[62]

The purpose of these assessments was to give a narrative assessment of the potential for bias in the studies and, in the event that statistical synthesis (meta-analysis) was appropriate, to inform sensitivity analysis: poor reporting in trial reports is linked with a lack of clarity in protocols, which is in turn linked with exaggeration of the treatment effect.[63]

Data abstraction

The most complete dataset feasible was assembled. Where the team was aware that conference PowerPoint presentations contained more recent data than publications, these were retrieved where possible. For time to event outcomes (overall survival, disease-free survival and recurrence), the following were recorded: (1) the number of events and/or proportions of women experiencing an event in each arm; and (2) HRs and 95% confidence intervals (CIs).

Analysis

Overall survival (see the section 'Overall and breast cancer-specific survival', p. 28) is defined as the time from randomisation until death from any cause, and is measured in the ITT population.[64] Breast cancer-related survival (see the section 'Overall and breast cancer-specific survival', p. 28) was abstracted from papers as reported. The reader should be aware that definitions of this outcome differ subtly, for instance: "death after recurrence" does not necessarily mean that the woman died of breast cancer; likewise, "death following cancer event", which may not necessarily be a breast cancer event; similarly "death: breast cancer-related" may mean either death with disease or death from disease; "deaths as a result of breast cancer" is more easily understood.

Disease-free survival (DFS) is usually defined as the time from randomisation until recurrence of tumour or death from any cause.[64] Deaths occurring without prior documentation of disease recurrence should be scored as events or should be censored in the statistical analysis. Where deaths are censored, this is often called 'time-to-recurrence' or simply 'recurrence', but nomenclature is not a reliable guide to what is being measured: there is one trial included in the evidence review below which has an outcome called "disease-free survival" where deaths without disease are censored. Definitions of the disease-specific primary outcomes are given in the section 'Quality and characteristics of included studies' (p. 21).

It is worth noting that both disease-specific end-points have their merits and demerits. Trial end-points where death without disease is scored as an event are analysed as DFS in this review (see the section 'Disease-free survival', p. 31). The Food and Drug Administration (FDA) states that this approach is less prone to bias, but "Limitations of this approach are a potential decrease in statistical power of the study (by diluting the cancer-related events with deaths not related to cancer) and a potential to prolong falsely the DFS estimates in patients who die after a long unobserved period. The latter could introduce bias if the frequency of long-term follow-up visits is dissimilar on the study arms or if there is non-random drop-out due to toxicity."[64]

Trial end-points where deaths without disease have been censored are analysed as 'breast cancer recurrence' in this review. The FDA states that: "This method has the potential for bias in the *post hoc* determination of the cause of death. Furthermore, any method that censors patients, whether at death or at the last visit, assumes that the censored patients have the same risk of recurrence as non-censored patients. This critical assumption needs close examination in any setting where deaths are to be censored. In settings where deaths due to causes other than cancer are common (e.g. studies of patients with early metastatic prostate cancer), censoring deaths can be appropriate."[64] We calculate 'breast cancer recurrence' (see the section 'Breast cancer recurrence', p. 33) by adding together first events that are either loco-regional or distant recurrences, or new primary cancers in the contralateral breast. Death, with or without breast cancer, is not counted as an event in this outcome.

First events are recorded only when reporting loco-regional recurrences (LRRs) (see the

section 'Loco-regional recurrence', p. 35), distant recurrences (DRs) (see the section 'Distant recurrence', p. 36) and the occurrence of cancer in the contralateral breast (see the section 'Contralateral breast cancer', p. 38). For the purposes of this analysis, 'loco-regional recurrence' is defined as recurrence within the ipsilateral breast, chest wall, local lymph nodes or skin at the surgical site. 'Distant recurrence' is defined as recurrence at any other site apart from the contralateral breast. Where metastatic disease occurs simultaneously with a local or contralateral recurrence, metastatic disease has been treated as the first event. In each case, death does not count as an event.

The adverse events of interest are those associated with AIs (bone health, see the section 'Adverse events: bone health', p. 40; cardiovascular events, see the section 'Adverse events: cardiovascular events', p. 42; hypercholesterolaemia, see the section 'Adverse events: hypercholesterolaemia', p. 45) or tamoxifen (endometrial cancer and vaginal bleeding, see the section 'Adverse events: gynaecological', p. 43). They are recorded as reported in the primary studies, however defined.

Finally, health-related quality of life is recorded as reported, however defined (see the section 'Health-related quality of life', p. 46).

The absolute risk reduction (ARR) and number-needed-to-treat (benefit) (NNTB) for time-to-event outcomes were calculated using methods described by Altman and Andersen.[65] This method uses the numbers of patients still at risk (alive) at the time corresponding to the estimated probabilities (reported or imputed), or HRs and 95% CIs, to calculate CIs for each statistic.

Where baseline population characteristics, interventions, outcome definitions and follow-up periods were judged to be similar, NICE requested that we assess whether there was any evidence to support a difference in treatment effect between AIs. In the absence of head-to-head comparisons, the method described by Altman and Bland[66] was used to compare two HRs (with tamoxifen as a common comparator) using a test of interaction (or 'indirect comparison').

Results

Quantity and quality of research available

Number of citations identified

The search of bibliographic databases and research registers, together with the handsearching of the ASCO and ESMO abstracts, were conducted from May to June 2005. Excluding duplicates, this search retrieved 2364 citations pertaining to an unknown number of studies. Handsearching (including the manufacturers' submissions, received in September 2005) retrieved a further 20 citations. Finally, in December 2005, 22 abstracts were retrieved from the SABCS website and two academic-in-confidence presentations from SABCS were accepted from one of the manufacturers (AstraZeneca).

A flow chart (*Figure 3*) showing the progress of studies through the review is provided in accordance with the QUOROM statement.[58]

Number and type of studies included

A total of 103 citations pertaining to seven prospective RCTs and two secondary studies met the inclusion criteria and were included (*Figure 3*). Bibliographies pertaining to each study are given in Appendix 3. The design of the studies discussed in the text is illustrated in *Figure 4*.

Primary adjuvant strategies

The 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial compared three primary adjuvant strategies: 5 years of anastrozole; 5 years of tamoxifen; and 5 years of anastrozole with tamoxifen. The study recruited 9366 women between 1996 and 2000. After published interim analyses at 33[67] and 47[68] months, the combination treatment arm was closed in 2003, because of low efficacy. An analysis with a median follow-up of 5.7 years, which has been published in a research letter[69] and a conference PowerPoint presentation,[70] is the basis for most work in this report. The population of the ATAC trial fell outside the remit for this review as defined by the Department of Health: ER positivity was not an eligibility criterion and around 16% of participants were negative or never demonstrated to be positive for either oestrogen or progesterone. In the absence of studies of otherwise similar design which evaluated the correct population, we were instructed by NICE to incorporate the ATAC trial in the review, despite it not meeting their own study inclusion criteria. Although the ITT population is preferred in the text, the hormone (oestrogen and/or progesterone) receptor-positive subgroup is reported in tables where available.

The Breast International Group (BIG)/Femara R-Tamoxifen (FEMTA) trial, also known as BIG 1–98, compares two primary adjuvant and two sequencing strategies: (A) 5 years of tamoxifen;

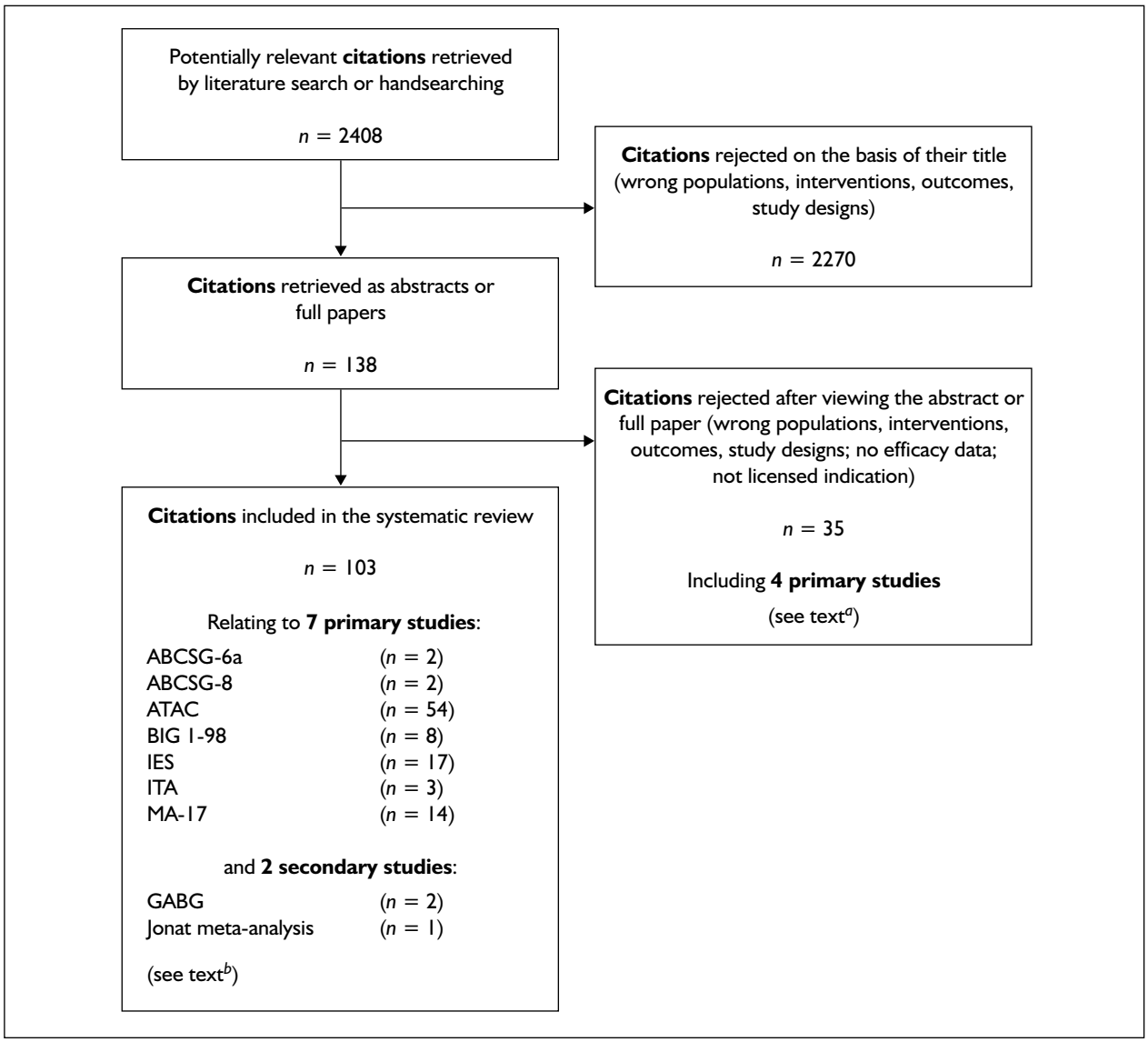

FIGURE 3 *QUOROM flow diagram.* [a] *'Number and type of studies excluded', p. 21.* [b] *'Number and type of studies included', p. 17.*

(B) 5 years of letrozole; (C) 2 years of tamoxifen, followed by 3 years of letrozole; and (D) 2 years of letrozole, followed by 3 years of tamoxifen. The trial recruited participants between March 1998 and May 2003. An analysis with a median follow-up of 26 months has been published in a peer-reviewed journal article;[71] it combined all women treated with tamoxifen (arms A and C), and all women treated with letrozole (arms B and D), with events in the planned sequence arms truncated at 24 months (when participants crossed over).[72] This analysis is the basis for the work in this report.

Unplanned switching strategies

The German Adjuvant Breast Cancer Group (GABG) performed what they described as a "prospectively planned, event-driven combined analysis" of two RCTs: Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 8 and Arimidex®–Nolvadex® (ARNO) 95. At the time of writing, no data have been presented from either of these trials individually (see the section 'Number and type of studies excluded', p. 21 for further details). In the strict sense, the combined analysis did not fit the inclusion criteria, being neither a systematic review and meta-analysis of RCTs nor, in and of itself, an RCT. On the advice of NICE's Decision Support Unit (DSU), and with a number of reservations, this study was included as its size and the paucity of other evidence were likely to make it pivotal in any decision (see Appendix 4 for full discussion). The study compared a 36-month anastrozole switching strategy with tamoxifen in women who had already survived disease free for 2 years on

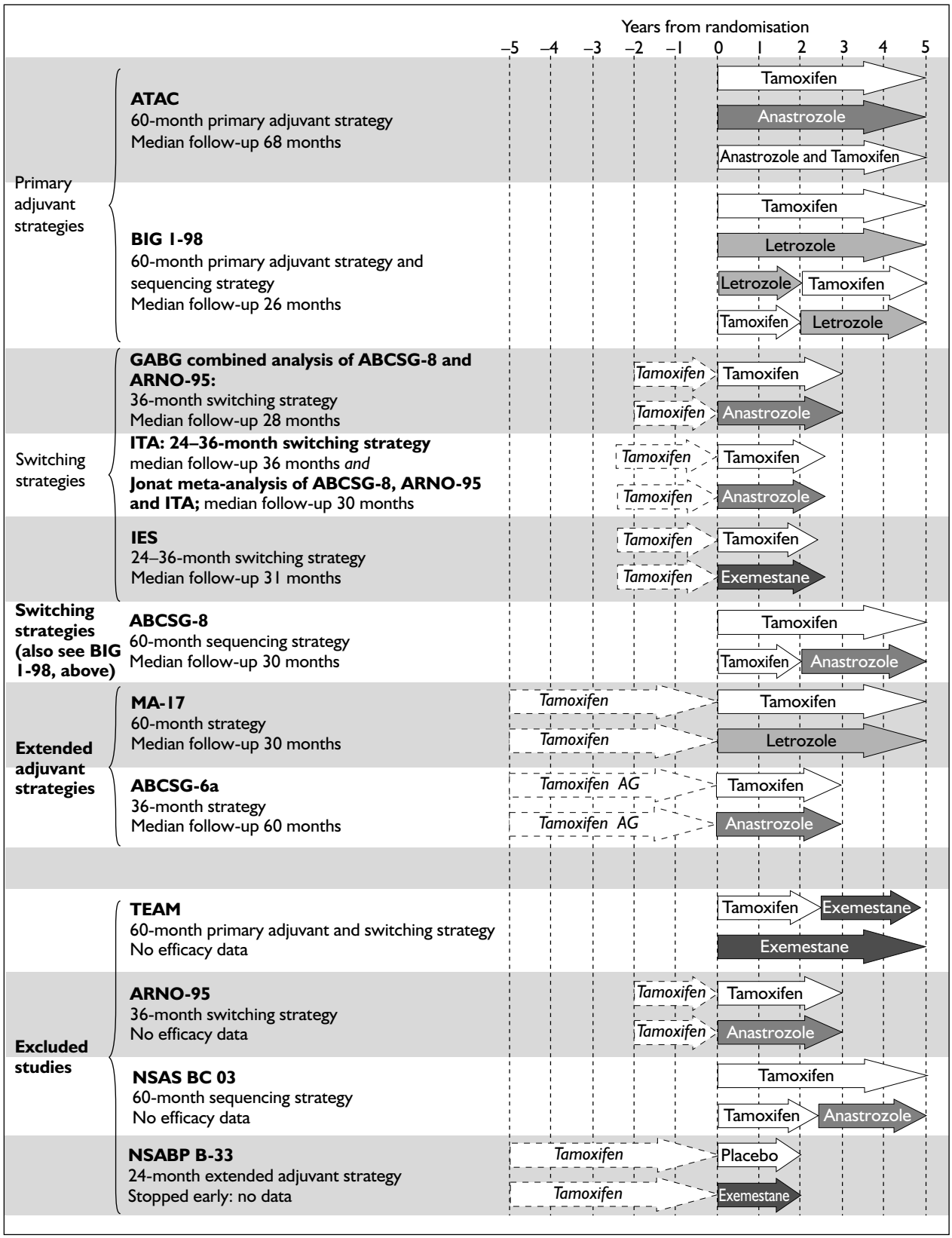

FIGURE 4 *Design of studies discussed in the text. Arrows with dotted outline indicate adjuvant hormonal therapy that occurred prior to randomisation. AG, aminoglutethimide.*

adjuvant tamoxifen. It recruited 3224 participants between January 1996 and August 2003 and was stopped for efficacy at the first interim analysis (April 2004) due to a predetermined stopping rule. A full journal article has been published, containing an analysis with a median follow-up of 28 months,[73] which is the basis for the work in this results section.

The Italian Tamoxifen Arimidex (ITA) trial compared a 24–36-month anastrozole unplanned switching strategy with tamoxifen in women who had already survived disease free for 24–36 months on adjuvant tamoxifen. It recruited 448 participants between March 1998 and December 2002. A full journal article has been published, containing an analysis with a median follow-up of 36 months,[74] which is the basis for the work in this results section.

Shortly before the submission of this report, Jonat, of Kiel University in Germany, presented a retrospective individual patient data (IPD) meta-analysis of 4006 women from three randomised trials: ABCSG-8, ARNO-95 and ITA, at SABCS 2005. The study compared a 24–36-month anastrozole unplanned switching strategy with tamoxifen in women who had already survived disease free for 2 years on adjuvant tamoxifen. Although the analysis has been presented at a conference, there is no abstract and neither the conference presentation nor any first-party publication of the data is in the public domain at the time of writing. An 'academic-in-confidence' version of the conference PowerPoint presentation[75] was made available to the assessment team by the manufacturer (AstraZeneca UK Limited). Although the assessment team cannot vouch for the methodological quality of this study, NICE requested that data from the presentation are provided in the full version of this report only, for the appraisal committee's information.

The Intergroup Exemestane Study (IES)[76] compared a 24–36-month exemestane unplanned switching strategy with tamoxifen in women who had already survived disease free for 24–36 months on adjuvant tamoxifen. It recruited 4742 participants between February 1998 and February 2003 and was stopped at the second interim analysis (December 2003) due to a predetermined stopping rule for efficacy. A full journal article has been published containing an analysis with a median follow-up of 31 months,[76] which is the basis for the work in this results section.

Planned sequence strategies

Although no AI currently has a licensed indication for 'planned sequence' strategies, the project protocol stated that, where evidence allows, they would be evaluated. The ABCSG-8 trial (see above on switching strategies) compared the standard 60-month primary adjuvant tamoxifen strategy with a planned sequencing strategy involving 24 months of tamoxifen treatment followed by 36 months of anastrozole. It recruited 3901 participants between January 1996 and June 2004.[73] At the time of writing, the only data publicly available are from a conference abstract,[77] with only 3700 patients described as "eligible for the analysis" in March 2005. An academic-in-confidence version of the conference PowerPoint presentation[77] was made available to the assessment team by the manufacturer (AstraZeneca UK Limited). Although the assessment team cannot vouch for the methodological quality of this study, NICE requested that data from the presentation are provided in the full version of this report only, for the appraisal committee's information.

Extended adjuvant strategies

The National Cancer Institute of Canada (NCIC) Clinical Trials Group (CTG) MA-17 trial was designed to compare an extended adjuvant strategy of 5 years of letrozole with placebo in women who had survived disease free after 5 years of primary adjuvant tamoxifen. The study recruited 5187 women between 1998 and 2002. It was stopped 1 year early, in 2003 (median follow-up 2.4 years), after the first prespecified interim efficacy analysis, when a difference in events between treatment arms exceeded the predefined stopping boundary. Study participants were notified of the results, and those who had been taking placebo were offered the option to cross over to letrozole treatment. A full journal article has been published, containing an analysis with a median follow-up of 28 months,[70] which is the basis for the work in this results section.

The ABCSG-6a trial compared an extended adjuvant strategy of 3 years of anastrozole with no treatment (note: not placebo). The trial re-randomised women who had survived another trial, ABCSG-6,[78] disease free. The women had previously been randomised to 5 years of adjuvant tamoxifen or tamoxifen plus aminoglutethimide, which is an older, less selective, active, but less potent AI. As with the ATAC study, the ABCSG-6a trial population did not satisfy the Department of Health remit on this occasion because half of the participants had previously received endocrine

therapy additional to tamoxifen. Once again, we were instructed by NICE to incorporate the study in the review for the sake of 'completeness'. The results should be interpreted with caution, despite the fact that ABCSG-6 had determined no significant differences between 5 years of tamoxifen alone and with aminoglutethimide in terms of either DFS or overall survival.[78] The included trial, ABCSG-6a, study recruited 856 women between March 1996 and March 2001. At the time of writing, the only data available are from a conference abstract[79] and associated PowerPoint presentation,[79] which are the basis for the work in this results section.

Number and type of studies excluded

Four studies were excluded from the study.

The German ARNO-95 switching trial randomised women who had already survived disease free for 2–3 years of either anastrozole or further tamoxifen. At the time of writing, this trial has not disseminated data outside the GABG combined analysis[73] and Jonat meta-analysis[75] (see the section 'Number and type of studies included', p. 17) and it is not referred to again outside this context.

The Tamoxifen Exemestane Adjuvant Multinational (TEAM) sequencing trial randomised postmenopausal women with early-stage breast cancer to tamoxifen or to exemestane for 5 years (*Figure 2*). Subprotocols on the incidence of menopausal symptoms[80,81] and lipidaemic profiles[82,83] have been presented, but there are no clinical effectiveness data available at this time and the study is not referred to further in this chapter.

The National Surgical Adjuvant Study of Breast Cancer (NSASBC) 03 is a Japanese sequencing trial designed to compare the following as adjuvant hormonal therapy in postmenopausal women with hormone-responsive breast cancer: (1) 5 years' sequential treatment with tamoxifen (for 1–4 years) followed by anastrozole (for the remainder of the 5-year period) with (2) 5 years' tamoxifen treatment. Primary end-points are DFS and adverse events. Recruitment started in 2003 with a target of 2500 participants.[84] No survival outcome data is available and the study is not referred to further in this chapter.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-33 study was a US trial designed to evaluate 2 years of exemestane in the extended adjuvant setting, for postmenopausal women completing at least 5 years of tamoxifen therapy.[85] Based on the results of MA-17, a trial evaluating letrozole in the extended adjuvant setting (see the section 'Number and type of studies' included', p. 17) further accrual to NSABP B-33 was suspended, and the trial subsequently closed without reporting efficacy data.[86]

Quality and characteristics of included studies

Seven primary and two secondary studies were included (see the section 'Number and type of studies included', p. 17). Five were large multinational studies (ATAC,[69] BIG 1-98,[71] IES,[76] the Jonat meta-analysis[75] and MA-17[87]) and four were national-level multicentre studies (ABCSG-6a,[79] ABCSG-8,[77] GABG[73] and ITA[74]) All except three studies (ABCSG-6a,[79] ABCSG-8[77] and the Jonat meta-analysis[75]) reported a power calculation. Only one study (ITA[74]) admitted being underpowered due to recruitment problems.

Three studies were funded wholly by the pharmaceutical industry (ATAC,[69] ITA[74] and BIG 1-98[71]), two were funded by a combination of industry and public money (MA-17;[87] GABG[73]) and one was funded by a combination of industry and charitable sources (IES[76]). The source of funding was unclear in three cases (ABCSG-6a,[79] ABCSG-8[77] and the Jonat meta-analysis[75]).

All of the studies were published or otherwise disseminated in the English language although, in five cases, the principal authors were not from the anglophone world (ABCSG-6a,[79] ABCSG-8,[77] BIG 1-98,[71] GABG,[73] ITA[74] and the Jonat meta-analysis[75]). Two studies were based in the UK (ATAC[69]), four in Austria (ABCSG-6a,[79] ABCSG-8,[77] GABG,[73] the Jonat meta-analysis[75]), one in Italy (ITA[74]), one in Canada (MA-17[87]) and one in Switzerland (BIG 1-98[71]).

In five cases (ATAC,[69] BIG 1-98,[71] GABG,[73] ITA,[74] MA-17[87]), the most mature results were written up in peer-reviewed journal articles. In the case of the ATAC trial,[69] this was in the form of a 'research letter' in which the quality of reporting was not in conformity with the Consolidated Standards of Reporting Trials (CONSORT) statement,[88] although ATAC had previously reported interim analyses in full journal articles.[67,68] The most mature data from the IES trial were available only in the form of a conference abstract and PowerPoint presentation.[89] Three studies (ABCSG-6a,[79] ABCSG-8[77] and the Jonat meta-analysis[75]) had not published results in a peer-reviewed journal. Public domain data for ABCSG-6a and ABCSG-8 were available only from conference

abstracts[79,77] and, in the case of the former, a PowerPoint presentation.[79] First-hand data from the Jonat meta-analysis[75] and more full data on ABCSG-8[77] were not in the public domain at the time of writing, but were offered on an academic-in-confidence basis by AstraZeneca UK Limited.

Where reported, the mean or median age of study arms (as reported) ranged between 61 years (BIG 1-98[71]) and 64 years (ATAC[69] and IES[76]). Only one study specified upper age limits: one constituent trial of the GABG combined analysis (ABCSG-8) recruited women aged up to 80 years and the other (ARNO-95) up to 75 years.[73] Age profiles were well balanced between arms in all trials where reported (ABCSG-6a[79] and ABCSG-8[77] did not report age data).

There was considerable variation between trials in terms of other prognostic factors. In most study arms, the percentage of women who were node-negative at diagnosis ranged from 50% (MA-17;[73] BIG 1-98[71]) to 75% (GABG[73]) However, one trial recruited only node-positive women (ITA[74]). Only one study demonstrated an obvious imbalance between arms (ABCSG-6a[79]), but it is not clear whether this was significant.

The percentage of women with a tumour size of up to 2 cm (known as T_1 tumours in the TNM system) at baseline ranged from 44% (ITA[74]) to 70% (GABG[73]). It was not reported in two studies (ABCSG-6a[79] and IES[76]). In the ABCSG-8 report, 74% of women had T_1 tumours.[77] There were obvious imbalances in the ITA[74] study (favouring the anastrozole arm), although it was not clear whether this was significant.

ITA[74] tried to recruit only women who had ER-positive disease (although 10% were ER-unknown). IES[76] recruited women with ER-positive or -unknown disease (1% negative). ABCSG-8,[77] GABG,[73] BIG 1-98[71] and MA-17[87] recruited women who were ER- and/or PR-positive. ATAC recruited women who were HR-positive or -negative (16% were neither ER- or PR-positive).[69] The inclusion criteria for ABCSG-6a are unclear.[79] There were no obvious imbalances in HR status between arms.

Prior chemotherapy was given to 67% of women in ITA,[74] 45% in MA-17,[87] 32% in IES,[76] 25% in BIG 1-98,[71] 21% in ATAC[69] and none in GABG.[73] None of the women in ABCSG-8 received prior chemotherapy.[77] It was not reported for ABCSG-6a.[79] There were no obvious imbalances in the distribution of prior chemotherapy between study arms.

In summary, baseline characteristics were well balanced between treatment arms within the included studies. There was some variation in terms of the distribution of prognostic factors between trials. The GABG[73] study had the best prognosis population, with the highest number of node-negative women (75%) and T_1 tumours at staging (70%), with no women who had been treated with chemotherapy. The ITA[74] study had the worst prognosis population, with 100% node-positive women, the lowest number of T_1 tumours at staging (44%) and the highest percentage of women given chemotherapy.

Three studies (ATAC,[69] BIG 1-98[71] and IES[76]) reported clearly adequate methods for the generation and concealment of the allocation schedule; in all the other studies, details of these facets of trial design associated with the prevention of selection bias were absent. The blinding of outcome assessors, care-givers and patients was clearly adequate in two studies (ATAC,[69] IES[76]) and probably adequate in one case (MA-17[87]). The quality of the method of blinding was unclear in three studies (ABCSG-6a,[79] ABCSG-8[77] and GABG[73]) and clearly not planned in one (ITA[74]), which was an open-label trial.

The greatest threat to validity was that only three studies reported an ITT analysis [ATAC,[70] ABCSG-6a[79] and ABCSG-8[77] at their most recent follow-up (none of them, currently, in a peer-reviewed publication)]. In four cases (ITA,[74] BIG 1-98,[71] IES,[89] MA-17[87]) the exclusions were minor (less than 1%). One study was more problematic. Although all the women randomised in the GABG[73] study were analysed, this combined study selected fewer than 80% of randomised participants from its two component trials. As Abrams argues in the DSU statement in Appendix 4, inclusion of only the data on all patients post 2 years breaks randomisation. Conventional ITT analysis of both trials (ABCSG-8 and ARNO-95), individually, is now desirable.

In a related point, follow-up data for the two sequencing arms in BIG 1-98[71] are truncated at 2 years and conflated with the two primary adjuvant therapy arms in the analysis. It is not clear if and how this might constitute a violation of the ITT principle.

The study characteristics are summarised in *Table 10*, baseline population characteristics in *Table 11* and details of quality assessment in *Table 12*.

TABLE 10 *Study characteristics*

Trial	Population	Interventions	Outcomes	Comments
Primary adjuvant strategies				
ATAC[69]	Postmenopausal women; histologically proven operable invasive breast cancer; completed primary surgery and CT where given; candidates for AET; included patients with hormone receptor-positive, -unknown or -negative status (though some analysis looked at hormone receptor-positive tumour patients)	T_1: anastrozole 1 mg/day for 5 years from surgery, or after CT (n = 3125). T_2: tamoxifen 20 mg/day for 5 years from surgery, or after CT (n = 3116). T_3: anastrozole 1 mg/day + tamoxifen 20 mg/day for 5 years from surgery, or after CT (n = 3125)	Primary outcome: DFS, defined as time to earliest recurrence of local/distant recurrence, new primary or death from any cause. Secondary outcomes: time to recurrence; contralateral breast cancer; OS; adverse events. Subprotocols: pharmacodynamic and pharmacokinetic profiles; modulation of lipoprotein profiles; endometrial status; bone mineral metabolism; quality of life	Hypotheses: H_1: anastrozole is non-inferior or superior to tamoxifen. H_2: anastrozole + tamoxifen is superior to tamoxifen alone as adjuvant therapy. Power calculation: superiority of anastrozole or anastrozole + tamoxifen over tamoxifen = 20% reduction in event rate (DFS): 80% power at 5% significance level with 9000 participants Funding: AstraZeneca (pharmaceutical)
BIG 1-98[71]	Postmenopausal women, histologically confirmed operable, breast cancer; mastectomy, lumpectomy, or quadrantectomy; ER+ and/or PR– tumour	T_1: letrozole (2.5 mg/day) for 5 years. T_2: letrozole (2.5 mg/day) for 2 years, then tamoxifen (20 mg/day) for 3 years; (T_1 + T^2, n = 4003) T_3: tamoxifen (20 mg/day) for 5 years; T_4: tamoxifen (20 mg/day) for 2 years, then letrozole (2.5 mg/day) for 3 years (T_3 + T_4, n = 4007)	Primary outcome: DFS, defined as time from randomisation to first incidence of: invasive recurrence in ipsilateral breast, chest wall, regional site or distant site; contralateral breast; second (non-breast) malignancy (primaries); death without prior cancer event. Secondary outcomes: OS; systemic-disease-free survival; DFS without 2nd primary events; TTR; TTM	Hypothesis: unclear Power calculation: Planned sample size was 7935 to provide 80% power to detect a 20% reduction in the risk of recurrence/relapse at the 5% (two-sided) significance level[90] Funding: Novartis (pharmaceutical)
Switching strategies				
GABG[73]	Postmenopausal women; age ⩽80 years (ABCSG 8) or ⩽75 years (ARNO 95); histologically verified, locally radically treated invasive or minimally invasive breast cancer; HR+ tumours; no preoperative CT, hormone therapy or RT; tumour infiltration of up to ten (ABCSG trial 8) or nine (ARNO 95) lymph nodes; absence of organ metastases; radical mastectomy or breast-conserving surgery with axillary lymph node dissection or sentinel lymph node biopsy, with or without RT	Following 2 years of adjuvant tamoxifen (not part of study treatment in ARNO-95): anastrozole versus tamoxifen alone. T_1: anastrozole (1 mg/day), 3 years (n = 1618). T_2: tamoxifen (20 or 30 mg/day), 3 years (n = 1606)	Primary outcome: 'event-free survival' defined as time to relapse at any site or incidence of contralateral breast cancer (note: not death without recurrence). Secondary outcomes: distant recurrence-free survival, tolerability, overall and breast cancer-related survival	Hypothesis: unclear Power calculation: needed 278 events to detect HR of 0.7 for superiority in event-free survival with a two-sided 5% significance level and 80% power. Interim analysis planned 139 events Funding: ABCSG-8, AstraZeneca (pharmaceutical); ARNO-95, GABG (public)

continued

TABLE 10 *Study characteristics (cont'd)*

Trial	Population	Interventions	Outcomes	Comments
ITA[74]	Postmenopausal women; histologically confirmed primary breast cancer; ER+ tumour; positive axillary nodes; no recurrence; surgery; 2–3 years adjuvant tamoxifen	T_1: anastrozole (1 mg/day) for 2–3 years (n = 223). T_2: tamoxifen for 2–3 years (20 mg/day) (n = 225)	Primary outcome: disease recurrence, defined as "including both loco-regional and distant recurrences (except contralateral breast cancer)".[74] (Note: not death without recurrence) Secondary outcomes: event-free survival (LRR or DR, including contralateral, or non-breast cancer-related deaths); OS; adverse events	Hypothesis: H_1: switching patients to anastrozole results in a 50% reduction in the risk of recurrence. Power calculation: a total of 996 patients (498 per arm) would be required to give the trial a statistical power of an 80% chance of detecting such a difference in favour of anastrozole Funding: AstraZeneca (pharmaceutical)
Jonat meta-analysis[75]	Combined population of GABG and ITA	T_1: anastrozole (1 mg/day) for 2–3 years (n = 2009). T_2: tamoxifen for 2–3 years (20 mg/day) (n = 1997)	Primary outcome: DFS, incorporating death without disease as an event Secondary outcomes: OS, time to recurrence, time to distant recurrence	Funding: unclear
IES[76]	Postmenopausal women; histologically confirmed, completely resected unilateral invasive breast carcinoma; ER– positive or -unknown; surgery and 2–3 years adjuvant tamoxifen; adequate haematological, renal and liver function	T_1: exemestane 25 mg/day for 2–3 years (n = 2362). T_2: tamoxifen 20/30 mg/day for 2–3 years (n = 2380). Less than 5% of the tamoxifen arm received 30 mg/day tamoxifen	Primary outcome: DFS defined as "time from randomisation to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause"[76] Secondary outcome: OS; contralateral breast cancer; long-term tolerability (not defined); breast cancer-free survival (time to recurrence)	Hypothesis: unclear Power calculation: 4400 participants to detect an absolute difference of 3.6% in DFS 3 years after randomisation; 88% power and two-sided level of significance of 4.3% after adjustment for interim analyses. *A priori*: principal analysis conducted after 716 end-point events Funding: Pfizer (pharmaceutical); Cancer Research UK (charitable)
Planned sequencing strategies				
ABCSG-8[77]	See GABG above	See GABG above	See GABG above	

continued

TABLE 10 *Study characteristics (cont'd)*

Trial	Population	Interventions	Outcomes	Comments
Extended adjuvant strategies				
MA-17[87]	Postmenopausal at start of adjuvant tamoxifen therapy lasting 4.5–6 years; histologically confirmed primary breast cancer; ER+ and/or PR+ tumour; discontinuation of tamoxifen <3 months pre-enrolment; ECOG performance status <2; life expectancy >5 years; any axillary lymph node status	T_1: letrozole (2.5 mg/day) oral (n = 2593); T_2: oral placebo (n = 2594)	Primary outcome: 'DFS', defined as "time from randomisation to the recurrence of the primary disease (in the breast, chest wall or nodal or metastatic sites) or the development of a new primary breast cancer in the contralateral breast". (Note: not secondary cancer or death without recurrence) Secondary outcomes: OS; adverse events; HRQoL	Hypothesis: unclear Power calculation: assumed a 4-year DFS rate of 88% in the placebo group and the detection of a difference of 2.5%in the 4-year DFS rate, with 80% power at a two-sided α level of 0.05. Required 4800 women over a 4-year period with 2 years of follow-up, accounting for 515 events Fundings NCIC, US National Cancer Institute (public); Novartis (pharmaceutical)
ABCSG-6a[79]	Postmenopausal women, early breast cancer, post-surgery and 5 years adjuvant tamoxifen (± aminoglutethimide) therapy	T_1: anastrozole 1 mg/day for 36 months T_2: no treatment	Primary outcome: 'event-free survival': this and secondary outcomes as per GABG (see p. 23)	Unclear

AET, adjuvant endocrine therapy; CT, computed tomography; HRQoL, health-related quality of life; OS, overall survival; RT, radiotherapy; TTM, time-to-metastases; TTR, time-to-recurrence.

TABLE 11 *Baseline population characteristics*

Trial	Mean age (SD)[a] (years)	Node-negative (%)	Tumour <2 cm (%)	HR-positive
Primary adjuvant strategies				
ATAC[69]	ANA, 64.1 (9.0); TAM, 64.1 (9.0); ANA + TAM, 64.3 (9.1)	ANA, 60.0; TAM, 61.5; ANA + TAM, 60.9	ANA, 63.9; TAM, 62.9; ANA + TAM, 64.1	ANA, 83.7; TAM, 83.4; ANA + TAM, 84.0 (ER+ and/or ER–)
BIG 1-98[71]	LET, 61 (38–89); TAM, 61 (38–90) (median and range)	LET, 58.5; TAM, 58.8	LET, 63.5; TAM, 62.3	99.8% of those randomised ER+ and/or PR+ (study requirement)
Unplanned switch				
GABG[73]	TAM, 62.0 (41.4–80.0); ANA, 62.3 (46.0–80.3) (median and range)	TAM, 1188 (74%); ANA, 1201 (74%)	TAM, 1119 (70%); ANA, 1136 (70%)	ER+ only: TAM, 96%; ANA, 96%. ER+ and/or PR+: TAM, 98%; ANA, 98%
ITA[74]	ANA, 62.9; TAM, 62.6 (median; range not available)	0%	ANA, 49; TAM, 44	ANA, *n* = 203 (91%); TAM, *n* = 194 (86%) (ER+ only)
Jonat meta-analysis[75]	ANA, 63 (38–76); TAM, 63 (43–77) (median and range)	ANA, 66; TAM, 66.5	NR	Unclear
IES[76]	EXE, 64.3 (8.1); TAM, 64.2 (8.2)	EXE, 51.3; TAM, 50.9	NR	EXE, 81.2; TAM, 81.3
Planned sequence strategies				
ABCSG-8[77]	NR	74% (no data by arm)	74% (no data by arm)	All ER+ and/or PR+
Extended adjuvant strategies				
MA-17[87]	LET, 62.4; PLA, 62.0 (median, no range reported)	LET, 50.0; PLA, 49.3	LET, 58%; PLA, 58%[8]	LET, 98%; PLA, 98% (ER+ and/or PR+)
ABCSG-6a[79]	NR	ANA, 65.9%; NT, 68.9%	NR	ANA, 93.5%; NT, 95.3% (states ER+)

ANA, anastrozole; EXE, exemestone; LET, letrozole; NT, no treatment; NR, not reported; PLA, placebo; SD, standard deviation.
[a] Unless indicated otherwise.

TABLE 12 *Quality assessment*

	Allocation concealment	Randomisation	Blinding	Withdrawals	Comments
Primary adjuvant strategies					
ATAC	Adequate (central randomisation)	Adequate (computer-generated number)	Adequate (outcome assessors, care-givers and patients – placebo control)	Unclear	More than 80% of randomised participants (discounting the arm that was stopped early) were included in the analysis but not all withdrawn patients were accounted for; analysis was not ITT: the primary analysis (hormone receptor-positive only) excludes women with hormone receptor-negative and -unknown tumours at baseline
BIG 1-98[71]	Adequate	Adequate	Unclear	Unclear	More than 80% of randomised participants were included in the analysis; all withdrawn patients were accounted for; not strictly an ITT analysis as 18 people, 0.2% of those randomised, who withdrew consent were not followed up
Unplanned switching strategies					
GABG	Unclear	Unclear	Unclear	Unclear	Less than 80% of randomised participants from original trials were included because their treatment was not advanced enough in time. Within the confines of the GABG, all patients, including the ineligibles, were analysed
ITA	Unclear	Unclear	No (open label)	Unclear	More than 80% of randomised participants were included in the analysis; the reasons for withdrawal were not given for all participants; analysis by ITT
Jonat meta-analysis[75]	Not applicable	Not applicable	Not applicable	See comments	347 (12%) of the ABCSG-8 trial participants were not analysed (they relapsed and/or died in the first 2 years); this amounts to 9% of the combined population
IES	Adequate (central randomisation)	Adequate (computer-generated number)	Adequate (outcome assessors, care-givers and patients – placebo control)	Yes	100% of randomised participants were analysed at the last published follow-up (30.6 months[76]); at a more recent follow-up (37.4 months; data from conference presentation only[89]) 18 (0.4%) participants were excluded from the analysis for reasons that are not clear (explanation in conference presentation not legible)
Planned sequence strategy					
ABCSG-8[77]	Unclear	Unclear	Unclear	Unclear	
Extended adjuvant strategies					
MA-17	Unclear	Unclear	Adequate (described as "double blind")	Unclear	More than 80% of randomised participants were included in the analysis; all withdrawn patients were accounted for; not strictly an ITT analysis: 30 women were excluded from the analysis
ABCSG-6a	Unclear	Unclear	Unclear (presumably open label as the comparator is "no treatment" rather than placebo)	Adequate	100% follow-up; analysis was by ITT

Overall and breast cancer-specific survival

Summary statistics for overall and breast cancer-specific survival are presented for all studies (where available) in *Tables 13* and *14*.

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC; median follow-up 68 months) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.97, 95% CI 0.85 to 1.12, $p = 0.7$; data from letter in journal[69]). In the tamoxifen group, 13.6% of participants died versus 13.3% in the anastrozole group (data from conference presentation only[70]): an extra 0.3% of participants receiving anastrozole benefited from the treatment. For every death prevented over 68 months, 354 women would have to be treated using anastrozole. Overall survival rates for the hormone receptor-positive population were similar (*Table 13*). The difference in "time to breast cancer death" (data from conference presentation only[70]) was not significant at the 5% level (HR = 0.88, 95% CI 0.74 to 1.05, $p = 0.2$). In the tamoxifen group, 8.6% of participants died of breast cancer versus 7.6% in the anastrozole group: an extra 1% of participants receiving anastrozole benefited from the treatment. For every breast cancer death to be prevented over 68 months, 101 women would have to be treated using anastrozole. The outcome for the hormone receptor-positive population was similar (*Table 14*).

The 60-month primary adjuvant letrozole strategy (BIG 1-98; median follow-up 26 months; data from full journal article[71]) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.86, 95% CI 0.70 to 1.06, $p = 0.16$). In the tamoxifen group, 4.8% of participants died versus 4.1% in the letrozole group: an extra 0.6% of participants receiving letrozole benefited from the treatment. For every death prevented over 26 months, 155 women would have to be treated using letrozole. The difference in "death following cancer event" (data from conference presentation only[72]) was significant at the 5% level (HR not reported). In the tamoxifen group, 3.8% of participants died following a cancer event versus 2.8% in the letrozole group: an extra 1.1% of participants receiving letrozole benefited from the treatment. For every death following a cancer event to be prevented over 26 months, 93 women would have to be treated using letrozole.

Switching strategies

One study evaluating a 36-month anastrozole switching strategy (GABG; median follow-up 28 months; data from full journal article[73]) demonstrated a difference in overall survival that was not significant at the 5% level (HR not reported). In the tamoxifen group, 3.7% of participants died versus 2.8% in the anastrozole group: an extra 0.9% (95% CI –1.1 to 2.8%) of participants receiving anastrozole benefited from the treatment. For every death to be prevented over 28 months, 113 women would have to be treated using anastrozole. The difference in "deaths: breast cancer related" (the trial's prespecified outcome) was not significant at the 5% level (HR not reported). In the tamoxifen group, 1.9% of participants died following a cancer event versus 1.5% in the anastrozole group: an extra 0.4% (95% CI –1.0 to 1.9%) of participants receiving anastrozole benefited from the treatment. For every breast cancer-related death to be prevented over 28 months, 226 women would have to be treated using anastrozole.

Another study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) did demonstrate a difference in overall survival that was borderline significant at the 5% level (HR not reported). In the tamoxifen group, 4.4% of participants died versus 1.8% in the anastrozole group: 2.7% (95% CI 1.0 to 4.3%) of participants receiving anastrozole benefited from the treatment. For every death prevented over 36 months, 38 women would have to be treated using anastrozole. The difference in "deaths as a result of breast cancer" (the trial's prespecified outcome) was not significant at the 5% level (HR not reported). In the tamoxifen group, 3.1% of participants died as a result of breast cancer versus 1.8% in the anastrozole group: an extra 1.3% (95% CI –0.2 to 2.8%) of participants receiving anastrozole benefited from the treatment. For one death from breast cancer to be prevented, 76 women would have to be treated using anastrozole.

The 24–36-month anastrozole switching strategy (Jonat meta-analysis; median follow-up 30 months; data from conference presentation[75]) resulted in a difference in overall survival that was significant at the 5% level (HR = 0.71, 95% CI 0.52 to 0.98, $p = 0.038$). It was not clear whether the necessary summary statistics were available to calculate the ARR and number-needed-to-treat (NNT).

The 24–36-month exemestane switching strategy (IES; median follow-up 37 months; data from conference presentation only[89]) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.83, 95% CI 0.67 to 1.02, $p = 0.08$). In the tamoxifen group, 7.9% of

TABLE 13 *Overall survival*

Trial	Strategy (months)	Follow-up (months)	No. followed up		Overall mortality				HR (95% CI)	ARR (95% CI)	NNTB (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC[69]	60	68	3092	3094	411	13.3	420	13.6	0.97 (0.85 to1.12)	0.003 (not estimable)	354.24 (not estimable)
ATAC hormone receptor-positive[70]	60	68	2618	2598	296	11.3	301	11.6	0.97 (0.83 to1.14)	0.003 (–0.020 to 0.025)	357.79 (39.46 to ∞)
BIG 1-98[71]	60	26	4003	4007	166	4.1	192	4.8	0.86 (0.70 to 1.06)	0.006 (not estimable)	155.1 (not estimable)
Switching strategies											
GABG[73]	36	28	1602	1597	45	2.8	59	3.7	NR	0.009 (not estimable)	112.94 (not estimable)
ITA[74]	24–36	36	223	225	4	1.8	10	4.4	NR	0.027 (not estimable)	37.73 (not estimable)
Jonat meta-analysis[75]	24–36	30	2009	1997	66	3.3	90	4.5	0.71 (0.52 to 0.98)	0.012 (–0.004 to 0.029)	81.86 (34.71 to ∞)
IES[89]	24–36	37	2352	2372	152	6.4	187	7.9	0.83 (0.67 to 1.02)	0.015 (–0.007 to 0.036)	67.77 (27.74 to ∞)
Extended adjuvant											
MA-17[87]	60	30	2583	2587	51	2.0	62	2.4	0.82 (0.57 to 1.19)	0.004 (–0.007 to 0.016)	235.18 (62.88 to ∞)
MA-17 node-positive	60	30	2516	2519	NR	NR	NR	NR	0.61 (0.38 to 0.98)	Not estimable	Not estimable

ARR, absolute risk reduction; Control, tamoxifen or placebo; HR, hazard ratio; NNTB, number-needed-to-treat (benefit); NR, not reported.

TABLE 14 *Breast cancer-related survival*

Trial	Strategy (months)	Follow-up (months)	No. followed up		Breast cancer-related death				HR (95% CI)	ARR (95% CI)	NNTB (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC[a 70]	60	68	3092	3094	235	7.6	265	8.6	0.88 (0.74 to 1.05)	0.010 (not estimable)	101.24 (46.43 to ∞)
ATAC hormone receptor-positive[a]	60	68	2618	2598	152	5.8	172	6.6	0.87 (0.70 to 1.09)	0.008 (–0.010 to 0.026)	122.77 (37.88 to ∞)
BIG 1-98[b 71,72]	60	26	4003	4007	111	2.8	154	3.8	NR	0.011 (not estimable)	93.43 (not estimable)
Switching strategies											
GABG[c 73]	36	28	1602	1597	24	1.5	31	1.9	NR	0.004 (not estimable)	225.73 (not estimable)
ITA[d 74]	24–36	36	223	225	4	1.8	7	3.1	NR	0.013 (not estimable)	75.91 (not estimable)
IES[c 89]	24–36	37	2352	2372	95	4.0	124	5.2	NR	0.012 (not estimable)	81.79 (not estimable)
Extended adjuvant											
MA-17[d]	60	30	2583	2587	16	0.6	22	0.9	NR	0.002 (not estimable)	431.17 (not estimable)
ABCSG 6a[d]	36	60	387	469	NR	NR	NR	NR	NR	Not estimable	Not estimable

[a] "Time to breast cancer death."
[b] "Death following cancer event."
[c] "Death: breast cancer-related."
[d] "Deaths as a result of breast cancer."

participants died versus 6.4% in the exemestane group: an extra 1.5% (–0.7 to 3.6%) of participants receiving exemestane benefited from the treatment. For every death prevented over 37 months, 68 women would have to be treated using exemestane. The difference in "breast cancer-free survival" (the trial's reported outcome) was significant at the 5% level when reported at 31 months (HR = 0.63, 95% CI 0.51 to 0.77, $p < 0.001$[76]). An HR was not available in the conference presentation of the 37-month follow-up[89] but, in the intervening period, the "breast cancer-related" death rate had risen from 2.8 to 5.2% in the tamoxifen group and from 2.3 to 4.0% in the exemestane group. At 37 months, an extra 1.2% of participants receiving exemestane benefited from the treatment. For every breast cancer-related death to be prevented over this period, 82 women would have to be treated using exemestane.

Extended adjuvant strategies
The 60-month extended adjuvant letrozole strategy (MA-17; median follow-up 30 months; data from full journal article[87]) resulted in a difference in overall survival that was not significant at the 5% level (HR = 0.82, 95% CI 0.57 to 1.19). In the placebo group, 2.4% of participants died versus 2.0% in the letrozole group: an extra 0.4% (–0.8 to 1.6%) of participants receiving letrozole benefited from the treatment. For death to be prevented, 235 women would have to be treated using letrozole. The trialists found that the difference in overall survival was significant at the 5% level when they analysed only women whose disease had been node-positive (HR = 0.61, 95% CI 0.38 to 0.98). The ARR and NNT for this subgroup were not estimable, because event numbers were not reported. The difference in "breast cancer as cause of death" (the trial's prespecified outcome) was not significant at the 5% level (HR not reported). In the placebo group, 0.9% of participants died as a result of breast cancer versus 0.6% in the letrozole group: an extra 0.2% of participants receiving letrozole benefited from the treatment. For one death from breast cancer to be prevented, 431 women would have to be treated using letrozole.

No data were available for this outcome from the study evaluating the 36-month extended adjuvant anastrozole strategy.[79]

Disease-free survival
Summary statistics for disease-free survival are presented for all studies (where available) in *Table 15*.

Primary adjuvant strategies
The 60-month primary adjuvant anastrozole strategy (ATAC;[69] median follow-up 68 months; data from letter in journal) resulted in a difference in DFS that was significant at the 5% level (HR = 0.87, 95% CI 0.78 to 0.97, $p = 0.01$). In the tamoxifen group 79.0% of participants were alive and disease free versus 81.3% in the anastrozole group: rounding figures up, an extra 2.4% of participants receiving anastrozole benefited from the treatment. For one extra woman to be alive and disease free over 68 months, 41 women would have to be treated using anastrozole. The trialists found that the difference in DFS was significant at the 5% level when they analysed only women whose disease had been hormone receptor-positive (HR = 0.83, 95% CI 0.73 to 0.94, $p = 0.005$). In the tamoxifen group, 83.8% of participants were alive and disease free versus 80.9% in the anastrozole group: rounding figures up, an extra 2.9% of participants receiving anastrozole benefited from the treatment. For one extra woman to be alive and disease free over 68 months, 34 women would have to be treated using anastrozole.

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from full journal article) resulted in a difference in DFS that was significant at the 5% level (HR = 0.81, 95% CI 0.70 to 0.93, $p = 0.003$). In the tamoxifen group, 89.3% of participants were alive and disease free versus 91.2% in the letrozole group: an extra 1.9% of participants receiving letrozole benefited from the treatment. For one extra woman to be alive and disease free over 26 months, 52 women would have to be treated using letrozole.

Switching strategies
Neither the GABG nor ITA reported DFS as defined in this report.

The 24–36-month anastrozole switching strategy (Jonat meta-analysis; median follow-up 30 months; data from conference presentation[75]) resulted in a difference in DFS that was significant at the 5% level (HR = 0.59, 95% CI 0.48 to 0.74, $p < 0.0001$). It was not clear whether the necessary summary statistics were available to calculate the ARR and NNT.

The 24–36-month exemestane switching strategy (IES;[76] median follow-up 37 months; data from conference presentation) resulted in a difference in DFS that was significant at the 5% level (HR = 0.73, 95% CI 0.62 to 0.86, $p = 0.0001$).

TABLE 15 *Disease-free survival*

Trial	Strategy (months)	Follow-up (months)	No. followed up		Events				HR (95% CI)	ARR (95% CI)	NNTB (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC	60	68	3092	3094	575	18.6	651	21.0	0.87 (0.78 to 0.97)	0.024 (–0.004 to 0.053)	40.91 (18.83 to ∞)
ATAC hormone receptor-positive	60	68	2618	2598	424	16.2	497	19.1	0.83 (0.73 to 0.94)	0.029 (0.002 to 0.057)	34.08 (17.51 to 633.77)
BIG 1-98	60	26	4003	4007	351	8.8	428	10.7	0.81 (0.70 to 0.93)	0.019 (0.004,0.034)	52.28 (29.20 to 248.98)
BIG 1-98 ER+/PR+	60	26	2542	2513	179	7	208	8.3	0.84 (0.49 to 1.03)	0.01 (not estimable)	78.12 (not estimable)
BIG 1-98 ER+/PR–	60	26	808	823	89	11	107	13	0.83 (0.62 to 1.10)	0.02 (not estimable)	47.98 (not estimable)
BIG 1-98 ER+/ PR-unknown	60	26	579	575	70	12.1	92	16	0.72 (0.53 to 0.98)	0.04 (not estimable)	23.80 (not estimable)
BIG 1-98 node-positive	60	26	1660	1651	205	12.3	274	16.6	0.71 (0.59 to 0.85)	0.04 (not estimable)	22.18 (not estimable)
BIG 1-98 node-negative	60	26	2292	2295	140	6.1	147	6.4	0.99 (0.76 to 1.21)	0.00 (not estimable)	1614.80 (not estimable)
Switching strategies											
GABG	36	28	1602	1597	NR	NR	NR	NR	NR	Not estimable	Not estimable
ITA	24–36	36	223	225	NR	NR	NR	NR	NR	Not estimable	Not estimable
Jonat meta-analysis	24–36	30	2009	1997	NR	NR	NR	NR	0.59 (0.48 to 0.74)	Not estimable	Not estimable
IES	24–36	37	2352	2372	262	11.0	353	14.9	0.73 (0.62 to 0.86)	0.038 (0.014 to 0.062)	26.07 (16.02 to 69.81)
IES ER+/PR+	24–36	31	1312	1307	NR	NR	NR	NR	0.66 (0.51 to 0.87)	Not estimable	Not estimable
IES ER+/PR–	24–36	31	351	384	NR	NR	NR	NR	0.58 (0.38 to 0.90)	Not estimable	Not estimable
IES ER+/PR-unknown	24–36	31	254	245	NR	NR	NR	NR	0.67 (0.39 to 1.16)	Not estimable	Not estimable
IES ER– or ER-unknown	24–36	31	445	444	NR	NR	NR	NR	0.85 (0.57 to 1.29)	Not estimable	Not estimable
IES node-negative	24–36	31	1211	1211	NR	NR	NR	NR	0.68 (0.48 to 0.95)	Not estimable	Not estimable
IES node-positive (1–3 nodes)	24–36	31	715	706	NR	NR	NR	NR	0.71 (0.51 to 0.98)	Not estimable	Not estimable
IES node-positive (4+ nodes)	24–36	31	321	330	NR	NR	NR	NR	0.58 (0.42 to 0.81)	Not estimable	Not estimable
Extended adjuvant											
MA-17[87]	60	30	2583	2587	NR	NR	NR	NR	NR	Not estimable	Not estimable
ABCSG 6a	36	60	387	469	NR	NR	NR	NR	NR	Not estimable	Not estimable

In the tamoxifen group, 85.1% of participants were alive and disease free compared with 89.0% in the exemestane group: after rounding, an extra 3.8% of participants receiving exemestane benefited from the treatment. For one woman to benefit from exemestane, 26 women would have to be treated using it.

Extended adjuvant strategies
Neither of the included studies that evaluated extended adjuvant strategies reported DFS as defined in this review.

Breast cancer recurrence
Summary statistics for breast cancer recurrence (censoring death without breast cancer) are presented for all studies (where available) in *Table 16*.

Primary adjuvant strategies
The 60-month primary adjuvant anastrozole strategy (ATAC;[69] median follow-up 68 months; data from letter in journal) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.79, 95% CI 0.70 to 0.90, $p = 0.0005$). In the tamoxifen group, 16.1% of participants relapsed compared with 13.0% in the anastrozole group: an extra 3.1% of participants receiving anastrozole benefited from the treatment. To prevent recurrence in one extra woman over 68 months, 32 women would have to be treated using anastrozole. The trialists found that the difference in disease recurrence was significant at the 5% level when they analysed only women whose disease had been hormone receptor-positive (HR = 0.74, 95% CI 0.64 to 0.87, $p = 0.0002$). In the tamoxifen group, 14.2% of women relapsed compared with 10.8% in the anastrozole group: an extra 5.2% of participants receiving anastrozole benefited from the treatment. To prevent recurrence in one extra hormone receptor-positive woman over 68 months, 19 women would have to be treated using anastrozole.

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from conference presentation) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.72, 95% CI 0.61 to 0.88, $p < 0.001$). In the tamoxifen group 7.7% of participants had a recurrence compared with 5.6% in the letrozole group: an extra 2.1% (0.8 to 3.4%) of participants benefited from receiving letrozole. For one extra woman to be recurrence-free over 26 months, 48 women would have to be treated using letrozole.

Switching strategies
One study evaluating a 36-month anastrozole switching strategy (GABG;[73] median follow-up 28 months; data from full journal article) demonstrated a difference in disease recurrence that was significant at the 5% level (HR = 0.59, 95% CI 0.44 to 0.81, $p = 0.0008$). In the tamoxifen group, 7.0% of participants had a recurrence compared with 4.2% in the anastrozole group: an extra 2.7% (0.5 to 4.9%) of participants receiving anastrozole benefited from the treatment. For every recurrence to be prevented over 28 months, 37 women would have to be treated using anastrozole.

Another study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) demonstrated a difference in recurrence but it remains unclear as to whether it was significant at the 5% level. In the tamoxifen group, 15.1% of participants had a recurrence compared with 5.8% in the anastrozole group: recurrence was prevented in an additional 9.3% of participants receiving anastrozole. For every recurrence prevented over 24–36 months, 11 women would have to be treated using anastrozole.

The 24–36-month anastrozole switching strategy (Jonat meta-analysis; median follow-up 30 months; data from conference presentation[75]) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.55, 95% CI not reported, $p < 0.0001$). In the tamoxifen group, 8.0% of participants had a recurrence compared with 4.6% in the anastrozole group: recurrence was prevented in an additional 3.4% of participants receiving anastrozole. For every recurrence prevented over 24–36 months, 30 women would have to be treated using anastrozole.

The 24–36-month exemestane switching strategy (IES; median follow-up 37 months; data from conference presentation[89]) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.70, 95% CI 0.58 to 0.83, $p = 0.00005$). In the tamoxifen group, 12.2% of participants had a recurrence compared with 8.7% in the exemestane group: recurrence was prevented in an additional 3.5% of participants receiving exemestane. For disease recurrence to be prevented in one additional woman over 36 months, 29 women would have to be treated using exemestane.

Planned sequence strategy
The 60-month planned sequence strategy (ABCSG-8; median follow-up 55 months; data

TABLE 16 *Breast cancer recurrence*

Trial	Strategy (months)	Follow-up (months)	No. followed up		Any breast cancer event[a]				HR (95% CI)	ARR (95% CI)	NNTB (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC	60	68	3092	3094	402	13.0	498	16.1	0.79 (0.70 to 0.90)	0.031 (0.005 to 0.057)	32.32 (17.51 to 208.63)
ATAC hormone receptor-positive	60	68	2618	2598	282	10.8	370	14.2	0.74 (0.64 to 0.87)	0.052 (0.028 to 0.079)	18.78 (12.72 to 35.89)
BIG 1-98	60	26	4003	4007	228	5.7	310	7.7	0.72 (0.61 to 0.88)	0.020 (not estimable)	47.53 (33.97 to 111.63)
Switching strategies											
GABG	36	28	1602	1597	68	4.2	111	7.0	0.59 (0.44 to 0.81)	0.027 (0.005-0.049)	36.96 (20.33 to 202.73)
GABG ER+/PR+	36	28	1272	1247	NR	NR	NR	NR	0.66 (0.46 to 0.93)	Not estimable	Not estimable
GABG ER+/PR–	36	28	283	281	NR	NR	NR	NR	0.42 (0.19 to 0.92)	Not estimable	Not estimable
GABG node-positive	36	28	416	417	NR	NR	NR	NR	0.67 (0.44 to 1.02)	Not estimable	Not estimable
GABG node-negative	36	28	1201	1188	NR	NR	NR	NR	0.54 (0.35 to 0.84)	Not estimable	Not estimable
ITA	24–36	36	223	225	13	5.8	34	15.1	NR	0.093 (not estimable)	10.77 (not estimable)
Jonat meta-analysis	24–36	30	2009	1997	92	4.6	159	8.0	0.55 (NR)	0.034 (not estimable)	29.56 (not estimable)
IES	24–36	37	2352	2372	205	8.7	290	12.2	0.70 (0.58 to 0.83)	0.035 (not estimable)	28.56 (20.24 to 50.82)
Planned sequence strategy											
ABCSG-8	60	55	1297	1282	79	6.1	101	7.9	0.76 (NR)	0.018 (not estimable)	55.95 (not estimable)
Extended adjuvant											
MA-17[87]	60	30	2583	2587	92	3.6	155	6.0	0.58 (0.45 to 0.76)	0.024 (0.007 to 0.041)	41.7 (24.35 to 144.34)
MA-17 node-positive	60	30	1171	1189	NR	NR	NR	NR	0.61 (0.45 to 0.84)	Not estimable	Not estimable
MA-17 node-negative	60	30	1292	1276	NR	NR	NR	NR	0.45 (0.27 to 0.73)	Not estimable	Not estimable
ABCSG 6a	36	60	387	469	30	7.8	56	11.9	0.64 (0.41 to 0.99)	0.042 (not estimable)	24.24 (14.58 to 892.51)

[a] Any loco-regional, distant or contralateral first event (not death without breast cancer).

from conference presentation)[77] resulted in a difference in disease recurrence that was not significant at the 5% level (HR = 0.76, 95% CI not reported; $p = 0.0683$). In the tamoxifen group, 7.9% of participants had a recurrence compared with 6.1% in the tamoxifen–anastrozole sequence group: recurrence was prevented in an additional 1.8% of participants in the sequential treatment group. For disease recurrence to be prevented in one additional woman over 55 months, 56 women would have to be treated using the treatment sequence. Note that, due to double counting of some events, usable data were not available for any other outcome in this study.

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.58, 95% CI 0.45 to 0.76, p not reported). In the placebo group, 6.0% of participants had a recurrence versus 3.6% in the letrozole group: an extra 2.4% (0.7 to 4.1%) of participants remained disease free as a result of receiving letrozole treatment. For each additional recurrence to be prevented over 30 months, 48 women would have to be treated using letrozole.

The 36-month extended adjuvant anastrozole strategy (ABCSG-6a;[79] median follow-up 60 months; data from conference abstract) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.64, 95% CI 0.41 to 0.99, $p = 0.047$). In the placebo group, 11.9% of participants had a recurrence versus 7.8% in the anastrozole group: an extra 4.2% (95% CI not estimable) of participants remained disease free as a result of receiving anastrozole treatment. For each additional recurrence to be prevented over 60 months, 24 women would have to be treated using anastrozole.

Loco-regional recurrence

Summary statistics for LRR are presented for all studies (where available) in *Table 17*.

Primary adjuvant strategies

At the most recent follow-up, LRR was not reported for the 60-month primary adjuvant anastrozole strategy (ATAC[69,70]). It is unclear whether the difference in LRR was conventionally significant at either the 33-month (data from full journal article[67]) or the 47-month (data from conference presentation[91]) follow-ups. At the 47-month follow-up, 2.7% of those in the anastrozole group experienced an LRR compared with 3.2% of those in the tamoxifen group: after rounding, an extra 0.6% of participants benefited from receiving anastrozole. For every LRR to be prevented over 47 months, 181 women would have to be treated using anastrozole.

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from conference presentation) reported only rates. In the tamoxifen group 1.2% of participants had an LRR compared with 0.8% in the letrozole group: an extra 0.4% (95% CIs not estimable) of participants benefited from receiving letrozole. For every LRR to be prevented over 26 months, 250 women would have to be treated using letrozole.

Switching strategies

It is not clear whether the study evaluating a 36-month anastrozole switching strategy (GABG[73]) demonstrated a difference in LRR which was significant at the 5% level (HR not reported). In the tamoxifen group, 1.5% of participants had an LRR compared with 1.1% in the anastrozole group: an extra 0.4% (95% CI not estimable) of participants receiving anastrozole benefited from the treatment. For every LRR to be prevented over 28 months, 226 women would have to be treated using anastrozole.

Another study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36-months; data from full journal article) demonstrated a difference in recurrence which was significant at the 5% level (HR = 0.15, 95% CI 0.03–0.65, $p = 0.049$). In the tamoxifen group 5.8% of participants had a recurrence compared with 0.9% in the anastrozole group: an extra 4.9% (95% CI not estimable) of participants receiving anastrozole benefited from the treatment. For every LRR to be prevented over 36 months, 20 women would have to be treated using anastrozole.

The 24–36-month exemestane switching strategy (IES; median follow-up 37 months; data from conference presentation) resulted in a difference in LRR that was not significant at the 5% level (HR not reported). In the tamoxifen group, 2.4% of participants had an event compared with 1.8% in the exemestane group: LRR was prevented in an additional 0.5% of participants receiving exemestane. For LRR to be prevented in one additional woman over 37 months, 182 women would have to be treated using exemestane.

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months;

data from full journal article) resulted in a difference in disease recurrence that was not significant at the 5% level (HR not reported). In the placebo group, 1.3% of participants had a recurrence versus 0.7% in the letrozole group: LRR was prevented in an additional 0.6% (–0.2 to 1.4%) of participants receiving letrozole treatment. For each additional LRR to be prevented over 30 months, 173 women would have to be treated using letrozole.

At the most recent follow-up, LRR was not reported by the study evaluating a 36-month extended adjuvant anastrozole strategy (ABCSG-6a[79]).

Distant recurrence

Summary statistics for DR are presented for all studies (where available) in *Table 18*.

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC; median follow-up 68 months; data from letter in journal[69] and conference presentation[70]) resulted in a difference in DR that was significant at the 5% level (HR = 0.86, 95% CI 0.74 to 0.99, $p = 0.04$). In the tamoxifen group, 12.1% of participants experienced DR as a first event, compared with 10.5% in the anastrozole group: an extra 1.6% of participants receiving anastrozole benefited from the treatment. To prevent DR in one extra woman over 68 months, 61 women would have to be treated using anastrozole. The trialists found that the difference in DFS was not significant at the 5% level when they analysed only women whose disease had been hormone receptor-positive (HR = 0.84, 95% CI 0.70 to 1.00, $p = 0.06$). In the tamoxifen group, 10.2% of participants experienced distant recurrence as a first event, compared with 8.6% in the anastrozole group: an extra 1.6% of hormone receptor-positive participants receiving anastrozole benefited from the treatment. To prevent DR in one extra hormone receptor-positive woman over 68 months, 64 women would have to be treated using anastrozole.

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from conference presentation) reported that the difference in DR was significant at the 5% level (HR = 0.73, 95% CI 0.60 to 0.88, $p = 0.001$). In the tamoxifen group, 5.8% of participants had an event compared with 4.4% in the letrozole group: an extra 1.4% (95% CI not estimable) of participants benefited from receiving letrozole. For one extra woman to be DR free over 26 months, 71 women would have to be treated using letrozole.

Switching strategies

One study evaluating a 36-month anastrozole switching strategy (GABG;[73] median follow-up 28 months; data from full journal article) demonstrated a difference in DR that was significant at the 5% level (HR = 0.54, 95% CI 0.37 to 0.80, $p = 0.0016$). In the tamoxifen group, 4.4% of participants had an event, compared with 2.4% in the anastrozole group: an extra 2.0% of participants receiving anastrozole benefited from the treatment. For every DR to be prevented over 28 months, 50 women would have to be treated using anastrozole.

Another study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) demonstrated a difference in DR which was not significant at the 5% level (HR = 0.49, 95% CI 0.22 to 1.05, $p = 0.06$). In the tamoxifen group, 8.4% of participants had a recurrence compared with 4.5% in the anastrozole group: rounding up, DR was prevented in an additional 4.0% of participants receiving anastrozole. For every recurrence prevented over 24–36 months, 25 women would have to be treated using anastrozole.

The 24–36-month anastrozole switching strategy (Jonat meta-analysis; median follow-up 30 months; data from conference presentation[75]) resulted in a difference in DR that was significant at the 5% level (HR = 0.61, 95% CI not reported, $p = 0.0015$). In the tamoxifen group, 5.1% of participants experienced a DR compared with 2.9% in the anastrozole group: DR was prevented in an additional 2.2% of participants receiving anastrozole. For every recurrence prevented over 24–36 months, 46 women would have to be treated using anastrozole.

At 31-months, the 24–36-month exemestane switching strategy (IES; data from full journal article[76]) had resulted in a difference in DR that was significant at the 5% level (HR = 0.66, 95% CI 0.52 to 0.83, $p = 0.0004$). HRs were not reported at the most recent follow-up (median 37 months; data from conference presentation[89]), although event rates were available. In the tamoxifen group, 8.8% of participants had experienced a DR event compared with 6.4% in the exemestane group: DR was prevented in an additional 2.5% of participants receiving exemestane. For DR to be prevented in one additional woman over 31 months, 42 women would have to be treated using exemestane.

TABLE 17 *Loco-regional recurrence*

Trial	Strategy (months)	Follow-up (months)	No. followed up		1st local event				HR (95% CI)	ARR (95% CI)	NNT (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC	60	47	3125	3116	84	2.69	101	3.24	NR	0.006 (not estimable)	180.72 (not estimable)
BIG 1-98	60	26	4003	4007	34	0.85	49	1.22	NR	0.004 (not estimable)	267.74 (not estimable)
Switching strategies											
GABG	36	28	1602	1597	17	1.1	24	1.5	NR	0.004 (not estimable)	226.43 (not estimable)
ITA	24–36	36	223	225	2	0.9	13	5.8	0.15 (0.03 to 0.65)	0.049 (not estimable)	20.45 (17.86 to 50.42)
Jonat meta-analysis	24–36	30	2009	1997	19	0.95	35	1.8	NR	0.008 (not estimable)	123.93 (not estimable)
IES	24–36	37	2352	2372	43	1.8	56	2.4	NR	0.005 (not estimable)	182.46 (not estimable)
Extended adjuvant											
MA-17	60	30	2583	2587	18	0.7	33	1.3	NR	0.006 (not estimable)	172.79 (not estimable)
ABCSG 6a	36	60	387	469	10	2.6	15	3.2	NR	0.006 (not estimable)	162.78 (not estimable)

TABLE 18 *Distant recurrence*[a]

Trial	Strategy (months)	Follow-up (months)	No. followed up		1st distant event (1)				HR (95% CI)	ARR (95% CI)	NNT (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC	60	68	3092	3094	324	10.5	375	12.1	0.86 (0.74 to 0.99)	0.016 (–0.007 to 0.040)	60.92 (25.01 to ∞)
ATAC hormone receptor-positive	60	68	2618	2598	226	8.6	265	10.2	0.84 (0.70 to 1.00)	0.016 (–0.010 to 0.042)	63.79 (23.93 to ∞)
BIG 1-98	60	26	4003	4007	177	4.4	232	5.8	0.73 (0.60 to 0.88)	0.014 (not estimable)	65.39 (43.96 to 147.78)
Switching strategies											
GABG	36	28	1602	1597	39	2.4	71	4.4	0.54 (0.37 to 0.80)[b]	0.020 (0.002 to 0.038)	49.72 (26.47 to 408.22)
ITA	24–36	36	223	225	10	4.5	19	8.4	0.49 (0.22 to 1.05)[c]	0.040 (not estimable)	23.73 (15.33 to ∞)
Jonat meta-analysis	24–36	30	2009	1997	59	2.9	102	5.1	0.61 (NR)	0.022 (not estimable)	46.06 (not estimable)
IES	24–36	37	2352	2372	150	6.4	208	8.8	NR	0.025 (not estimable)	41.26 (not estimable)
Extended adjuvant											
MA-17	60	30	2583	2587	57	2.2	94	3.6	0.60 (0.43-0.84)[b]	0.014 (0.001 to 0.028)	70.09 (35.89 to 1489.39)
ABCSG 6a	36	60	387	469	16	4.1	35	7.5	NR	0.033 (not estimable)	30.05 (not estimable)

[a] Includes simultaneous identification of LRR and DR except where stated.
[b] DR as a first event only.
[c] Unclear as to whether figures include DR as a first event only or simultaneous identification of local and distant events.

Planned sequence strategy
The 60-month planned sequence strategy (ABCSG-8; median follow-up 55 months; data from conference presentation) recorded an outcome called "Distant recurrence-free survival". This outcome is not reported here as there is not enough information on how the outcome was defined.

Extended adjuvant strategies
The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) resulted in a difference in DR that was significant at the 5% level (HR = 0.60, 95% CI 0.43 to 0.84, $p = 0.002$). In the placebo group, 3.6% of participants had an event versus 2.2% in the letrozole group: LRR was prevented in an additional 1.4% of participants receiving letrozole treatment. For each additional DR to be prevented over 30 months, 30 women would have to be treated using letrozole.

The 36-month extended adjuvant anastrozole strategy (ABCSG-6a;[79] median follow-up 60 months; data from conference abstract) resulted in a difference in disease recurrence that was significant at the 5% level (HR = 0.64, 95% CI 0.41 to 0.99, $p = 0.047$). In the placebo group, 7.5% of participants had a recurrence versus 4.1% in the anastrozole group: an extra 3.3% of participants remained disease free as a result of receiving anastrozole treatment. For each additional recurrence to be prevented over 60 months, 30 women would have to be treated using anastrozole.

Contralateral breast cancer
Summary statistics for the occurrence of contralateral breast cancer are presented for all studies (where available) in *Table 19*.

Primary adjuvant strategies
The 60-month primary adjuvant anastrozole strategy (ATAC; median follow-up 68 months; data from letter in journal[69] and conference presentation[70]) resulted in a difference in the rate of contralateral breast cancers that was significant at the 5% level (odds ratio 0.58, 95% CI 0.38 to 0.88, $p = 0.01$). In the tamoxifen group, 1.9% of participants developed cancer in the contralateral breast compared with 1.1% in the anastrozole group: an extra 0.8% of participants receiving anastrozole benefited from the treatment. For contralateral breast cancer to be prevented in one extra woman over 68 months, 126 women would have to be treated using anastrozole. The difference in the hormone receptor-positive population was also significant at the 5% level (odds ratio 0.47, 95% CI 0.29 to 0.75, $p = 0.001$). In the tamoxifen group, 2.0% of participants developed cancer in the contralateral breast compared with 1.9% in the anastrozole group: an extra 1.0% of participants receiving anastrozole benefited from the treatment. For contralateral breast cancer to be prevented in one extra hormone receptor-positive woman over 68 months, 93 such women would have to be treated using anastrozole.

It is not clear whether the 60-month primary adjuvant letrozole strategy (BIG 1-98; median follow-up 26 months; data from full journal article[71]) resulted in a difference in the rate of contralateral breast cancers which was significant at the 5% level (HR not reported). In the tamoxifen group, 0.7% of participants had an event compared with 0.4% in the letrozole group: an extra 0.3% (95% CI not estimable) of participants benefited from receiving letrozole. For contralateral breast cancer to be prevented in one extra woman over 26 months, 333 women would have to be treated using letrozole.

Switching strategies
It is not clear whether the study evaluating a 36-month anastrozole switching strategy (GABG;[73] median follow-up 28 months; data from full journal article) demonstrated a difference in the rate of contralateral breast cancers that was significant at the 5% level (HR not reported). In the tamoxifen group, 1.0% of participants had an event compared with 0.7% in the anastrozole group: an extra 0.3% of participants receiving anastrozole benefited from the treatment. To prevent contralateral breast cancer in one additional woman over 28 months, 396 women would have to be treated using anastrozole.

It is not clear whether the study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) demonstrated a difference in the rate of contralateral breast cancer which was significant at the 5% level (HR not reported). In the tamoxifen group, 0.9% of participants developed a contralateral compared with 0.4% in the anastrozole group: rounding down, contralateral cancer was prevented in an additional 4.0% of participants receiving anastrozole. For every contralateral cancer prevented over 24–36 months, 227 women would have to be treated using anastrozole.

The 24–36-month exemestane switching strategy (IES; median follow-up 37 months; data from

TABLE 19 *Contralateral breast cancer*

Trial	Strategy (months)	Follow-up (months)	No. followed up		1st contralateral event				HR (95% CI)	ARR (95% CI)	NNT (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC	60	68	3092	3094	35	1.1	59	1.9	0.58 (0.38 to 0.88)[a]	0.008 (not estimable)	125.56 (84.89 to 440.73)
ATAC hormone receptor-positive	60	68	2618	2598	26	1.0	53	2.0	0.47 (0.29 to 0.75)	0.010 (not estimable)	92.94 (69.25 to 197.60)
BIG 1-98	60	26	4003	4007	16	0.4	27	0.7	NR	0.003 (not estimable)	333.33 (not estimable)
Switching strategies											
GABG	36	28	1602	1597	12	0.7	16	1.0	NR	0.003 (not estimable)	395.55 (not estimable)
ITA	24–36	36	223	225	1	0.4	2	0.9	NR	0.004 (not estimable)	227.04 (not estimable)
Jonat meta-analysis	24–36	30	2009	1997	14	0.7	22	1.1	NR	0.006 (not estimable)	169.08 (not estimable)
IES	24–36	37	2352	2372	12	0.5	26	1.1	0.50 (0.26 to 0.97)	0.006 (not estimable)	172.58 (128.70 to 366.44)
Extended adjuvant											
MA-17[87]	60	30	2583	2587	17	0.7	28	1.1	0.63 (0.18 to 2.21)	0.004 (–0.003 to 0.012)	235.75 (85.27 to ∞)
ABCSG 6a	36	60	387	469	6	1.6	10	2.1	NR	0.006 (not estimable)	171.88 (not estimable)

[a] In the ATAC study, an odds ratio, rather than a hazard ratio, was reported in the publication.

conference presentation) resulted in a difference in the rate of contralateral breast cancer that was significant at the 5% level (HR = 0.50, 95% CI 0.26 to 0.97, $p = 0.04$). In the tamoxifen group, 1.1% of participants had an event compared with 0.5% in the exemestane group: contralateral breast cancer was prevented in an additional 0.6% of participants receiving exemestane. For contralateral cancer to be prevented in one additional woman over 37 months, 173 women would have to be treated using exemestane.

Extended adjuvant strategies
The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) resulted in a difference in DR that was not significant at the 5% level (HR = 0.63, 95% CI 0.18 to 2.21, p not reported). In the placebo group, 1.1% of participants had an event versus 0.7% in the letrozole group: contralateral breast cancer was prevented in an additional 0.4% of participants receiving letrozole treatment. For each additional contralateral cancer to be prevented over 30 months, 236 women would have to be treated using letrozole.

It is unclear whether the 36-month extended adjuvant anastrozole strategy (ABCSG-6a;[79] median follow-up 60 months; data from conference abstract) resulted in a difference in the rate of contralateral breast cancers that was significant at the 5% level (HR not reported). In the placebo group, 2.1% of participants developed a cancer in the contralateral breast versus 1.6% in the anastrozole group: an extra 3.3% of participants remained disease free as a result of receiving anastrozole treatment. For each additional contralateral cancer to be prevented over 60 months, 172 women would have to be treated using anastrozole.

Adverse events: bone health
Summary statistics for the occurrence of fractures and the development of osteoporosis are presented for all studies (where available) in *Table 20*.

Primary adjuvant strategies
At 33 months, the relative risk of a fracture in the 60-month primary adjuvant anastrozole strategy was already 1.59 (95% CI not reported, $p < 0.0001$), with 115 (3.7%) women in the tamoxifen arm and 183 (5.9%) in the anastrozole arm experiencing a fracture (ATAC; data from full journal article[67]). By 68 months, 7.7% of participants in the tamoxifen group had experienced a fracture compared with 11.0% in the anastrozole group: an extra 3.3% of participants receiving anastrozole were harmed by the treatment. One extra woman would experience a fracture over 68 months for every 30 women treated using anastrozole. The odds ratio for hip fracture, the subcategory most frequently associated with mortality, was not significant (1.20, 95% CI 0.74 to 1.93, $p = 0.5$).[69] In the tamoxifen group, 1.0% of participants experienced a hip fracture compared with 1.2% in the anastrozole group: an extra 0.2% of participants receiving anastrozole experienced a hip fracture. One extra woman would experience a hip fracture over 68 months for every 514 women treated with anastrozole.

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from full journal article) resulted in a difference in the fracture rate that was significant at the 5% level (HR not reported, $p < 0.001$) favouring tamoxifen. In the tamoxifen group, 4.0% of participants experienced a fracture compared with 5.7% in the letrozole group: an extra 1.7% of participants receiving letrozole were harmed by the treatment. One extra woman would experience a fracture over 26 months for every 60 women treated using letrozole. The HR for hip fracture was not reported.

Switching strategies
The 36-month anastrozole switching strategy (GABG[73]) resulted in a difference in the fracture rate that was significant at the 5% level (HR not reported; $p = 0.015$). In the tamoxifen group, 1.0% of participants experienced a fracture compared with 2.1% in the anastrozole group: an extra 1.1% of participants receiving anastrozole were harmed by the treatment. One extra woman would experience a fracture over 36 months for every 90 women treated using anastrozole. The hip fracture rate was not reported.

The study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) demonstrated no difference in the fracture rate: 0.9% of women in each arm experienced a fracture (HR not reported). The hip fracture rate was not reported.

It is not clear whether the 24–36-month exemestane switching strategy (IES;[76] median follow-up 31 months; data from full journal article) resulted in a difference in fracture rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 2.3% of participants

TABLE 20 *Adverse events: bone health*

Trial	Strategy (months)	Follow-up (months)	No. followed up		All fractures				Hip		Wrist		Spine		Other		Osteoporosis			
			AI	Control	AI	%	Control	%	AI	Control	AI	Control	AI	Control	AI	Control	AI	%	Control	%
Single intervention strategies																				
ATAC[69]	60	68	3092	3094	340	11.0	237	7.7	37	31	72	63	45	27	220	142	NR	NR	NR	NR
BIG 1-98[71]	60	26	3975	3988	225	5.7	159	4.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Switching strategies																				
GABG[73]	36	28	1602	1597	34	2.1	16	1.0	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
ITA[74]	24–36	36	223	225	2	0.9	2	0.9	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
IES[76]	24–36	31	2309	2332	72	3.1	53	2.3	NR	NR	NR	NR	NR	NR	NR	NR	171	7.4	134	5.7
Extended adjuvant																				
MA-17[87]	60	30	2572	2577	137	5.3	119	4.6	5	8	33	22	15	10	102	88	209	8.1	155	6.0
ABCSG 6a[79]	36	60	387	469	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR

experienced a fracture compared with 3.1% in the exemestane group: an extra 0.8% of participants receiving exemestane were harmed by the treatment. One extra woman would experience a fracture over 36 months for every 118 women treated using exemestane. The hip fracture rate was not reported.

Fracture and osteoporosis rates were not reported by the Jonat meta-analysis.[75]

Extended adjuvant strategies
The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) did not result in a difference in the fracture rate that was significant at the 5% level (HR not reported, $p = 0.25$). In the placebo group, 4.6% of participants experienced a fracture compared with 5.3% in the letrozole group: an extra 0.7% of participants receiving letrozole were harmed by the treatment. One extra woman would experience a fracture over 30 months for every 141 women treated using letrozole. The hip fracture rates were 0.003% in the placebo group and 0.002% in the letrozole group. The rate of new osteoporosis was highly significant at a median follow-up of 30 months[87] (letrozole 8.1%; placebo 6.0%; $p = 0.003$), whereas at the previous follow-up (median 2.4 years, or 28.8 months)[92] it had been a non-significant trend (letrozole 5.8%; placebo 4.5%; $p = 0.07$).

Fracture rates were not reported by the study evaluating a 36-month extended adjuvant anastrozole strategy (ABCSG-6a).[79]

Adverse events: cardiovascular events
Cardiovascular events could not be tabulated due to radically differing event definitions from trial to trial in the published material. The review team were unsuccessful in their attempts to access standardised data from pivotal trials via the manufacturers.

Primary adjuvant strategies
The 60-month primary adjuvant anastrozole strategy (ATAC;[69] median follow-up 68 months; data from letter in journal) reported "ischaemic cardiovascular disease". This is commonplace in reporting cardiovascular disease (CVD) outcomes, giving a better chance of finding significant results, but does not separate life-threatening or disabling [Common Terminology Criteria for Adverse Events (CTCAE) Grade 4] events, such as myocardial infarction, from severe (CTCAE Grade 3) events such as angina. There was no significant difference between the arms [anastrozole, 127/3092 (4.1%); tamoxifen, 104/3094 (3.4%); HR 1.23, 95% CI 0.95 to 1.60, $p = 0.1$]. ATAC also reported "ischaemic cerebrovascular events", which does not separate Grade 4 events, such as stroke, from Grade 3 conditions, such as TIA: the results found that there were significantly more events in the tamoxifen arm (anastrozole, 62/3092; tamoxifen, 88/3094; HR 0.70, 95% CI 0.50 to 0.97, $p = 0.03$). They also reported "venous thromboembolic events" (anastrozole, 87/3092; tamoxifen, 140/3094; HR 0.61, 95% CI 0.47 to 0.80, $p = 0.0004$) and deep venous thromboembolic events (anastrozole, 48/3092; tamoxifen, 74/3094; HR 0.64, 95% CI 0.45 to 0.93, $p = 0.02$).

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from full journal article) reported differences in the number of thromboembolic events that were significant at the 5% level [letrozole, 61/3975 (1.5%); tamoxifen, 140/3988 (3.5%); HR not reported, $p < 0.001$], favouring letrozole. There were no significant differences in all cardiac events,[71] but there was a significant difference in Grade 3–5 cardiac events [letrozole, 85/3975 (2.1%); tamoxifen, 44/3988 (1.1%); HR not reported, $p = 0.0003$[72]], favouring tamoxifen. There was no significant difference in ischaemic heart disease, but there was a significant difference in cardiac failure [letrozole, 31/3975 (0.8%); tamoxifen, 14/3988 (0.4%); $p = 0.01$] and "other cardiac events" [letrozole, 19/3975 (0.5%); tamoxifen, 8/3988 (0.2%); $p = 0.04$]. There were more deaths without recurrence in the letrozole arm (55 versus 38 in the tamoxifen arm), including three times as many from cardiac events (16 versus five).[71] There was no significant difference between arms in the recording of cardiovascular accident (CVA) or transient ischaemic attack (TIA) events.

Switching strategies
One study evaluating a 36-month anastrozole switching strategy (GABG;[73] median follow-up 28 months; data from full journal article) reported no significant difference in myocardial infarction or "embolism". There was a significant difference in thromboses favouring anastrozole (not defined; anastrozole, 3/1602; tamoxifen, 12/1597, $p = 0.034$).

Another study evaluating a 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) reported no significant difference between treatments in terms of "cardiovascular disease" (not defined) or "venous disorders" (not defined).

No data were available for this outcome from the Jonat meta-analysis.[75]

The 24–36-month exemestane switching strategy (IES;[76] median follow-up 31 months; data from full journal article) reported "cardiovascular disease other than myocardial infarction". It also reported separately "thromboembolic disease" and "thromboembolic events", but did not define what these categories included. Thromboembolic disease was significantly more frequent in the tamoxifen arm (exemestane, 24/2309; tamoxifen, 45/2332; $p = 0.003$). Thromboembolic events were reported as significantly more frequent in the tamoxifen arm (exemestane, 30/2309; tamoxifen, 55/2332; $p = 0.007$). Deaths from vascular (exemestane, 12/2362; tamoxifen, 6/2380), cardiac (exemestane, 10/2362; tamoxifen, 8/2380), thrombotic (exemestane, 1/2362; tamoxifen, 1/2380) or pulmonary (exemestane, 0/2362; tamoxifen, 1/2380) causes were recorded separately (HRs and *p*-values not reported). In the updated analysis (median follow-up 37 months; data from conference presentation[89]) there were twice as many deaths from vascular causes in women in the exemestane arm (0.6% versus 0.3%) and twice as many myocardial infarctions (0.9% versus 0.4%, $p = 0.02$, but non-significant, presumably due to multiple significance testing). Conversely, there was more thromboembolic disease in the tamoxifen arm (3.3%) than in the exemestane arm (1.9%), and this difference was significant at the 5% level ($p < 0.001$).

Extended adjuvant strategies

The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) reported that cardiovascular "events" (in the text) or "disease" (in the paper's Table 4) were observed in 149 (5.8%) and 144 (5.6%) of patients in the letrozole and placebo arms, respectively ($p = 0.76$). This includes potentially fatal events, such as myocardial infarction and stroke, and also non-fatal conditions such as angina and TIA. Thromboembolic events were reported as a subcategory of CVD with pulmonary embolism, the potentially fatal event, not separated out from other non-fatal conditions. There were five cardiovascular-related deaths and two fatal strokes in women receiving letrozole and five cardiovascular-related deaths and one fatal stroke in women receiving placebo.

No data were available for this outcome from the study evaluating the 36-month extended adjuvant anastrozole strategy.

Adverse events: gynaecological

Summary statistics for the occurrence of gynaecological events are presented for all studies (where available) in *Table 21*.

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC;[69] median follow-up 68 months; data from letter in journal) resulted in a difference in the endometrial cancer rate that was significant at the 5% level (HR not reported; $p = 0.02$). In the tamoxifen group, 0.8% of participants developed endometrial cancer compared with 0.2% in the anastrozole group: after rounding, an extra 0.5% of participants receiving anastrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 68 months, 187 women would have to be treated using anastrozole. In the tamoxifen group, 10.2% of participants experienced a vaginal bleeding compared with 5.4% in the anastrozole group: an extra 4.8% of participants receiving anastrozole benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 68 months, 21 women would have to be treated with anastrozole. The ATAC trialists also observed a fourfold increase in hysterectomy rates (anastrozole, 1.3%; tamoxifen, 5.1%; $p < 0.0001$).

The 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from full journal article) did not result in a difference in the rate of "invasive endometrial cancers" (the trial's outcome) that was significant at the 5% level (HR not reported, $p = 0.18$). In the tamoxifen group, 0.3% of participants developed endometrial cancer compared with 0.1% in the letrozole group: an extra 0.2% of participants receiving letrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 26 months, 500 women would have to be treated using letrozole. In the tamoxifen group, 6.6% of participants experienced a vaginal bleeding compared with 3.3% in the letrozole group: an extra 3.3% of participants receiving letrozole benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 26 months, 30 women would have to be treated with letrozole.

Switching strategies

It is not clear whether the 36-month anastrozole switching strategy (GABG[73]) resulted in a difference in the endometrial cancer rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 0.4% of participants developed endometrial cancer compared with

TABLE 21 *Adverse events: gynaecological*

Trial	Strategy (months)	Follow-up (months)	No followed up		Endometrial cancers				HR (95% CI)	ARR (95% CI)	NNTB (95% CI)	Vaginal bleeding			
			AI	Control	AI		Control					AI		Control	
					n	%	*n*	%				*n*	%	*n*	%
Primary adjuvant strategies															
ATAC[69]	60	68	2229	2236	5	0.2	17	0.8	NR	0.005 (not estimable)	186.58 (not estimable)	167	5.4	317	10.2
BIG 1-98[71]	60	26	3089	3157	6	0.1	15	0.3	NR	0.002 (not estimable)	500.00 (not estimable)	NR	3.3	NR	6.6
Switching strategies															
GABG[73]	36	28	1602	1597	1	0.1	7	0.4	NR	0.004 (not estimable)	266.03 (not estimable)	198	17.7	195	17.5
ITA[74]	24–36	36	223	225	NR	NR	NR	NR	NR	Not estimable	Not estimable	NR	NR	NR	NR
IES[76]	24–36	31	2362	2380	5	0.2	11	0.5	NR	0.003 (not estimable)	399.20 (not estimable)	93	4.0	129	5.5
Extended adjuvant															
MA-17[87]	60	30	2572	2577	4	0.2	11	0.4	NR	0.003 (not estimable)	368.55 (not estimable)	145	5.6	196	7.6
ABCSG-6a[79]	36	60	387	469	NR	NR	NR	NR	NR	Not estimable	Not estimable	NR	NR	NR	NR

TABLE 22 *Adverse events: hypercholesterolaemia*

Trial	Strategy (months)	Follow-up (months)	No. followed up		Hypercholesterolaemia				HR (95% CI)	ARR (95% CI)	NNT (95% CI)
			AI	Control	AI		Control				
					n	%	*n*	%			
Primary adjuvant strategies											
ATAC[69]	60	68	3092	3094	NR	NR	NR	NR	NR	Not estimable	Not estimable
BIG 1-98[72]	60	26	4003	4007	NR	43.6	NR	19.2	NR	–0.244 (not estimable)	4.10 (not estimable)
Switching strategies											
GABG[73]	36	28	1602	1597	NR	NR	NR	NR	NR	Not estimable	Not estimable
ITA[74]	24–36	36	223	225	19	8.5	6	2.67	NR	–0.059 (not estimable)	17.08 (not estimable)
IES[76]	24–36	31	2362	2380	NR	NR	NR	NR	NR	Not estimable	Not estimable
Extended adjuvant											
MA-17[87]	60	30	2572	2577	418	16.3	411	15.9	NR	–0.003 (not estimable)	329.85 (not estimable)

NNTH, number-needed-to-treat (harm).

0.1% in the anastrozole group: after rounding, an extra 0.4% of participants receiving anastrozole benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 36 months, 266 women would have to be treated using anastrozole. The GABG study analysed vaginal bleeding and discharge as one outcome: there was no significant difference between treatment arms.[73]

The study evaluating a 24–36-month anastrozole switching strategy (ITA[74]) did not report the incidence of endometrial cancer or vaginal bleeding. The Jonat meta-analysis[75] did not report the incidence of endometrial cancer or vaginal bleeding.

It is not clear whether the 24–36-month exemestane switching strategy (IES;[76] median follow-up 31 months; data from full journal article) resulted in a difference in endometrial cancer rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 0.5% of participants developed endometrial cancer compared with 0.2% in the exemestane group: after rounding, an extra 0.3% of participants receiving exemestane benefited from the treatment. For endometrial cancer to be prevented in one extra woman over 31 months, 399 women would have to be treated using exemestane. In the tamoxifen group, 5.5% of participants experienced vaginal bleeding compared with 4.0% in the exemestane group: after rounding, an extra 1.5% of participants receiving exemestane benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 31 months, 66 women would have to be treated using exemestane.

Extended adjuvant strategies

It is unclear whether the 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) resulted in a difference in the endometrial cancer rate that was significant at the 5% level (HR not reported). In the placebo group, 0.4% of participants developed endometrial cancer compared with 0.2% in the letrozole group: an extra 0.2% of participants receiving letrozole benefited from the treatment For endometrial cancer to be prevented in one extra woman over 30 months, 369 women would have to be treated using letrozole. In the placebo group, 7.6% of participants experienced a vaginal bleeding compared with 5.6% in the letrozole group: an extra 2.0% of participants receiving letrozole benefited from the treatment. For vaginal bleeding to be prevented in one extra woman over 30 months, 51 women would have to be treated with anastrozole.

Endometrial cancer and vaginal bleeding rates were not reported by the study evaluating a 36-month extended adjuvant anastrozole strategy (ABCSG-6a).[79]

Adverse events: hypercholesterolaemia

Summary statistics for the development of hypercholesterolaemia are presented for all studies (where available) in *Table 22*.

Primary adjuvant strategies

The 60-month primary adjuvant anastrozole strategy (ATAC;[69] median follow-up 68 months; data from letter in journal) did not report hypercholesterolaemia rates.

It is unclear whether the 60-month primary adjuvant letrozole strategy (BIG 1-98;[71] median follow-up 26 months; data from full journal article) resulted in a difference in the hypercholesterolaemia rate that was significant at the 5% level (HR not reported). In the tamoxifen group, 19.2% of participants developed hypercholesterolaemia compared with 43.6% in the letrozole group: an additional 24.4% of participants receiving letrozole developed hypercholesterolaemia as a result of their treatment. Over 26 months, one additional woman would develop hypercholesterolaemia for every four women treated with letrozole.

Switching strategies

The 36-month anastrozole switching strategy (GABG[73]) and the 24–36-month exemestane switching strategy (IES[76]) did not report hypercholesterolaemia rates.

It is not clear whether the 24–36-month anastrozole switching strategy (ITA;[74] median follow-up 36 months; data from full journal article) resulted in a difference in hypercholesterolaemia rates that was significant at the 5% level. In the tamoxifen group, 2.7% of participants developed hypercholesterolaemia with 8.5% in the anastrozole group: an extra 5.9% of participants developed hypercholesterolaemia as a result of their treatment. One additional woman would develop hypercholesterolaemia over 36 months for every 17 women treated using anastrozole.

The Jonat meta-analysis[75] did not report hypercholesterolaemia rates.

Extended adjuvant strategies
The 60-month extended adjuvant letrozole strategy (MA-17;[87] median follow-up 30 months; data from full journal article) did not result in a difference in the hypercholesterolaemia rate that was significant at the 5% level (HR not reported, $p = 0.79$). In the placebo group, 15.9% of participants developed hypercholesterolaemia compared with 16.3% in the letrozole group: after rounding, an extra 0.3% of participants receiving letrozole developed hypercholesterolaemia as a result of their treatment. One additional woman would develop hypercholesterolaemia over 36 months for every 330 women treated using letrozole.

Hypercholesterolaemia rates were not reported by the study evaluating a 36-month extended adjuvant anastrozole strategy (ABCSG-6a)[79].

Health-related quality of life
Only three studies have reported health-related quality of life data. The quality of these studies is critically appraised in Appendix 5.

The ATAC trial (60-month primary adjuvant strategy; follow-up for quality of life sub-protocol 24 months; full journal article[93]) recruited 1021 women (11% of those randomised in the main study) to a study subprotocol and followed them up every 3 months.[93] The investigators used two disease-specific instruments only, the Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B)[94] with an additional Endocrine Subscale (ES) questionnaire (18 items),[95] both of which are validated[95,96] and were used without modification. The primary end-point was the trial outcome index of the FACT-B questionnaire, which aggregates scores from the physical and functional well-being and the breast cancer subscales. Secondary end-points were the total ES score and the emotional well-being and social well-being subscales of the FACT-B. Response rates were "approximately 85%" for all time points. There were no significant differences in the primary or secondary end-points across treatment groups, but some small differences in side-effect profiles.

The IES trial (24–36-month switching strategy, follow-up for quality of life subprotocol 24 months; abstract only[97]) recruited 582 women (12% of those randomised in the main study) to a substudy and followed them up every 3–6 months. The investigators used two disease-specific instruments only, the FACT-B[94] and ES[95] questionnaires, both of which are validated (see above). The primary end-point was the FACT-B trial outcome index (see above). Secondary end-points included the total ES score and individual endocrine symptoms. Response rates were 85% for all time points. There were no significant differences in the primary or secondary end-points across treatment groups, except for vaginal discharge (exemestane, 1.4%; tamoxifen, 7.8%; $p = 0.002$).

The MA-17 trial (60-month extended adjuvant strategy; follow-up for quality of life subprotocol 36 months; data from full journal article[98]) recruited 3612 women (70% of those randomised in the main study) to the quality of life substudy and followed them up at 6-month (first year) or 12-month (thereafter) intervals. The investigators used one generic instrument, the Medical Outcomes Study Short Form with 36 Items General Health Survey (SF-36),[99] and one condition-specific instrument, the Menopause Specific Quality of Life (MENQOL) questionnaire.[100] Both are validated,[100–102] and were used without modification. The primary and secondary end-points were not specified. The SF-36 summarises subscales into two global scores: the physical and mental component scores (PCS and MCS). MENQOL summarises subscales into four domains: vasomotor, physical, psychosocial and sexual.

Response rates were "more than 90% for all time points". Over 36 months, there was no significant difference between treatment arms on the SF-36 summary scores; significant differences favoured placebo on physical function ($p = 0.011$), bodily pain ($p = 0.009$) and general health ($p = 0.034$) individual scales. There was a significant difference between treatment arms, favouring placebo, on the physical ($p = 0.04$) and vasomotor scales (<0.001) of the MENQOL instrument.

Discussion of results
Strength of the evidence (internal validity)
No study had a clearly inadequate approach to the generation or concealment of the allocation schedule. Blinding was only clearly inadequate in one study (ITA), but another (ABCSG-6a) also randomised women to 'no treatment' rather than placebo, which may indicate that it, too, had an open-label design. Where DFS (or some variation) is the primary end-point, as in all of the evaluated studies, differences between study arms in the frequency of, or reason (for example, drug toxicity or anxiety) for unscheduled assessments is likely to introduce bias. This potential bias can be minimised by blinding patients and investigators to the treatment assignments if feasible. Whereas blinding is often impractical in oncology trials due

to the need for toxicity-related dose modification, there is no impediment to blinding Phase III trials of hormonal therapies.

None of the prospective studies reported large numbers of withdrawals, but only three presented ITT analyses. ITT analyses guard against conscious or unconscious attempts to influence the results of the study and bias introduced when dropping out is related to the outcome. It may also better reflect the way in which treatments will perform in the wider population by ignoring adherence and inappropriate prescribing. Finally, it preserves the baseline comparability between treatment groups achieved by randomisation. The only truly acceptable rate of loss to follow-up is 0%, but this is often unrealistic. Some researchers suggest the use of a simple five-and-20 rule of thumb, with fewer than 5% loss to follow-up leading to little bias, and greater than 20% loss to follow-up posing serious threats to validity.[103]

In most cases, the proportion of participants excluded from analysis was small (less than 1%), but there are questions surrounding the validity of the primary analyses presented by the GABG combined analysis. This study broke the randomisation of its two component trials and selected only patients whose treatment was advanced (excluding 35% of those randomised to ABCSG-8 and ARNO-95). There is no evidence that the design and conduct of this study resulted in systematic error and, although concerns have been raised (see Appendix 4), it is difficult to make judgements about the effect of its design and conduct until both of its component studies, ABCSG-8 and ARNO-95, have reported individually and in full.

Applicability of the results (external validity)
There are two key concerns regarding the extent to which it is possible to generalise from the assembled dataset to the NHS population. These have to do with (1) the loss of information when the point of randomisation is not within the first year after surgery and (2) the cessation of studies before the treatment period is over because there are enough events for efficacy to be demonstrated.

Studies of unplanned switching randomise only women who are alive and disease free 2–3 years after surgery; extended adjuvant studies randomise only women who are alive and disease free 5 years after surgery. In the strict sense, only studies which randomised at zero years after surgery and contain a 5-year tamoxifen arm (ATAC and BIG 1-98) satisfy the Department of Health population remit for this technology assessment: women currently eligible for 5 years' adjuvant tamoxifen. The external validity of trials which randomise thereafter is compromised because (1) they represent different, narrower populations (only women who have experienced prior adjuvant treatment and who have not yet died or relapsed) and (2) nothing is known about the distribution of 'true' (zero years after surgery and, where given, chemotherapy) baseline characteristics for each trial population. The treatment effects of these strategies must be interpreted against the background that around 12% of women on tamoxifen in the ATAC trial died and/or relapsed in the first 3 years[67] and 21% in the first 5 years[69] (see also the section 'Prognosis', p. 4 and, in particular, *Table 4*). It is in the interests of the NHS to know what the most effective strategy is for the entire adjuvant period and the whole population: decision-makers of all types need to assess the most effective way of keeping all women alive and disease free from surgery. Trials which randomise at 2–3 years or 5 years after surgery do not serve this end, because the different point of randomisation makes it impossible to compare strategies head-to-head. At this time, there is no licence or public domain data for planned sequence (as opposed to unplanned switching) strategies. It is important for future reviewers and decision-makers to expect less impressive outcomes for planned sequences of therapy (from BIG 1-98,[90] ABCSG-8[73] and NSAS BC 03[84]) than for the unplanned switching trials reviewed in this report, because they **will** incorporate the first 2 years after surgery, when women are at the highest risk of relapse and/or death. The limited early results from ABCSG-8 confirm this (see the section 'Breast cancer recurrence', p. 33).

In three studies (GABG, IES and MA-17), event-driven analyses led to trials being stopped early for benefit and the median follow-up of each was shorter than the term of treatment. Two questions arise when studies are stopped early on the grounds of benefit: (1) whether currently significant clinical benefits would still have been significant at a later time point and (2) whether currently non-significant harms would be significant by a later time point.[104] Writing in 2003–4, after the cessation of MA-17 was reported in the *New England Journal of Medicine*,[92] some commentators feared that long-term adverse effects associated with letrozole therapy had been underestimated because of the early cessation of the study.[105–108] At this time, there were only statistically significant increases in the rates of

arthritis, myalgia and arthralgia. Since then, the developing bone health profile (see the section 'Adverse events: bone health', p. 40) suggests that this is the case, where between the 28.8-month[92] and the 30-month[87] median follow-ups, the osteoporosis rate in the letrozole arm rose 2.2% and the difference between arms went from a non-significant ($p = 0.07$) to a highly significant trend ($p = 0.003$) in favour of placebo. Unfortunately, without the blinded placebo group (who were offered a switch to letrozole when the trial was unmasked), it will be impossible to assess the potential long-term excess in cardiovascular events and fractures among women taking letrozole.[105]

In the context of the NHS population, it should be noted that, individually, none of the trials have established an advantage in terms of either all-cause mortality or quality of life. The expectation that DFS or its variants automatically translate into overall survival or quality of life is a false one, because unexpected adverse events may increase deaths from other causes and decrease quality of life in the novel treatment arm, thus obliterating the benefit in cause-specific deaths.[64,107] Although the details remain academic-in-confidence within this report, the significant difference in overall survival presented by Jonat at SABCS 2005[75] has been well publicised. As noted above, the switching strategy is the easiest for which to demonstrate benefit because of the loss of data in the first two, high-risk, years of adjuvant treatment. With tamoxifen, a meta-analysis of sufficient power did eventually demonstrate not only a survival benefit but also what is known as a 'carryover effect' – a continuing divergence of survival curves for some years after the treatment is stopped.[37] The ATAC trialists see the same phenomenon in their own most recent data,[69] which, if they are correct, would present the possibility that benefits might conceivably grow rather than be cancelled out by AEs.

An apparently minor issue is the lack of available data on (or indeed a license for) the use of AIs before tamoxifen in a planned sequence: only one ongoing trial (BIG 1-98[90]) has the potential to evaluate such a strategy. However, with the greatest hazard of recurrence in an ER-positive population being in the second and third years after surgery [see the section 'Prognosis' (p. 4) and *Table 4*], it is possible that clinicians will want to offer AIs first in a planned sequence – giving 'the best drug first' to prevent the growth of micrometastases.[109] There is also the potential that this strategy could be worse, in that "an AI may theoretically sensitise remaining breast cancer cells to the oestrogenic deleterious effects of tamoxifen" (Coleman R, University of Sheffield: personal communication, 2005). There is currently no evidence for such a strategy and it is likely to have different clinical and cost implications to those evaluated in this report.

Assessment of effectiveness

No individual study reported a significant difference in overall survival between any AI and tamoxifen (or placebo in the extended adjuvant setting), although it is worth noting that one anastrozole switching study, with a much worse prognosis population (all node-positive) than the others, demonstrated a considerably higher ARR (0.027) than the rest (all <0.01), despite being underpowered. A meta-analysis of three trials did find a significant difference in overall survival when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen (details are academic-in-confidence).

Compared with 5 years' tamoxifen, DFS (absence of disease recurrence or death from any cause) was significantly increased: in the primary adjuvant setting with anastrozole (68 months' follow-up: HR 0.87, 95% CI 0.78 to 0.97; ARR 0.024) and letrozole (26 months' follow-up: HR 0.83, 95% CI 0.73 to 0.94; ARR 0.019), and with an exemestane switching strategy (31 months' follow-up: HR 0.68, 95% CI 0.56 to 0.82; ARR 0.035). Other trials did not report this outcome.

Breast cancer recurrence (censoring death as an event) was significantly improved with: primary adjuvant anastrozole (68 months' follow-up: HR 0.79, 95% CI 0.70 to 0.90; ARR 0.031) and letrozole (26 months' follow-up: HR 0.74, 95% CI 0.64 to 0.87; ARR 0.021), anastrozole switching (28 months' follow-up: HR 0.59, 95% CI 0.44 to 0.81; ARR 0.027); extended adjuvant anastrozole (60 months' follow-up: HR 0.64, 95% CI 0.41 to 0.99; ARR 0.042) or letrozole (30 months' follow-up: HR 0.58, 95% CI 0.45 to 0.76; ARR 0.024).

The AIs and tamoxifen have different side-effect profiles, with tamoxifen responsible for small but statistically significant increases in endometrial cancer and, sometimes, thromboembolic events and stroke. AIs show a trend towards increases in osteoporosis, the statistical significance of which increases with follow-up time. The disease-specific benefits of AIs are demonstrable early on, but their harmful effects are realised more slowly, meaning that benefits may conceivably be reduced

or cancelled out with longer follow-up. The absence of tamoxifen treatment also increases the risk of hypercholesterolaemia and cardiac events in women of this age (see the section 'Current service provision', p. 5).

There was no significant difference in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies.

Chapter 4

Economic analysis

This part of the assessment focuses on the health economics of AIs in early breast cancer in comparison with standard therapies. It includes a review of existing economic evaluations of the relevant therapies, a critique of each of the industry submission economic evaluations and a detailed explanation of the methodologies and results of the independent assessment group economic model.

The following sections in this chapter present and discuss (1) the results of the systematic review of economic literature and a subsequent review of relevant economic evaluations, (2) the reviews of the three industry submissions, (3) the independent assessment group's modelling approach and (4) the results of the analysis.

Systematic review of existing economic literature

The primary objective of this review was to identify and evaluate studies exploring the cost-effectiveness of AIs in the treatment of early-stage breast cancer. The secondary objective was to evaluate methodologies used to inform our own economic evaluation.

Identification of studies

The aim of the search was to provide a comprehensive retrieval of economic evaluations of the hormonal therapies – anastrozole, letrozole and exemestane – in the treatment of early-stage breast cancer.

Sources searched

Eight electronic databases were searched, providing coverage of the biomedical and health technology assessment literature (BIOSIS, CINAHL, EMBASE, OHE HEED, HTA, MEDLINE and PreMEDLINE and NHS EED). The ASCO and ESMO conference abstracts and two current research registers (Current Controlled Trials and National Research Register) were also searched. The websites of the following organisations were also searched: AHRQ, CCOHTA, eMC, EMEA, INAHTA Clearinghouse, National Guidelines Clearinghouse, NCCHTA and SIGN. The economic assessments submitted by sponsors were identified as studies for inclusion in the review. In addition, the sponsor submissions were handsearched for further references to studies.

Keyword strategies

The keyword strategies developed in the review of clinical effectiveness were used, with the RCT methodological filter being replaced by a filter aimed at restricting search results to economic and cost-related studies. An example search strategy for the MEDLINE database is provided in Appendix 2.

Search restrictions

The same limits and restrictions used in the review of clinical effectiveness were applied with the exception of the methodological filter as described above. All searches were undertaken in June 2005.

Inclusion and exclusion strategy

Studies were selected for inclusion according to predetermined inclusion and exclusion criteria. Studies were included if they reported the cost-effectiveness of AIs in the adjuvant treatment of early-stage breast cancer. Studies which were considered to be methodologically unsound, that were not reported in sufficient detail or that did not report an estimate of cost-effectiveness (e.g. costing studies) were excluded.

Two reviewers independently screened all titles and abstracts. Disagreement was settled through discussion. Full papers were obtained for any titles/abstracts that were considered relevant or where the title/abstract information was not sufficient to make a decision.

Reviews discussing cost-effectiveness studies of AIs were not included in this review but were retained for use in discussion.

Quality assessment strategy

The quality of studies was assessed using the Drummond checklist.[110]

Results of review

Quantity and quality of research available

Electronic literature searches identified 1024 potentially relevant publications. The inclusion and exclusion criteria were applied using the titles, abstracts and, when available on-line, full papers. Only one full study satisfied all inclusion and exclusion criteria and formed the basis of the review reported in this section. No studies were excluded on the grounds that they were methodologically unsound.

Search results

The following studies published in full were identified.

UK studies

None.

International studies

***Hillner (2004)*[111]**

A cost-effectiveness study comparing 5 years of anastrozole with 5 years of tamoxifen immediately following surgery, based on 47 months' interim results from the ATAC study. The model was built in DATA v. 4.0 from a USA healthcare perspective. The model uses daily cycles and runs until patients reach 90 years of age.

Seven health states were modelled: well and receiving adjuvant therapy, adjuvant therapy halted, LRR or contralateral recurrence, DR, vaginal bleeding or venous thromboembolism, hip fracture and death. The annual rates for LRR (0.8%), contralateral disease (0.3%) and systemic recurrence (1.9%) were taken from the interim results from the ATAC trial and assumed to be constant for the life of the patient. Median survival following metastatic recurrence was assumed to be 21 months.[112]

AE rates were taken from the ATAC trial (for all patients, rather than the subset of hormonal receptor-positive). Vaginal bleeding, thromboembolism and hip fracture were included in the model. However, endometrial cancer was not, resulting in lower costs and mortality in the tamoxifen arm than might have been expected. The interim analysis did not show any difference in risk of hip fracture between treatment arms. The modelling of hip fractures was conservative in that it used the 4-year difference in overall fracture rate, assuming that this would eventually be translated into a difference in hip fracture incidence.

Utility penalties were applied based on values taken from Harvard School of Public Health CEA Registry.[113] Costs were based on a USA healthcare perspective, making comparison with UK studies difficult. The inclusion of quality of life weighting for non-fatal outcomes favoured anastrozole in the short term, but on the assumption that anastrozole is associated with an increased risk of hip fracture, then the long-term benefit was reduced by approximately 25%.

Anastrozole was projected to result in an improvement in DFS. However, given the overall low rate of recurrence and the extended survival of women with ER-positive breast cancer, the predicted overall survival gain in the anastrozole arm was less than 2% greater than the corresponding rate in the tamoxifen arm. This did, however, translate into a cost per quality-adjusted life-year (QALY) of US$76,000 over a 20-year horizon. The cost per QALY reached US$202,000 if the time horizon was restricted to 8 years.

The paper was generally well presented. The structure of the model appears reasonable, although the model did not take into account the impact of endometrial cancer, which may have resulted in the results being less favourable to the AI. It should be noted that the study was based on interim results from the ATAC trial, used different discount rates to those used in the UK and had a 20-year time horizon rather than a lifetime approach, and therefore is not directly comparable with the independent model described in the section 'ScHARR economic model – model structure and assumptions' on p. 65.

Cost-effectiveness evidence from industry submissions

As part of their industry submissions to NICE, the three manufacturers of AIs – AstraZenaca, Novartis and Pfizer – provided cost-effectiveness models and accompanying reports. These were critiqued using the Drummond checklist (see Appendix 6). This section describes the main aspects of these models.

AstraZenaca – cost-effectiveness of anastrozole

Two separate models are included with the submission:

1. The primary adjuvant model comparing 5 years of tamoxifen versus 5 years of anastrozole on the basis of results from the ATAC trial.[69]

2. The unplanned switching model, comparing switching to anastrozole after 2–3 years of tamoxifen rather than remaining on tamoxifen for the remainder of the 5 years. It is based on combined analysis of the ARNO and ABCSG-8 trials.[73] The results of the ITA trial,[74] a smaller trial of 448 node-positive patients, were not modelled.

AstraZeneca – adjuvant model

Structure of the model

The model has seven health states:

1. on adjuvant therapy (anastrozole or tamoxifen)
2. on switch adjuvant
3. off treatment, in remission
4. LRR (including contralateral)
5. DR
6. death from breast cancer
7. death from other causes.

The model does not differentiate between loco-regional and contralateral breast cancer. This is not unreasonable, given that there was only a small group of patients experiencing contralateral disease and, although there might be some difference in terms of recurrence and relapse rates, data on this are limited. Prognosis for patients with contralateral disease is better than that for patients with LRR. The impact of AIs on this group of patients may therefore be overestimated.

The median age of patients in the ATAC trial was 64 years. The time frame of the analysis was 25 years, at which point the majority of the patients would have died. A 3-month cycle length was used for the first 5 years with a 6-month cycle length used thereafter.

Patients withdrawing from first-line treatment due to AEs are assumed to be switched to the other drug for the remainder of the 5-year period. A maximum of one switch is allowed. It is assumed that drop-out from causes other than adverse events and recurrence, or death, do not occur within the first 5 years.

Clinical data

ATAC trial data were used to model recurrence-free survival (defined as DFS excluding non-breast cancer deaths). Recurrence was estimated using two Weibull regressions based on the tamoxifen arm and anastrozole arm, one with a treatment coefficient and one without. No explanation as to why Weibull curves were used is given, although the fit of the regression is shown in the submission and looks reasonable.

These curves were used to model recurrences while benefits were assumed to last. In the base-case scenario it is assumed that the recurrence curves continued to show incremental benefit for anastrozole out to 10 years. In other words, the benefit of anastrozole over tamoxifen seen in the 68-month follow-up period was assumed to carry over until year 10. From 10 years onwards, the same time-dependent rates of recurrence are applied to both treatment arms, based on extrapolation of a Weibull curve fitted to the pooled data without adjusting for a treatment effect.

The extension of benefits for 5 years beyond the therapy period, as assumed in the base case, is supported in the submission by the recurrence curves at 68 months, which are still diverging, and by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reports on the continued effect of tamoxifen after treatment is stopped.[108] However, it should be noted that the EBCTCG study compared tamoxifen with no tamoxifen (i.e. no active agent) and showed a divergence, some of which may have been due to second cancers and the late recurrences known to be obtained which will have been delayed or prevented by tamoxifen. In the majority of AI studies, AIs are compared with tamoxifen, so both arms have an active agent and it may therefore not be appropriate to compare these trials directly with the example from the EBCTCG data.

Two alternative scenarios for extrapolation of benefits were also tested – benefits continue until 6 years and benefits continue for lifetime. A more conservative scenario (for instance, showing the impact of assuming that the benefits of AIs seen over the trial period are gradually lost over time, i.e. there is a catch-up period following therapy in which the recurrence rates for patients on AIs are higher than those for patients on tamoxifen) was not considered. Although a scenario of this kind may be considered overly conservative, it is possible that for some patients the benefits of AIs are in delaying relapse, rather than preventing it.

The probability of distant relapse (as a percentage of all first recurrences) was obtained from the ATAC trial. Probabilities of progressing from LRR or DR were obtained from published literature. Several studies were identified from the literature, although an indication of the sources searched was not given. Progression-free survival was extracted from Kamby and Sengelov[114] on the basis that this included a population similar to that seen in the ATAC trial and had the longest follow-up. The

probability of breast cancer death after LRR without distant metastasis was based on the proportion of patients in the ATAC trial who developed LRR in the two monotherapy arms. The median survival after distant metastasis was assumed to be between 18 and 24 months, based on the systematic review by Stockler and colleagues.[115] No indication of sources searched was given.

Adverse events
AEs in the adjuvant model are based on the ATAC trial (all patients). All prespecified events are included in the model. AEs are split into life threatening – hip fracture, deep vein thrombosis/ pulmonary embolism, ischaemic cerebrovascular event and endometrial cancer – and non-life threatening – vertebral fracture, wrist/Colles fracture, other fracture, hysterectomy (no endometrial cancer), ischaemic CVD, vaginal bleeding, hot flushes, musculoskeletal disorders, mood disturbances, fatigue, nausea/vomiting, vaginal discharge, vaginal bleeding and cataracts. No justification for the inclusion of hysterectomy (no endometrial cancer) is given and it is not immediately apparent why it should be.

The risks of hip fracture and endometrial cancer were extended for 3 years beyond the 5-year treatment period. In both cases it seems reasonable to extend the risk but no justification for the 3-year period was given and there was no discussion of whether this risk might be extended for a longer period. The risk of DVT and ischaemic CVD events was extended 6 months beyond the trial period. Mortality due to hip fractures is assumed to increase with age, whereas death due to other AEs remains constant over time.

Other fractures, particularly vertebral fractures, have been shown to have a mortality risk[116] and therefore the full impact of fractures may be underestimated by not taking this into account.

The model assumed that moderate and severe AEs were treated. All life-threatening AEs were assumed to be serious. Serious events were assumed to be hospitalised. All non-serious, non-life threatening AEs were assumed to require only outpatient treatment and medication.

There appears to be an error in the estimation of non-cancer mortality: the annual rate has not been converted into a quarterly rate. The impact of this error would be to overestimate non-cancer deaths. Correcting the error would reduce the cost-effectiveness ratio.

Utilities
Utilities were based on a cross-sectional study including 32 UK patients. Values were based on the chained standard gamble method:

DFS, no adverse events	0.989
New contralateral breast cancer	0.914
LRR	0.911
Hormonal therapy for DR	0.882
Chemotherapy for DR	0.710
Current health	0.933
Common AEs (tamoxifen)	0.970
Common AEs (anastrozole)	0.962
Vaginal bleeding	0.933
Endometrial cancer	0.913
Wrist fracture	0.916
Deep vein thromboembolism	0.922
Pulmonary embolism	0.890
Spinal fracture	0.894
Hip fracture	0.858
Hysterectomy	0.899

The values appear high, with significant events such as LRR and contralateral disease being given values above 0.9. This typically occurs when it is patients rather than the general population who elicit the values. In a similar study in the USA with 44 patients, lower absolute values for utility estimates were obtained.[117] Recent evidence suggests that fractures of the spine are associated with a utility of 0.626 in the first year.[116]

Costs and resource use
The model uses an NHS perspective and only direct medical costs are included (*Table 23*). No indication of the financial year to which costs related was given.

Drug costs were taken from the 2005 BNF (BNF 48). Costs of medical management were taken from a physician survey conducted by The MEDTAP Institute at United BioSource Corporation, combined with unit cost from the MEDTAP Unit Cost Database and NHS Reference Costs. Following diagnosis of LRR or DR, the costs applied were assumed to be the same across treatment groups.

Bisphosphonate treatment costs were included for 5% of the patients while on anastrozole and 0% of tamoxifen patients.

Sensitivity analysis
Probabilistic sensitivity analysis (PSA) was undertaken using a Monte Carlo simulation of 5000 runs. Transition probabilities and utilities were given beta distributions and costs were given a log-normal distribution. The selection of

TABLE 23 *Cost of Medical Management (taken from AstraZeneca submission)*

	Mean cost (£)	SD (£)
Treatment/diagnosis (cost/event)		
At treatment initiation	90	38
Diagnosis of recurrence	808	92
Treatment for LRR	2606	2085[a]
Treatment for DR	3563	2850[a]
Follow-up and monitoring (cost/cycle)		
Follow-up for LRR	143	66
Follow-up for DR	199	95
Routine follow-up in first year	70	20
Routine follow-up in subsequent years	43	17
Follow-up off treatment due to remission	24	18
Follow-up off treatment due to AEs	52	43
Death (cost/event)		
Death from breast cancer[b]	3783	3404
Death from other causes	500	450

Source: Physician Survey, MEDTAP Unit Cost Database and NHS Reference Costs, except where stated.
[a] Assumed 80% of the mean.
[b] Coyle *et al.* (1999).[118]

distributions is considered reasonable. In addition, the sensitivities of the individual components of the ICER were explored using one-way sensitivity analysis (tornado charts in Crystal Ball).

Results
The additional drug costs (£3301) in the anastrozole arm are partially offset by the lower cost of recurrence and death in this arm (–£2025). The costs of AEs are a relatively small proportion of total costs in both arms and balance each other out in the two arms. The anastrozole arm is predicted to achieve a small gain in survival [11.0 versus 10.7 life-years gained (LYG) in the anastrozole and tamoxifen arms, respectively] and a similar gain in QALYs (10.7 versus 10.4 QALYs in the anastrozole and tamoxifen arms, respectively).

The incremental cost-effectiveness of anastrozole versus tamoxifen at 25 years was £7610 per QALY in the hormone receptor-positive trial population. This assumes the extension of recurrence benefits up to 10 years from start of treatment. Results of the short-term benefit scenario, where recurrence benefits are assumed to extend only to 6 years, are £12,463 per QALY. In the long-term benefit scenario, where recurrence benefits extend to 25 years ('lifetime'), the cost per QALY drops to £5331.

Based on a 3.5% discount rate, the cost per QALY increases slightly to £7811. Results based on this discount rate are of interest to NICE given that the rates of 6% (costs) and 1.5% (outcomes) have been superseded by rates of 3.5% for costs and benefits for future technology assessments. Limiting the analysis period to 10 years, rather than 25 years, has the largest impact on results, with the cost per QALY rising to £33,728.

The results of probabilistic sensitivity analysis showed that at 25 years, based on the 10-year benefit from treatment (base-case) scenario, there is a 90% likelihood that the cost per QALY will be lower than £15,000 and a greater than 95% likelihood that it will be less than £20,000.

Discussion
The model structure provides a reasonable representation of the treatment pathways for breast cancer. However, the base-case scenario of extending the benefit seen in the therapy period out to 10 years seems optimistic and is largely unsupported by evidence at present. However, it should be noted that the scenario of 6 years' benefit still produced a cost per QALY below £13,000. More conservative scenarios in which recurrence rates for anastrozole were greater than for tamoxifen were not considered.

The utility values used are considered to be too high, although sensitivity analysis shows that these values do not have a major impact on the cost-effectiveness results. The largest impact on results is a reduction in the time horizon to 10 years, which raises the cost per QALY to over £30,000.

AstraZenaca – unplanned switching model
The unplanned switching model compares switching to anastrozole after 2–3 years of tamoxifen with the alternative of remaining on tamoxifen for the remainder of the 5 years.

Model structure
The model structure is the same as for the primary adjuvant analysis, with the same seven health states. The model follows a cohort of a 1000 patients, with a median age of 62 years, for 25 years. The cycle lengths are determined by the original ATAC model structure (which was based on 3 months for the 5-year treatment period and 6 months thereafter). The treatment period on AIs is only 3 years in the switching scenario (rather then 5 years in the primary adjuvant setting) and therefore the cycle length has been adjusted to 1.8 months during the first 3 years.

Clinical data
The clinical data are taken from the combined analysis of ARNO and ABCG-8 trials, the GABG study.[77] Recurrence-free survival, the proportion of DRs, tolerability and withdrawal probabilities were taken from this combined analysis.

The analysis assumes that the clinical benefits of anastrozole continue after the treatment period. Two different scenarios were analysed, first that the treatment benefits continue for 5 years beyond the end of the adjuvant treatment period specified in the protocol (base case) and second that treatment benefits continue for 1 year beyond the end of the 5-year adjuvant treatment period specified in the protocol. This is justified on the basis that there is evidence that the clinical benefit for tamoxifen and anastrozole continues after patients stop treatment.[69] However, it should be noted that there is no evidence to date on benefits extending beyond the treatment period from the switching setting.

The proportion of recurrences that were DRs was obtained from the GABG study.

Adverse events
The recorded AEs from the GABG study were matched to the corresponding AE categories in the ATAC analysis. A patient experiencing an AE may withdraw from treatment (and switch to a new treatment in the model) according to the withdrawal rates recorded in the ATAC trial (in the absence of ARNO/ABCSG withdrawal data). Withdrawn patients were switched to the other endocrine therapy, anastrozole or tamoxifen as appropriate. Patients withdrawing for reasons other than AEs were not considered in the model.

Utilities
Utility values used are the same as those used in the primary adjuvant model.

Costs and resource use
Resources used to manage patients in the different health states were taken from the ATAC trial analysis, as used in the primary adjuvant model (*Table 23*).

All costs are the same as used in the primary adjuvant model. All costs were discounted at a rate of 6% per year.

Sensitivity analysis
PSA was undertaken using a Monte Carlo simulation of 5000 runs. The same distributions for parameters were used as in the primary adjuvant model.

Results
Results are given in *Table 24*.

The base-case analysis produces a cost per QALY of £2446. For the scenario in which benefits are extended for only 1 year beyond the treatment period, the cost per QALY increases to £11,003. Restricting the time frame of the analysis to 10 years produces costs per QALY of £25,170 and £38,846 for the scenarios with benefits extending 5 years and 1 year beyond the treatment period, respectively. The PSA shows that there is a 90% probability that the cost per QALY will be less than £10,000 in the scenario in which benefits continue for 5 years beyond the therapy period and a 90% probability that the cost per QALY will be less than £28,000 in the scenario in which benefits continue for 1 year beyond the therapy period .

The cost of death from non-breast cancer causes and the hazard of relapse after a serious AE and a switch in therapy at year 4 are the two parameters with the greatest contribution to the variation in total costs of the anastrozole and the tamoxifen arms. The hazard of relapse after switching after a serious AE at year 4 is a key variable for all of the one-way sensitivity analyses.

Discussion
The model structure is the same as for the primary adjuvant analysis, with the same seven

TABLE 24 *Results table from AstraZeneca submission: switching analysis*

	QALY		Incremental QALY	Cost/QALY (£)
	Anastrozole	Tamoxifen		
Mean	11.27	10.92	0.3576	2,446
Lower 95% CI	10.65	10.25		NA
Upper 95% CI	11.76	11.46		14,875

NA, not applicable.

health states. The model shows that anastrozole has a high probability of being cost-effective at low levels of willingness to pay for a QALY under current treatment prices. The assumption of 5 years of extended benefit after 3 years of treatment with anastrozole is not well supported and is considered overly optimistic.

The lack of patient-level data from the GABG study meant that some assumptions had to be made regarding the similarities between the combined switching trial and the ATAC trial in order to use the same model structure as the adjuvant setting analysis. The impact of these assumptions is difficult to determine. Sensitivity analysis suggests that the model is robust to changes in model parameters, although it should be noted that this analysis is dependent on current treatment prices.

Novartis – cost-effectiveness of letrozole

Two models are included within the Novartis submission:

1. Primary adjuvant analysis comparing the planned provision of 5 years of letrozole with 5 years of tamoxifen for postmenopausal ER-positive women following diagnosis with early-stage breast cancer (adjuvant evaluation). This is based on the results of BIG 1-98.[90]
2. Extended (sequential) adjuvant analysis in which planned provision of 5 years of letrozole for postmenopausal ER-positive women diagnosed with early-stage breast cancer who remain disease free after 5 years adjuvant tamoxifen is compared with a do-nothing (placebo) comparator. This is based on the results of the MA-17 study.[119]

Novartis – primary adjuvant model

Model structure

A Markov model designed to estimate the incremental cost per QALY and per LYG with 5 years of letrozole adjuvant therapy compared with tamoxifen in postmenopausal women with hormone receptor-positive early-stage breast cancer from the perspective of the UK NHS is used. An annual cycle length is used but no explanation is given as to why this cycle length was chosen. The starting age of the population in the model is 61 years. A lifetime analysis is undertaken.

All patients start in the DFS (patients remaining disease free following primary surgery). From the DFS, patients may die from causes other than breast cancer, develop a new tumour in the contralateral breast or experience a recurrent event (LRR or a metastatic relapse in one of three dominant sites: soft tissue, bone or visceral). Since survival varies depending on the type of metastatic relapse, sites of metastases that have similar outcomes have been combined into common groupings. It is possible to go from DFS to contralateral to loco-regional but not from DFS to loco-regional to contralateral. A series of tunnel states for the contralateral, remission and the three metastases states are used to allow differential transition probabilities from these states to be described for each year that a patient remains in one of these states.

Clinical data

The results of BIG 1-98 have not been published in full, therefore the cost–utility analysis for BIG 1-98 is based on the Clinical Study Report (CSR) to estimate event rates in the letrozole and tamoxifen treatment groups. Three- and five-year aggregate "breast cancer event" rates, including invasive ipsi- and contralateral breast cancer relapses, are used to estimate annual event rates for the tamoxifen patient group assuming constant event rates in the first 3 years and in years four and five.

Separate HRs for contralateral disease (0.61), LRR (0.69) and metastatic recurrence (0.73) are used in the model. These HRs are estimated from the proportions of patients experiencing each type of breast cancer event in the trial. The HRs are applied to the relevant tamoxifen event rates to obtain the analogous rates for the letrozole patient group during the 5-year therapy period. Beyond the treatment period the recurrence rates from DFS are assumed to be the same in the treatment and comparator arms, based on the average annual rates taken from the trial data. Women remaining event free beyond 15 years are assumed to be cured.

Event rates for all patients experiencing a contralateral primary tumour are based on event rates reported for node-positive women receiving adjuvant chemotherapy taken for the EBCTCG 1998 overview.[120] Event rates for LRR are taken from a review and synthesis of seven studies. From metastases patients can only remain in this state or die. Survival for ER-positive postmenopausal women, by site of metastases, is estimated from patient-level data from the P025 trial comparing first-line tamoxifen with first-line letrozole, with crossover in advanced breast cancer patients.

Adverse events
AEs are incorporated within the breast cancer states. Only major AEs that are significantly different between the two treatments are modelled. However, it should be noted that lack of significance may simply be an artefact of low numbers. In the BIG 1-98 trial these are endometrial cancer, bone fractures, myocardial infarction, venous thromboembolic events and hypercholesterolaemia. More minor AEs, such as vaginal bleeding and hot flushes, were excluded. However, the impact of this is likely to be small.

Incidence of the key AEs and associated mortality rates used UK-based data. The general approach used was to apply published HRs for tamoxifen to the UK-specific incidence rates for each AE to estimate event rates in the tamoxifen patient group. HRs for the letrozole patient group, estimated from the BIG 1-98 trial, were applied to the tamoxifen incidence rates to estimate the event rates in the letrozole patient group. In cases where relevant UK-based incidence rates were not identified, the tamoxifen incidence rate observed in the BIG 1-98 trial is used as the baseline tamoxifen rate, to which observed HRs for letrozole are applied.

Utilities
Standard gamble values from Sorenson and Locker[117] were used. The utility value for DFS is 0.974. Utility for contralateral disease and LRR are given as 0.816 in year 1 and 0.974 (the same as utility for DFS) in subsequent years. This return to DFS values in the year following contralateral disease and LRR is considered to be optimistic as the utility may well be lower for patients who experience further disease following a disease-free interval. Utility for distant metastases is given as 0.578

These values appear to be high, relative to utility estimates from other sources.

Costs and resource use
The cost year is not stated. Costs for medication are from the BNF. Detailed breast cancer treatment costs post-relapse are estimated from a patient-level database collected at the Western General Hospital, Edinburgh.

[Confidential information removed].

The cost of surveillance beyond the first year in the adjuvant model, and in all years in the sequential adjuvant model (the first year in the sequential adjuvant model is the sixth year post-diagnosis), assumes an annual outpatient visit, at a mean cost of £93 based on the cost estimate for a clinical oncology outpatient visit presented in the NHS Reference Costs 2004.[121]

In addition to above-described surveillance costs, patients in the letrozole patient groups are assumed to undergo an annual bone mineral density screen as a result of the increased risk of osteoporosis. A cost of £34 for a bone mineral density screen is taken from a cost–utility analysis of treatments for osteoporosis.[122]

Costs of AEs were taken from a variety of sources and appear to be relevant to the UK population. A one-off cost (£2550) and an annual cost of monitoring (£146) for patients diagnosed with localised endometrial cancer were obtained from a UK-specific analysis that reported cost values derived from a physician survey.[123] Treatment costs for fractures are also informed by Kanis and colleagues,[122] which are based on a review of the literature. The main study used to inform the Kanis cost estimates appears to be a paper by Dolan and Torgeson,[124] which was based on patient survey data and other published sources. Treatment costs for myocardial infarction differentiate between resource use in the first year post-diagnosis and all subsequent years, with cost estimates, based on patient-level resource use data obtained from a published evaluation of glycoprotein IIb/IIIa inhibitors.[125] The cost of treating a venous thromboembolic event is based on the costs reported in the NHS Reference Costs 2004[121] for HRG code D11. An estimate of the yearly cost of statin treatment [40 or 80 mg non-generic simvastatin (£29.69/28) × 365 = £387] is assumed for the treatment of hypercholesterolaemia.

Sensitivity analysis
A wide range of deterministic sensitivity analyses and a PSA were undertaken. In the latter, beta distributions are defined for transition rates and for utilities and log-normal distributions are defined for costs. These distributions are considered appropriate. There is very limited description of the sensitivity analysis in the submission document.

Results
The base-case results indicate that the incremental cost per QALY of adjuvant treatment with letrozole rather than tamoxifen is £10,286 (95% CI £7006 to £22,344) and per life-year is £11,113 (95% CI £7603 to £24,572). The cost-effectiveness acceptability curve (CEAC) suggests that it is

almost certain that the cost per QALY gained is under £30,000 and 96% certain that it is under £20,000.

The deterministic sensitivity analysis demonstrates that the parameters included in the model which were most likely to increase the cost per QALY were the relative risk of recurrence/contralateral tumour with letrozole [incremental cost-effectiveness ratio (ICER) of £24,000 at the upper 95% CI], the probability of recurrence (ICER of £19,700 if the probability of recurrence is reduced by 50%) and age of patients in the analysis (ICER of £23,700 for women aged 71 years). The result for the deterministic sensitivity analysis with discount rates set at 3.5% for costs and benefits results in an increase in the ICER to £13,567.

Discussion

The model structure provides a detailed representation of the treatment pathways for breast cancer. The model structure differs from the breast cancer models in the other submissions in that it distinguishes between progression from contralateral disease and LRR and the model, also explicitly taking into account different kinds of metastases: soft tissue, bone and visceral. The model differentiates between the metastatic sites on the basis of prognosis but not by cost of treatment or utility. Sensitivity analysis does suggest, however, that varying the assumptions regarding the distribution of metastases sites between treatment groups makes little difference to the ICER. The impact of differentiating between different metastatic sites is relatively small. In the BIG 1-98 study, the proportions in each of the three kinds of metastases are reasonably similar for the tamoxifen and letrozole arms. The two arms are only differentiated through a relative risk reduction which is applied to the letrozole arm.

Only major AEs that are significantly different between the two treatments are modelled. In addition, more minor treatment effects such as arthralgia are ignored. The impact is likely to be small.

The model shows that letrozole has a high probability of being cost-effective at low levels of willingness to pay for a QALY under current treatment prices. The probability of recurrence or contralateral tumour would have to fall by 50% for the ICER to approach £20,000. However, the model does shows that age at start of treatment has a major impact on cost-effectiveness, with a cost per QALY of £23,700 for women aged 71 years compared with £10,286 for women aged 61 years.

Novartis – sequential (extended) adjuvant model

Model structure

The model structure is the same as that for the primary adjuvant analysis. In this analysis, patients in the DFS are defined as patients remaining disease free after 5 years of tamoxifen (in other words, year 6 post-surgery). The start age for patients in the model is 62 years. A lifetime analysis is undertaken.

Clinical data

The analysis is based on patient-level data from the MA-017 trial and the analysis differentiates between patients with node-negative and node-positive disease. Transition probabilities for patients in the DFS are calculated using patient-level data for years 1–4 (years 6–9 post-surgery). Event rates in year 5 are assumed to be the average event rate over the first 4 years of the trial. The data used come from the final trial database, which contains an additional period of follow-up to that reported by Goss and colleagues.[119]

Logistic regression is used to describe the probability of any event occurring in each year in the placebo treatment group with nodal status as a regression coefficient. The HRs for letrozole relative to tamoxifen are 0.61 and 0.48 for node-negative and node-positive patients, respectively. Event rates in the letrozole group are estimated by applying the relevant HR (node-positive or node-negative).

Multinomial regression is then used to describe the probability that an event experienced in each year is a contralateral tumour, LRR or one of the three metastases, with treatment group and nodal status as regression coefficients. Probabilities of the different types of events occurring in each year, in each treatment group, are the products of the probability of an event and the probability that the event is a particular type.

Event rates beyond the 5-year period are assumed to remain constant and equivalent, based on the average event rate from the placebo arm, based on MA-17 year 9. This is compared with, and shown to be similar to, event rates from the EBCTCG 1998 overview.[120] Women remaining event free beyond 15 years are assumed to be cured.

All other transition probabilities remain the same as the primary adjuvant model.

Adverse events

In the MA-17 study, the only major AE with a significantly different frequency between treatment

arms was the rate of osteoporosis. However, it should be noted that lack of significance may simply be an artefact of low numbers, particularly as this trial was stopped early. The impact of AEs is potentially underestimated.

The potential effect of osteoporosis is included in the model, by estimating the annual probability of osteoporosis. The additional risk of fracture (osteoporotic rates minus the general population rates) from Kanis and colleagues[122] is used to estimate the additional incidence of fracture risk. It is assumed that the probability of osteoporosis is the same in the letrozole group as that in the placebo group after the 5-year treatment period. This may well underestimate the impact of osteoporosis and fracture over the patient's lifetime given that the difference between the two populations is likely to continue beyond the trial period.

Utilities
These were as for the primary adjuvant model.

The MA-17 study included a quality of life substudy, which was used to estimate utility values based on the SF-36 algorithm. The MA-17 utility values for the DFS (the only state with a sufficient number of observations to allow estimation) was 0.74, substantially below the 0.97 in the Sorenson and Locker report.[117] The Sorenson and Locker value was used in the model to provide consistent estimates. An alternative approach would have been to scale down the utility values in the ratio of 0.74 to 0.97.

Costs and resource use
These were as for the primary adjuvant model.

Sensitivity analysis
This was as for the primary adjuvant model.

Results
In the sequential adjuvant setting, the base-case results indicate that the incremental cost per QALY of treatment is £7725 (95% CI £4104 to £33,099) and per LYG is £8556 (95% CI £4419 to £40,583). The CEAC suggests that there is a 95% probability that the cost per QALY gained is under £30,000 and 92% probability that it is under £20,000. Probabilistic results based on 3.5% discount rate for costs and benefits were not reported.

The deterministic sensitivity analysis demonstrated that the parameters most likely to increase the cost per QALY are the relative risk of recurrence/ contralateral tumour with letrozole (ICER of £21,200 at the upper 95% CI) and the probability of recurrence (ICER of £16,300 if the probability of recurrence is reduced by 50%). The ICERs for node-negative and node-positive patients are £11,784 and £5373, respectively. The impact of age is not as marked in this analysis – at age 72 years the ICER rises to £12,660 compared with the base case at 62 years of £7725. The result for the deterministic sensitivity analysis with discount rates set at 3.5% for costs and benefits produces an ICER of £10,229.

Discussion
As for the primary adjuvant analysis, the model structure provides a detailed representation of the treatment pathways for breast cancer. The impact of differentiating between different metastatic sites and between node-positive and node-negative patients is relatively small. The model shows that letrozole has a high probability of being cost-effective at low levels of willingness to pay for a QALY under current treatment prices.

Only major AEs that are significantly different between the two treatments are modelled. Lack of significance may simply be an artefact of low numbers, particularly as this trial was stopped early and therefore the impact of AEs may be underestimated.

Pfizer – cost-effectiveness of exemestane

The Pfizer submission included a Markov model to assess the cost-effectiveness of exemestane relative to continued tamoxifen therapy for adjuvant therapy of early-stage breast cancer. The model compares 2–3 years of tamoxifen followed by another 3–2 years of tamoxifen or 3–2 years of exemestane. This is based on data from the IES.[126]

Model structure
The model population consists of postmenopausal women in remission from early-stage breast cancer who have already received 2–3 years of adjuvant tamoxifen therapy at entry into the model. Adjuvant therapy on entry to the model is either continuation with 20 mg of tamoxifen daily or a switch to 25 mg of exemestane daily for the following 2–3 years.

The model comprises seven states:

- no recurrence
- remission
- LRR
- DR

- contralateral breast cancer
- death from breast cancer
- death from other causes.

The model takes a UK healthcare perspective and runs with 6-monthly cycles for a maximum of 38 years (lifetime model). No explanation is given for the selection of a 6-month cycle. The start age for the model population is 63 years. The model was initially developed with TreeAge and the model was independently rebuilt in Microsoft Excel, allowing validation to be undertaken between the two models.

Clinical data
Transition probabilities used in the first 36 months of the model are taken from the results of the IES study.[126] These include the transition from no recurrence to contralateral disease, LRR and DR and the transitions from LRR to DR and from DR to death. The transition probabilities for the post-treatment phase are the same in the comparator and the treatment arms.

Progression from no recurrence to LRR after the treatment period for the tamoxifen arm is taken from the EBCTCG 2005 paper.[37] This study looks at 15-year survival for patients with early-stage breast cancer treated with tamoxifen. Progression from LRR to DR is taken from Abner and colleagues,[127] a paper outlining prognosis following mastectomy for recurrence after conservative surgery and radiation therapy. In the model it is assumed that the probability of progressing from remission to DR and contralateral disease to DR is equal to the probability of progressing from LRR to DR (41% over 5 years). In reality, the risk of progressing from remission of contralateral disease will be less than the probability of progressing from recurrent disease to metastatic disease. The probability of remaining in the DR health state is taken from Chang and colleagues.[112] No details are provided in the submission as to how these papers were identified and the most appropriate paper selected. It is therefore not possible to determine if they represent the best available evidence at the time of model development.

Each of these transition probabilities was assumed to be constant from the end of the trial period until the end of the model. Although this involves a long period of extrapolation, it is important to note that the assumption that transition probabilities after the trial period do not differ between exemestane and tamoxifen excludes ongoing treatment effects associated with exemestane. Hence the overall effect of the extrapolation is likely to be to increase the value of the ICER for exemestane versus tamoxifen.

Mortality data from England and Wales were used to incorporate death from other causes.

Adverse events
Three major AEs, osteoporosis, endometrial cancer and thromboembolism, are incorporated into the model as AEs using separate health states. Other AEs are modelled as costs only – cardiac failure, hypertension, arthralgia, vaginal haemorrhage and myocardial ischaemia. These other events were considered too rare to justify a separate health state or clinical advice stated that the impact on quality of life was likely to be minimal.

Osteoporosis is a permanent state in the model and is included by replicating all the health states of the model. For patients with osteoporosis it is assumed that their breast cancer will progress at the same rate as if they did not have osteoporosis. The probability of osteoporosis over 36 months is 16.78% for exemestane and 10.46% for tamoxifen. The probability of osteoporotic fractures is based on the number of fractures attributed to osteoporosis among the group of patients with osteoporosis – in the exemestane group there were 16 osteoporotic fractures among a total of 241 patients over the 3-year trial period and in the tamoxifen group there were 22 osteoporotic fractures among 152 osteoporotic patients. These result in an overall probability of osteoporotic fractures among patients with osteoporosis over 3 years of 6.6% in the exemestane arm and 14.5% in the tamoxifen arm. The rate of osteoporotic fractures over the trial period was higher in the tamoxifen arm and therefore these results may not be representative of the typical expected fracture rates of these populations and may overestimate the fracture risk in the tamoxifen population. The potential long-term effect of fractures is not taken into account.

Thromboembolism is included as a reversible event with a separate health state. It is assumed that an episode of thromboembolism is successfully treated, and patients will then remain in the post-thromboembolitic state (no recurrence) or move to one of the other states that those in no-recurrence health states are able to move to.

Endometrial cancer is assumed to dominate other states in the model, so that patients can only remain in this state or mode to death. The cost of treatment in the Excel spreadsheet is £6568, which

TABLE 25 *Results from the Pfizer submission for switching therapy*

	Exemestane	Tamoxifen	Incremental
Cost (£)	7339	5079	2260
Outcome			
QALYs	13.24	12.91	0.33
LYG	13.61	13.26	0.35
Disease-free years	12.73	12.29	0.44
Cost-effectiveness			
Incremental cost per QALY (£)			6817
Incremental cost per LYG (£)			6473
Incremental cost per DFS year gained (£)			5158

is higher than that stated in the report. This cost is based on the assumption that all patients receive radiotherapy and chemotherapy, which is considered unlikely and will therefore overstate the cost of treatment

Utilities
Utilities are taken from a range of studies; the majority of them are published on the Harvard database. No recurrence is given a utility of 0.999. This is very high and does not take into account the age of the population. LRR and contralateral disease have a utility of 0.700, with remission after LRR of 0.85. DR has a utility of 0.517.

The utility value for thromboembolism (0.58) seems low, particularly because this is an acute episode and the utility value will apply for the whole cycle (6 months). On the other hand, the value used for osteoporotic fracture (0.860) appears somewhat high.

Costs and resource use
Resource use and unit costs are taken from a range of sources.[128] HRG costs were used for osteoporotic fractures, endometrial cancer and thromboembolic events.[121] Resource use for the diagnosis of endometrial cancer is based on the investigations recommended in current SIGN Guideline 61 (Scottish Intercollegiate Guidelines Network 2002[129]).

Costs for the minor AEs such as the management of cardiac failure and management of hypertension are based on recent NICE guidance. The costs associated with managing both arthralgia and vaginal haemorrhage were based on expert advice. The costs associated with managing myocardial ischaemia are based on the investigations recommended in current SIGN Guideline 51[130] for the management of stable angina. These costs are all expected to make only a small contribution to the total costs of management.

Sensitivity analysis
Probabilistic cost-effectiveness results are obtained using Monte Carlo simulation based on 1000 simulations. Costs in the model are incorporated using a gamma distribution, whereas utility values and transition probabilities are incorporated using beta distributions. These are commonly used distributions for these variables and are considered to be appropriate.

Results
The main results taken from the submission are given in *Table 25*.

Sensitivity analysis
Variations in the discount rates for costs and benefits separately have little impact on the cost per QALY. No sensitivity analysis was undertaken on the time frame of the analysis or the transition data within the model.

The results of PSA suggest that exemestane is generally more costly and more effective than tamoxifen. In most cases, the incremental cost per QALY gained is lower than the £20,000 level. The proportion of cases where exemestane would be considered cost-effective at this threshold (based on 1000 simulations) is given in *Table 26*.

Discussion
The basic model structure provides a reasonable representation of the treatment pathways for breast cancer.

In general, the assumptions used within the model are reasonable. However, the utility value for no recurrence is 0.999, which is considered to be very high and will overestimate the benefits from avoiding recurrences. In addition, the methodology used for modelling osteoporotic fractures may underestimate the potential risk of fractures in the exemestane arm.

TABLE 26 *Sensitivity analysis from the Pfizer submission for switching analysis*

Scenario	Incremental cost per QALY	Events (n = 1000)	%
Exemestane less expensive and more effective	Exemestane dominant	0	0
Exemestane more expensive and more effective	Less than £20,000	961	96.1
Exemestane less expensive and less effective	More than £20,000	0	0
Exemestane more expensive and more effective	More than £20,000	36	3.6
Exemestane less expensive and less effective	Less than £20,000	0	0
Exemestane more expensive and less effective	Tamoxifen dominant	3	0.3

TABLE 27 *Comparison of industry submission cost-effectiveness results in primary adjuvant setting*

	AstraZeneca submission (ATAC)			Novartis submission (BIG 1-98)		
	Anastrozole	Tamoxifen	Difference	Letrozole	Tamoxifen	Difference
Costs (£000)						
Drug	3.4	0.1	3.3	4.8	0.1	4.7
AEs	1.1	1.1	0.0	1.6	1.5	0.1
Follow-up costs	16.6	17.5	–0.9	5.7	6.6	–0.9
Total costs (£000)	21.1	18.7	2.4	12.1	8.2	3.9
Survival (years)						
LYG	11	10.7	0.3	16.3	16.0	0.35
QALY	10.7	10.4	0.3	15.5	15.1	0.4
Cost per QALY (£)			7,610			10,286

Comparison of results

Adjuvant treatment for newly diagnosed patients

Two of the submissions report on the role of AIs in the primary adjuvant setting for patients immediately following surgery – AstraZeneca (based on ATAC) and Novartis (based on BIG 1-98). The results of the economic evaluations based on these trials are compared in *Table 27*.

Both models indicate that treatment with AIs provides a small overall lifetime benefit to patients compared with treatment with tamoxifen. The additional cost of treatment with AIs over and above the cost of treatment with tamoxifen is partly offset by the reduced follow-up costs (cost of treatment of recurrent disease and cancer death). The estimated costs of treating AEs cancel each other out in the two arms. This is based on the assumption that future risk of endometrial cancer and hip fracture does not extend beyond the treatment period (in the case of the Novartis model) or is extended to 3 years beyond the treatment period (in the case of the AstraZeneca model). If the risk of one or other of these AEs is shown to extend well beyond the treatment period, the impact of reduced utilities and non-cancer deaths from these AEs would gain in significance. The greatest uncertainty is around the future risk of fracture.

It should be noted that although the incremental QALYs are similar in both models, the absolute values for the tamoxifen arm in both trials are very different. This is partly the result of differences in the model structure, given that the Novartis model provides a more detailed representation of transitions to contralateral disease and LRR and also models metastatic relapses in greater detail. An error in the mortality estimates in the AstraZeneca model also contributes to the lower QALY values.

The costs also differ between the two models. The incremental costs are higher in the Novartis model due to the higher cost of letrozole compared with anastrozole. The incremental costs relating to AEs and other costs are similar.

Unplanned switching

Two submissions report on the role of AIs in the adjuvant setting for patients 2–3 years after surgery – AstraZeneca (based on CABG) and Pfizer (based on IES). The results of the economic evaluations based on these trials are compared in *Table 28*.

TABLE 28 *Comparison of industry submission cost-effectiveness results in unplanned switching setting*

	AstraZeneca submission (ARNO/ABCSG-8)			Pfizer submission (IES)		
	Anastrozole	**Tamoxifen**	**Difference**	**Exemestane**	**Tamoxifen**	**Difference**
Costs (£000)						
Drug				2.3	0.06	2.3
AEs				0.7	0.5	–0.2
Follow-up costs				4.3	4.5	0.2
Total costs (£000)	17.0	16.1	0.9	7.4	5.1	2.3
Survival (years)						
LYG	11.51	11.17	0.34	13.26	13.61	0.35
QALY	11.27	10.92	0.36	13.24	12.91	0.33
Cost per QALY (£)			2446			6817

TABLE 29 *Industry submission cost-effectiveness results in extended adjuvant setting*

	Novartis submission (MA-17)		
	Letrozole	**Placebo**	**Difference**
Costs (£000)			
Drug	4.7	0	4.7
Follow-up costs including AEs	4.9	6.1	–1.1
Total costs (£000)	9.7	6.1	3.6
Survival (years)			
LYG	17.35	16.93	0.42
QALY	16.71	16.24	0.47
Cost per QALY (£)			7725

The incremental costs are lower in this patient setting given that the patients receive only 2–3 years of treatment on an AI rather than the 5 years in the primary adjuvant setting.

Again, although the incremental QALYs are similar in both models, the absolute values for the tamoxifen arm in both trials are very different. The same reasons are applicable as for the primary adjuvant setting.

Extended adjuvant

One submission reported on the role of AIs in the extended adjuvant setting – Novartis (based on MA-17). The results of the economic evaluation based on this trial are summarised in *Table 29*.

The additional drug costs of letrozole are partly offset by lower other costs (costs of recurrence and cancer deaths and costs of AEs).

The QALY gain is higher in this setting than in other settings due to the HR of 0.60 for letrozole in the MA-17 trial. This results in a lower cost per QALY.

Summary of key issues arising from industry submissions

- In all the submissions, the higher cost of therapy on AIs is partially offset by reduced costs of treatment and follow-up for recurrences.
- AEs appear to have a relatively low contribution to costs and mortality and the AEs in the two arms tend to balance each other out in each of the models. However, the models may not adequately reflect any long-term implications of loss of bone mineral density on future fracture rates.
- Model structure: the Novartis model differentiates between contralateral breast cancer and LRR. On the basis that prognosis for patients with contralateral disease is better than prognosis for patients with LRR, this is likely to give a higher ICER and makes results more conservative, compared with the other two submissions.
- Model structure: the Novartis model differentiates between sites of metastases. Sensitivity analysis within the Novartis submission shows that this does not have a major impact on the cost per QALY estimates.

- Key parameters influencing the ICER are HR, time horizon of analysis, age at the start of analysis, assumptions on benefits after treatment period and assumptions on rate of progression following recurrence.

ScHARR economic model – model structure and assumptions

Objective

The aim of the model is to review the cost-effectiveness of AIs compared with standard therapy in postmenopausal women with ER-positive early-stage breast cancer.

Treatment strategies

The use of the three AIs is proposed for the adjuvant treatment of early-stage breast cancer. The current licensed indications are summarised in the 'Summary' section on p. 12.

The three treatment strategies – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – are considered separately within the economic analysis. The primary adjuvant trials randomise at year 0, immediately after surgery. The switching trials randomise patients after they have received 2 or 3 years of tamoxifen. The extended adjuvant trial randomises patients after the end of the 5 years of primary adjuvant therapy. It is not possible to compare directly strategies that randomised halfway through or at the end of the standard 5-year adjuvant treatment period with a strategy which randomises at zero years after surgery. For instance, those randomised part-way through their adjuvant therapy are biologically different to those randomised immediately after surgery as they have missed their peak year for recurrence in year 2.

Structure of the model

A probabilistic state-transition model has been developed to explore the costs and health outcomes associated with treatment of postmenopausal women with ER-positive early-stage breast cancer with AIs compared with tamoxifen from a UK NHS perspective. Trial evidence is available for three treatment strategies. Resource use and utilities are taken from trial data where available or from published literature. Input parameters are assigned probability distributions to reflect their imprecision and Monte Carlo simulations are performed to reflect this uncertainty in the results. Results are presented in terms of cost per incremental QALY gained.

The model uses an annual cycle length, on the basis that the model spans a long period (the entire life history of the patient) and the probability data available for modelling purposes were typically presented as yearly probabilities, so the use of a shorter cycle length would therefore have had little impact on the results. The starting age of patients varies between 60 and 65 years according to the trial evidence used for the different treatment settings. The model is run for 35 years.

Disease pathway

Tamoxifen has been the mainstay of adjuvant therapy for postmenopausal women in the UK for many years. Current standard therapy is for patients with early-stage breast cancer to receive 5 years' treatment with tamoxifen immediately following surgery. A proportion of patients may also receive chemotherapy (typically Stage II, under 70 years of age). Patients may remain in a disease-free interval until they die with no evidence of cancer, experience a relapse (loco-regional or metastatic) or develop contralateral disease.

Patients experiencing the development of contralateral disease (approximately 0.5–1% per annum) are staged and operated on as *de novo* patients. Patients will also receive a further 5 years of hormonal therapy from the time of new diagnosis. Those patients experiencing an LRR receive further treatment [surgical resection if the disease is operable, plus radiotherapy (if radiotherapy-naive) and hormonal therapy]. They may then enter a further period of remission until death without evidence of cancer, or further relapse.

Metastatic/distant relapse (Stage IV) is not considered curable. Median survival is typically around 18 months–2 years, although there is wide variation between patients, depending on the distribution and extent of metastases at presentation. Patients experiencing a metastatic relapse will receive active palliative treatment to control symptoms and improve quality of life, a period of supportive care and ultimately a period of intensive end of life care for the last few days/weeks of life.

Health states

The model structure follows the disease pathway for early-stage breast cancer.

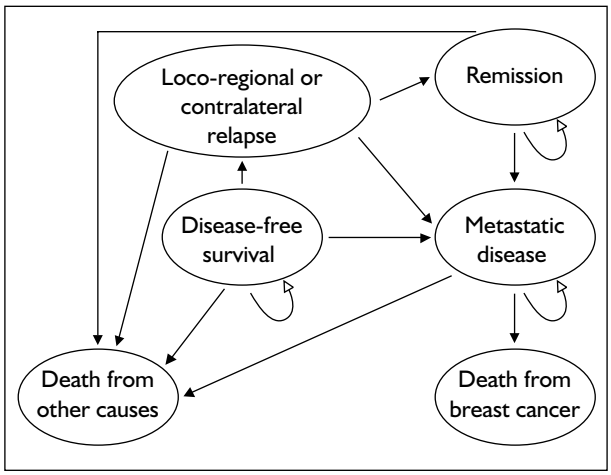

FIGURE 5 *Treatment pathways in the ScHARR model*

There are seven health states within the model:

- DFS
- contralateral disease
- LRR
- metastatic relapse (to include inoperable local progression)
- remission (post-LRR/post-contralateral disease)
- death from breast cancer
- death from other causes.

The model pathways are shown in *Figure 5*.

Model transitions

The following transitions are possible in the model:

1. Disease free
   Patients can remain in this state or move to
   (a) contralateral disease
   (b) LRR
   (c) metastatic relapse
   (d) death from other causes.
2. Contralateral disease
   Patients can move to
   (a) remission
   (b) metastatic relapse
   (c) death from other causes.
3. Loco-regional relapse
   Patients can move to
   (a) remission
   (b) metastatic relapse
   (c) death from other causes.
4. Remission
   Patients can remain in this state or move to
   (a) metastatic relapse
   (b) death from other causes.
5. Metastatic relapse
   Patients can remain in this state or move to
   (a) death from breast cancer
   (b) death from other causes.
6. death from breast cancer absorbing state.
7. death from other causes absorbing state.

Patients remain in contralateral disease and LRR states for one cycle (1 year) only. They then move to remission or one of the other states. It is assumed that it is only possible to die of breast cancer from the metastatic relapse state. For patients who experience contralateral disease and LRR it is assumed that the prognosis of these patients is similar, that is, the future likelihood of metastatic recurrence is the same. This is a simplifying assumption and in reality this is not the case. With regard to contralateral cancer, prognosis is usually determined by the first cancer and women who have a prophylactic mastectomy have no better survival than those who do not. This strongly implies that contralateral cancers have little or no impact on outcome. In contrast, women who develop LRR have a higher risk of developing metastatic disease than unaffected women and will therefore be expected to have a worse prognosis. The impact of this will be that patients with contralateral disease experience a worse prognosis within the model than might be expected and therefore the benefits of AIs may be overestimated.

Switching/withdrawal

Patients withdrawing from treatment due to AEs are assumed to switch to the alternative treatment during the remainder of the treatment period. No other drop-outs are assumed.

Model assumptions

The model employs a number of simplifying assumptions, which are detailed below.

- Benefits after treatment period – in the base-case analysis it is assumed that the benefits of AIs over the treatment period are gradually lost over the next 10-year period. The rate of recurrence for AIs after the trial period is assumed to be higher than for tamoxifen between 5 and 15 years post-surgery, to the extent that by year 15 the number of patients in DFS is the same in both arms. This is considered to be a conservative assumption.
- To simplify the model, it is assumed that following contralateral disease or LRR patients cannot experience further LRR, but that they can only experience metastatic relapse.
- After disease recurrence, the type of treatment received, the cost of treatment and survival are the same in both arms.

- The survival of patients who relapse is assumed to be independent of the time of relapse. This is unlikely to be true as patients who relapse shortly after surgery have a worse prognosis than those who relapse later. However, without patient-level data, this assumption is inevitable. Given that a large proportion of patients relapse within 2 years of surgery, survival for patients may be slightly overestimated.
- The survival of patients with metastatic relapse is equivalent to that of patients who are initially diagnosed with metastatic disease (i.e. patients who have not previously received adjuvant chemotherapy for early disease).
- Patients who have experienced an episode of early-stage breast cancer but are in remission after 15 years are assumed to have the same risk of progression as the general population.
- Death from breast cancer can only occur following progression to metastatic relapse.
- Death rates for non-breast cancer causes are based on UK mortality statistics and applied across all health states.

Clinical data

Transition probabilities from disease-free survival (DFS)

The ScHARR model is used to produce five sets of analyses, as follows:

1. primary adjuvant trials:
   (a) anastrozole (based on ATAC)
   (b) letrozole (based on BIG 1-98)
2. unplanned switching trials:
   (a) anastrozole (based on ARNO/ABCSG)
   (b) exemestane (based on IES)
3. extended adjuvant trials:
   (a) letrozole (based on MA-17).

The rate of recurrence following DFS is taken from the comparator arms in the relevant trials shown above. The HR from the relevant trial is applied to the tamoxifen recurrence rate to derive the overall recurrence rate in the AI arm.

Recurrences are then modelled as either loco-regional/contralateral or metastatic. The probability that a recurrence in the comparator arm (tamoxifen or placebo) is a local recurrence, contralateral disease or a metastatic recurrence is taken directly from the relevant trial and is used to estimate the number of each type of recurrence. The probability of different types of recurrence in the treatment arm is derived using the individual HRs for local recurrence, contralateral disease or a metastatic recurrence. The number of each type of recurrence (first events) in the comparator arm is multiplied by the individual HRs to give the expected number of first events in the treatment arm. This is used to derive the proportion of different types of recurrent events modelled in the treatment arm.

A table summarising the key clinical parameters from these trials used in the ScHARR analysis is included in Appendix 7.

Extrapolation of DFS curves

The maximum length of follow-up in AI trials to date is 68 months.[69] Many of the trials have significantly shorter follow-up. The costs and benefits of treatment with AIs will, however, extend over the patient's lifetime. It is therefore necessary to extrapolate the clinical data well beyond the trial period.

DFS curve for patients on tamoxifen

Patients may continue to have relapses for a long period, up to 15 years in a small number of cases. For patients with aggressive disease, relapses are most likely to occur by 3 years, but for patients with less aggressive disease relapses may well come later. Within the model, the recurrence curve for the population on tamoxifen is extrapolated based on historical data out to 15 years following surgery from the EBCTCG.[37] It is assumed that patients who have remained in DFS beyond 15 years have the same risk of progression as the general population.

DFS curve for patients on AIs

HRs from the trials are applied to the tamoxifen event rates to estimate event rates in the AI arm. A key assumption within the model is what happens to the event rates in the two arms beyond the initial treatment period.

Scenarios for extrapolating the recurrence event rates beyond the trial data are as follows.

In the base-case analysis, it is assumed that benefits of AIs over the treatment period are gradually lost over the next 10-year period. The rate of recurrence after the treatment period (between 5 and 15 years post-surgery) for patients treated with AIs is assumed to be higher than for patients treated with tamoxifen to the extent that by year 15 the number of patients in DFS is the same in both arms. In this scenario, the benefits of AIs are considered to be in delaying relapse, rather than preventing it. This is considered to be a conservative assumption.

A further scenario, 'Benefits maintained', is tested in sensitivity analysis. In this scenario, it is assumed that following the treatment period the annual

rate of recurrence in both arms is the same – based on the rate of recurrence between 5 and 15 years from the EBCTCG 2005 paper.[37] In this scenario the benefits of AIs achieved during the trial period are preserved, with no difference in the rates of recurrence between the two arms after the adjuvant treatment period.

The latest ATAC data show that the DFS curves are continuing to diverge even when treatment has finished, suggesting that the additional benefits will continue to be present after therapy, at least for a time, and may even become larger. It is therefore possible that both of the above scenarios could be considered conservative.

A more detailed explanation of the methods of extrapolation for each of the analyses in given in Appendix 8.

Transition probabilities from contralateral disease and loco-regional relapse

Patients who experience an LRR have a worse prognosis that those who do not. Progression rates to distant metastases will vary according to a number of factors, including age and nodal status of patients along with the site of recurrence and time to recurrence. Kamby and Sengelov[114] presented data for 140 patients with isolated local and regional node recurrence after receiving mastectomy. Patients were followed up for a median of 10.4 years. The rate of distant disease was 48% after 5 years and 72% after 10 years. Most distant relapses occurred within the first 3 years after LRR. Moran and Haffty[131] present survival and metastases-free survival data for patients diagnosed with LRR. With a median follow-up of 14 years, the 10-year distant metastasis-free rate was 59%. A paper by Abner and colleagues[127] considered 123 patients who had salvage mastectomy following recurrence in the breast. In this study, 41% of patients progressed from local breast cancer to distant stage breast cancer over a 5-year period.

The Novartis submission included a review and analysis of seven studies.[114,131–136] A combined metastases-free survival curve was generated from these studies. Based on this analysis, metastases-free survival at 5 years was estimated to be 52%.

Progression to metastases in the ScHARR model was based on the study of Kamby and Sengelov,[114] which had the longest follow-up period. Patients older than 75 years were not included in the study and therefore the median age of patients (not stated in the paper) may be slightly lower than those in the hormonal therapies trials. The rates in this paper were similar to those produced by the review and analysis in the Novartis submission. It is assumed patients who remain in remission for 15 years return to the risk of the normal population.

Transition probabilities from metastatic recurrence

The median survival after distant metastases is around 18–24 months. In the model, it is assumed that median survival is 17.8 months, based on Chang and colleagues.[112] No distinction is made between different metastatic sites in terms of survival rates, on the basis that the majority of trials would not be able to provide data on the distribution of metastatic sites across treatment groups. If the distribution of sites between treatment arms was markedly different, this would lead to differences in the survival and cost estimates between the treatment arms. However, the Novartis submission took account of this and demonstrated that the impact on cost-effectiveness was limited.

Resource use and costs

The model follows an NHS perspective and only direct medical costs are included. All costs are adjusted to 2004–5. Costs are discounted at a 6% rate according to existing NICE guidelines. Given that NICE guidelines for health technology appraisals are in the process of changing to the use of 3.5% discount rates for costs and benefits, these discount rates are tested in sensitivity analysis.

Drug costs

Drug costs, taken from BNF 50,[27] are given in *Table 30*.

TABLE 30 *Drug costs*

	Pack price (£)	No. of tablets	Cost per day (£)	Cost per annum (£)
Tamoxifen 20 mg	2.24 (generic)	30	0.075	
	8.71 (branded)	30	0.29	30.52
Anastrozole	68.56	28	2.45	894.25
Exemestane 25 mg	88.80	30	2.96	1080.80
Letrozole 2.5 mg	83.16	28	2.97	1084.05

TABLE 31 *Cost of diagnosis of loco-regional recurrence or contralateral disease*

	Proportion treated (%)	Frequency	Unit cost (£)	Total (£)	Sources
Physician visits					
Oncologist	100	2	88	176.36	NHS Reference Costs 2004[121] FU 100B
Laboratory tests					
FBC, calcium, LFTs, ESR	100	1	12.20	12.20	Sheffield Teaching Hospital Trust 2005–6
Radiological examination					
Biopsy	90	1	123	111	NHS Reference Costs 2003[138] J28 op excision biopsy (adjusted to 2004 prices)
Mammogram	90	1	122	110	NHS Reference Costs 2003[138] J25 op intermediate radiology (adjusted to 2004 prices)
Bone scan	90	1	155	140	NHS Reference Costs 2003[138] J25 op intermediate radiology (adjusted to 2004 prices)
Liver scan	90	1	123	111	NHS Reference Costs 2003[138] J33 op ultrasound scan (adjusted to 2004 prices)
Chest X-ray	100	1	83	83	NHS Reference Costs 2003[138] J35 op ultrasound scan (adjusted to 2004 prices)
CT of chest	10	1	177	18	NHS Reference Costs 2003[138] J24 op ultrasound scan (adjusted to 2004 prices)
CT of brain	10	1	177	18	NHS Reference Costs 2003[138] J24 op ultrasound scan (adjusted to 2004 prices)
CT of abdomen	5	1	177	9	NHS Reference Costs 2003[138] J24 op ultrasound scan (adjusted to 2004 prices)
Total				805	

ESR, erythrocyte sedimentation rate; FBC, full blood count; LFT, liver function test.

For tamoxifen, it is assumed that there is 96% generic prescribing and that compliance is 100%.

Resource use and costs: health states

Disease-free survival

On treatment

1. For costs of drug therapy – tamoxifen or AI – see the 'Drug costs' section on p. 68.
2. Follow-up is assumed to comprise one outpatient appointment per annum, at a cost of £88 per visit,[121] for the 5-year adjuvant treatment period. Follow-up practice varies widely – patients may be followed up more regularly in the first 2 years or follow-up may stop after 3 years, based on recent guidelines.[137]
3. Patients are assumed to receive a mammogram (annually for those patients treated with wide local excision and once every 2 years for those treated with mastectomy). An average of three mammograms per patient is assumed over the 5-year period, at a cost per mammogram of £122 (2003 Reference Cost HRG code J32 op).[138]

No costs are included in relation to bone mineral density screening and treatment for low bone mineral density for patients on AIs. This is the subject of a current review by the Osteoporosis Society and new guidelines are expected early in 2006. This would add further costs to the AI arm over the 5-year period. The impact of this is tested in sensitivity analysis.

After the treatment period

It is assumed that there are no costs associated with those patients who remain in the DFS state after completion of the treatment period.

Loco-regional recurrence and contralateral disease

Cost of diagnosis of recurrence/contralateral disease

The cost of diagnosis of LRR or contralateral disease is shown in *Table 31*. Assumptions regarding the proportion of patients undergoing tests were based on expert clinical opinion.

TABLE 32 *Cost of surgery for loco-regional recurrence or contralateral disease*

HRG code	HRG label	National average unit cost (£)
J01	Complex Breast Reconstruction using Flaps	4101.29
J04 and J05	Intermediate Breast Surgery w/o cc	1267.30
J11	Lymph Dissection Procedures	2237.84
J46 and J47	Total Mastectomy w/o cc	2459.28
Average		2516.43

Cost of treatment of recurrence/contralateral disease
Current guidelines state that a combination of the major therapeutic modalities – surgery, radiotherapy and systemic therapy – will be appropriate for patients experiencing contralateral disease or LRR[137] in breast cancer. Treatment for contralateral disease and ipsilateral recurrence is similar, although there may be some variation in terms of type of surgery and the type of chemotherapy regimen and endocrine therapy used. For the purposes of this analysis, it is assumed that the cost of treating these patients is the same. This is not strictly correct, but is expected to make little difference in the results.

- Surgery
  It is assumed that 90% of patients are treated with surgery, based on expert clinical opinion. An average cost figure for surgery for LRR or contralateral disease is derived, based on the average cost of the major procedures, taken from NHS Reference Costs 2004,[121] identified in *Table 32*.
- Radiotherapy
  It is assumed that one-third of patients will receive radiotherapy treatment – only those patients who have not previously received radiotherapy treatment. This is based on expert clinical opinion. The cost of radiotherapy is assumed to be £1858, based on NHS Reference Cost W15 (complex teletherapy with imaging >12 and <24 fractions).[138]
- Chemotherapy
  Only a small minority of patients receive chemotherapy, according to expert clinical opinion, and this is not included in the model.
- Endocrine therapy
  It is assumed that the majority (90%) of patients will receive endocrine treatment. Patients previously on tamoxifen may be switched to an AI and patients previously on an AI may be switched to tamoxifen. In practice, patients are likely to be switched to tamoxifen after an AI but there is little evidence to support this. An average cost of endocrine therapy is used in both arms.

Cost of remission (following contralateral disease and loco-regional recurrence)
This is as for the cost of follow-up for patients in the first 5 years of DFS, plus the cost of endocrine therapy.

The impact of a higher cost of recurrence/contralateral disease was tested in sensitivity analysis.

Distant recurrence
The choice of regimen will depend on the extent of the disease, previous treatment experience and the patient's fitness and wishes. The latest NICE guidance states that a course of chemotherapy should be no more than six cycles.[138]

First-line systemic therapy for advanced or metastatic breast cancer is

- chemotherapy for ER-negative patients – typically an anthracycline-containing regimen or sometimes a combination of cyclophosphamide, methotrexate and fluorouracil
- hormone-manipulation therapy for ER-positive patients.

For second-line or later therapy, a variety of agents, including taxanes and vinorelbine, should be available. Transtuzumab should be considered for patients who overexpress HER 2. Taxanes should be considered for second-line or later treatments (monotherapy) for treatment where initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate. Trastuzumab monotherapy should be available as an option for people with metastatic cancer overexpressing HER 2 at levels of 3+ who have received at least two chemotherapy regimens. Trastuzumab and paclitaxel should be available as an option for people overexpressing HER 2 at levels of 3+ who have not received chemotherapy and where initial cytotoxic chemotherapy including an anthracycline is inappropriate. Vinorelbine should be considered for monotherapy for second-line or later treatments where

initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate. In addition, capecitabine in combination with docetaxel may also be considered for people where initial cytotoxic chemotherapy (including an anthracycline) has failed or is inappropriate. Capecitabine monotherapy should be considered for people who have not previously had capecitabine in combination therapy or for whom people where anthracycline-based cytotoxic chemotherapy has failed or further anthracycline-based cytotoxic chemotherapy is contraindicated.

The cost of treatment of metastatic cancer is taken from Remak and Brazil.[139] The lifetime cost was estimated to be £14,905, based on treatment practices in 2002 and an assumed median survival of 18 months. Average monthly costs per patient on active treatment, supportive care and end-of-life care were estimated to be £810, £805 and £1569, respectively.

Within the ScHARR model, it is assumed that the monthly costs are £805 during both the active treatment and supportive care phases. The cost of end-of-life care is assumed to be part of the cost of death from breast cancer (see below). Given that Remak and Brazil's 2004 paper[139] is based on resource usage on 2002, it may underestimate the proportion of patients on taxanes and Herceptin and therefore underestimate the costs of metastatic relapse. The impact of assuming a higher annual cost is tested in sensitivity analysis.

Death from breast cancer

Patients may receive end-of-life care in a hospital, hospice or home setting. An average cost of dying in a variety of settings is estimated at £3146, based on costs taken from Coyle and colleagues' paper,[118] adjusted to present-day prices. The proportion of home care is assumed to be 20%.

Resource use and costs: adverse events

There are differences in the profiles of treatment-related AEs between the AIs and tamoxifen. AIs have been associated with bone loss and resultant higher rates of fracture and concerns over increased cardiovascular deaths. Tamoxifen has been associated with higher rates of vaginal bleeding, endometrial cancer, venous thromboembolic events and ischaemic cerebrovascular disorders.

In general, only AEs that are observed to differ significantly in frequency between the treatment groups are modelled. The exception to this is fractures. The majority of trials have demonstrated a significant difference in overall fracture rate. However, none of the trials to date have demonstrated a significant difference in hip fracture rate, but the lack of significance in hip fractures in these trials may be due to the small numbers of expected hip fracture events in women of this age. Due to the potential long-term risks of hip and other fractures in this population, as the population ages it was considered prudent to take this risk into account.

Minor AEs such as hot flushes, arthritis, arthralgia and myalgia were considered to have relatively minor cost and utility implications and were therefore not modelled.

In our model, we make the assumption that a cohort of patients develops the AE each year based on the AE rate over the trial period, converted into an annual rate to make it compatible with the cycle length. It is assumed that AEs are mutually exclusive (i.e. a patient developing endometrial cancer does not experience another (fatal or not fatal) AE. In general, we assume that after the 5-year adjuvant therapy period patients no longer develop AEs. The exception to this is fracture risk, which is modelled separately using the osteoporosis model used in the evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenopausal osteoporosis.[116] In the case of fractures, the risk is extended for a further 5 years, beyond the 5-year therapy period.

The costs of AEs are added to the cost of the health state that the patients are in. Some adverse events are assumed to have a reduction in quality of life (see the section 'Utility data', p. 75).

A number of the AEs are associated with a risk of mortality. AIs have been associated with bone loss and resultant higher fracture rates. Of these, hip and vertebral fractures are assumed to have mortality implications. In contrast, tamoxifen has been associated with higher rates of endometrial cancer, venous thromboembolic events and ischaemic cerebrovascular disorders events, which also have mortality implications.

The costs of AEs are given in *Table 33*.

Vaginal bleeding and discharge

Vaginal bleeding is included in the model due to the cost implications of referrals for suspected endometrial cancer. Postmenopausal women should not typically have bleeding and this always

TABLE 33 *Cost of adverse events*

Adverse event	Unit cost (£)	Source
Gynaecological		
Vaginal bleeding		
Diagnostic costs:		
Ultrasound ± biopsy	115	M03op, NHS Reference Costs 2003,[138] adjusted to 2004–5 values
Hysteroscopy and biopsy	148	M04op, NHS Reference Costs 2003,[138] adjusted to 2004–5 values
Endometrial cancer		
Diagnostic costs:		
Ultrasound ± biopsy	115	M03op, NHS Reference Costs 2003,[138] adjusted to 2004–5 values
Hysteroscopy and biopsy	148	M04op, NHS Reference Costs 2003,[138] adjusted to 2004–5 values
Treatment costs:		
Hysterectomy	1896	M07, NHS Reference Costs 2004[121]
Radiotherapy	3008	Average of W24 and W45, NHS Reference Costs 2004[121]
Cardiovascular events		
Ischaemic cerebrovascular events		
Treatment costs:		
Stroke year 1	8040	All taken from Ward *et al*. (2004)[140]
Stroke year 2+	2163	
TIA year 1	1064	
TIA year 2+	264	
Venous thromboembolic events		
Treatment costs:		
Deep vein thrombosis	721	Goodacre *et al*. (2004)[141]
Pulmonary embolism	1288	D10/D11 NHS Reference Costs 2004[121]

needs to be investigated. It is modelled as a non-life-threatening event, assuming cost and utility implications.

Patients presenting with symptoms of vaginal bleeding will undergo diagnostic tests. It is assumed that all patients, whether treated with AEs or tamoxifen, will receive the same investigations. This could be transvaginal ultrasound with or without biopsy and/or hysteroscopy and biopsy. It is assumed that hysteroscopy is undertaken on an outpatient basis, although in some cases it may require an inpatient stay. This may underestimate costs slightly. For the purposes of this analysis, it is assumed that 40% of patients receive an ultrasound, 40% receive a hysteroscopy and biopsy and 20% receive both.

No resource implications are modelled for vaginal discharge. This may underestimate costs slightly as a proportion of patients presenting with vaginal discharge may be referred for investigations. However, the likelihood of referral is dependent on the nature of the discharge. In addition, there may well be considerable overlap between patients presenting with vaginal discharge and those presenting with vaginal bleeding.

Endometrial cancer

Tamoxifen is known to induce uterine abnormalities from as early as 3 months of therapy.[142] Endometrial cancer is a very rare but serious AE, with cost, quality of life and mortality implications.

Patients presenting with symptoms of endometrial cancer (typically postmenopausal/abnormal vaginal bleeding) will undergo diagnostic tests – transvaginal ultrasound and/or hysteroscopy and biopsy. It is assumed that hysteroscopy is undertaken on an outpatient basis, although in some cases it may require an inpatient stay. For the purposes of this analysis, it is assumed that 40% of patients receive an ultrasound, 40% receive a hysteroscopy and biopsy and 20% receive both.

It is assumed that all patients will undergo surgery, although in reality a small minority may be considered too unfit. It is assumed that a standard hysterectomy is performed. A proportion of women, dependent on age and grade of tumour, will also receive radiotherapy. For the purposes of this analysis, it is assumed to be 50%. Radiotherapy cost is based on an average of teletherapy (HRG code w24) and low-dose brachytherapy (HRG code w45). The total one-off diagnostic and treatment cost is estimated to be £3558.

The annual cost of follow-up is assumed to be an average of two outpatient appointments per annum for 5 years. In reality, clinical practice varies widely – follow-up may be more frequent in the first year or two or may be stopped earlier than 5 years.

Long-term tamoxifen users with endometrial cancer have been shown to have a worse prognosis than non-tamoxifen users. This may be due to less favourable histology and higher stage.[28] Endometrial cancer-specific 3-year survival for patients receiving 2–5 years of tamoxifen is 85% compared with 94% for non-users.[28] We assume that the mortality implications from endometrial cancer occur within the first 2 years.

Hypercholesterolaemia and cardiovascular events

Hypercholesterolaemia

Hypercholesterolaemia has not been included as an AE within the ScHARR model due to the current uncertainty in the evidence base. The Novartis economic model based on BIG 1-98 did include hypercholesterolaemia – taking into account the cost of a statin for the estimated additional patients in the letrozole patient group identified as receiving lipid-lowering medications over the course of the 5-year treatment period. However, in the Novartis submission it is noted that the lipid levels recorded in the BIG 1-98 trial were non-fasting and should therefore be interpreted with caution.

A recent review of the effects of AIs on lipids concluded that the available data are mixed but that different AIs appear to have different effects on lipid profiles.[143] Bundred reported that studies on anastrozole generally indicate a limited effect on lipids but there is some evidence of increased hypercholesterolaemia.[143] Letrozole has been associated with AEs on lipid profiles in some studies including BIG 1-98, whereas exemestane appears to date to have either a limited impact or may be associated with slightly improved lipid profiles. Although the changes are small, the impact on lipid profiles is more of an issue for women with early-stage breast cancer than for those with advanced breast cancer.

A paper by Elisaf and colleagues[144] demonstrated the impact of letrozole on lipids, on a small group of women (n = 20), The impact on serum lipid parameters has been used to predict the impact on risk of cardiovascular events, using the Framingham equation. The results are given in *Table 34*. The impact on the 10-year risk for an average woman aged 65 years of a coronary heart disease (CHD) or CVD event is small, with increases typically below 2%.

TABLE 34 *Impact of changes in cholesterol on 10-year risk of a CHD or CVD event for a woman aged 65 years*[144]

Event	Baseline (%)	16 weeks (%)
CHD event	6.34	7.90
CHD death	0.71	1.02
CVD event	11.26	12.96
CVD death	2.81	3.44
Stroke	2.19	2.20

Omitting this from the model will potentially favour the AIs. Results from the Novartis model suggest that the additional costs are relatively small. Given the ongoing reductions in the price of statins over recent months, the impact of this will be further reduced.

The ASCO status report 2004[145] concluded that current information is not sufficient to determine the effects of AIs on CVD and CHD risk. The effect of AIs on cholesterol levels cardiac clinical monitoring needs to be clarified by further clinical research.

Ischaemic cerebrovascular events

One trial (ATAC) has been identified which demonstrates a significant difference between ischaemic cerebrovascular events in the two arms of the trial. For CVA/TIA the number of events are 62 (2%) for anastrozole and 86 (2.8%) for tamoxifen (p = 0.03). The rate of stroke:TIA in women is used to estimate the proportion of strokes. From Dennis and colleagues,[146] the incidence of TIA and stroke (per 1000) is 0.69 and 1.74, respectively. Therefore, it is estimated that 78% of all CVA/TIA events are stroke. Only stroke events are modelled as potentially life threatening. The ratio of non-fatal to fatal stoke is taken to be 81:19.[140]

We make the assumption that in each year, up to year 5, patients can develop a stroke (either fatal or not fatal) or a TIA. TIA and non-fatal stroke costs and quality of life reductions are calculated for year 1 and subsequent years.

Venous thromboembolism

The majority of trials record venous thromboembolic events as an AE. Event rates for deep vein thromboembolic (DVT) events (a blood clot in a deep vein, i.e. one that accompanies an artery) are taken from the trials, where available. In the ATAC trial these were 1.6% DVT events in the anastrozole arm compared with 2.4% in the

tamoxifen arm. The most serious complication of a DVT event is a pulmonary embolism (PE), where part of the blood clot breaks off and travels to the lung, creating a blockage in the artery. In the model, patients with a DVT event can either have fatal PE or not. The probability of a fatal PE given that a patient is being treated for a DVT event is estimated as 0.4% in the first year following the event.[147]

It should be noted that the industry submissions quote much higher mortality rates. For instance, Novartis used a 1-year mortality figure of 20% based on figures for venous thromboembolic events of 19%, rising to 30% at 3 years,[148] 1-year mortality associated with PE and DVT events as 39% and 21%, respectively.[149] These will give greater weight to the additional DVT events in the tamoxifen arm.

The cost of treating a DVT event is assumed to be £721 in the first year, with no additional costs assumed in subsequent years.[141] A PE requires emergency treatment and hospitalisation, and is costed at £1288 (HRG codes D10 and D11, NHS Reference Costs 2004[121]).

Fractures

The majority of the trials report statistically significant differences in the rate of overall fracture (see the section 'Adverse events: bone health', p. 40). However, it should be noted that, for those trials that do report hip fracture separately, none have shown a statistically significant difference in the rate to date. However, bone loss is evident in the AI arm of these trials. For instance, in the ATAC trial, bone loss expressed in terms of the percentage change from baseline at 2 years was –3.2% at total hip and –4% at lumbar spine for the AI arm, compared with 1.9% and 1.2%, respectively, in the tamoxifen arm. Patients with a lower bone mineral density are known to have a greater risk of future fracture, although bone mass density is only one relevant risk factor in predicting future fracture risk.

No data are yet available in the adjuvant setting to indicate the extent to which there is a continuation of risk of fracture beyond the trial period. In addition, it is not known the extent to which patients may obtain protective benefit from treatment with tamoxifen prior to treatment with AIs (such as in the switching and extended adjuvant settings).

Cost, quality of life and mortality implications of fractures are modelled using the osteoporosis model developed for Health Technology Assessment (HTA) work.[116] The impact of treatment with AIs and tamoxifen on fracture rates is assumed to continue for 10 years, 5 years beyond the treatment period. It is assumed that the relative risk of fractures is constant during years 1–5, and then the risk of fracture gradually returns to the normal population rate linearly over the next 5 years.

Fracture costs are in the process of being revised as part of the HTA osteoporosis work. Based on the available knowledge to date, the updated costs for fracture are included in the osteoporosis: £6000 for hip fracture, £500 for vertebral fracture, £450 for wrist and £1500 for proximal humerus (Stevenson M, University of Sheffield: personal communication, 2006). However, the final decision on the updated cost values has not been made and the costs used may not match the final costs adopted for future HTA work.

The key inputs to the osteoporosis model are the efficacy data in terms of ability to reduce the incidence of hip and vertebral fractures for each intervention. Efficacy data for tamoxifen compared with placebo are taken from Fisher and colleagues.[150] The HRs from the ATAC trial, comparing anastrozole and tamoxifen for individual fracture sites, are used along with the risk ratios from Fisher and colleagues comparing tamoxifen versus placebo, to give an indirect comparison of anastrozole versus placebo. These are used within the osteoporosis model to produce estimated cost and QALY results for anastrozole versus placebo and tamoxifen versus placebo, which are then combined.

The major area of uncertainty is the long-term risk of fracture resulting from treatment with AIs, that is, the extent to which bone loss experienced during the therapy period will impact on future fracture risk beyond the treatment period.

Bone loss in the ATAC trial was reported to be 2% per year for the first 2 years.[151] This may plateau out to 7–8% by 5 years and this bone loss is roughly equivalent to a change in T score of 1, which is roughly equivalent to double the fracture risk (Coleman RE, University of Sheffield: personal communication, 2005). This difference in fracture rates seen in the trials to date has been lower than this. A sensitivity analysis is undertaken in which the fracture risk for AIs is assumed to be double the risk compared with placebo.

Once therapy is complete, the difference in bone loss between groups may gradually diminish over

time but may not necessarily disappear completely. The osteoporosis model runs for 10 years and therefore does not capture any costs and benefits associated with differences in fracture risk beyond this period.

Utility data

Utility values associated with health states in the model are given in *Table 35*. The primary source of utility data used in the model is the Catalogue of Preference Weights from the CEA registry of Harvard School of Public Health,[113] which is a comprehensive database of preference weights for various health states sorted by disease areas, and from Tengs and Wallace,[152] which is a systematic review of health-related quality of life estimates from publicly available source documents.

In line with NICE recommendations, we selected a choice-based technique (such as standard gamble and time trade-off) or a generic instrument for obtaining health state values (such as EQ-5D or Health Utility Index) where available. When a preference-based score is not available, a rating scale is used as a second-best alternative. *Table 35* also shows who has elicited those values used to populate the economic model.

The value of 0.94 used for DFS relates to patients with early-stage breast cancer after lumpectomy or mastectomy.

It is assumed that the quality of life of patients with LRR is the same as that for patients with contralateral recurrence. The value of 0.74 is based on patients with breast cancer and who undergo chemotherapy. This value is slightly lower than the only value in Tengs and Wallace[152] corresponding precisely to local recurrence (a value of 0.8, based on standard gamble techniques).

The value of 0.85 for remission is described as "complete" remission from breast cancer. The same dataset also includes values for partial remission, of around 0.6–0.7, but these values are considered less relevant to this model.

For metastatic disease a value of 0.5 elicited by clinicians is used. Most of the values found in the literature span a range of 0.3–0.6. High values (0.8–0.85) can be found for health states described as metastatic before starting chemotherapy, but these seem too high, and therefore implausible. Values for metastatic are often elicited by experts or clinicians but not from patients. A value of 0.5 may be considered high as a metastatic state is a terminal state. It is worth noting that values from the industry submissions are higher than 0.5 (e.g. metastatic health state in the AstraZeneca submission is 0.63).

All these values are elicited by either patients or clinical experts rather than the general public. Values from the general public are usually preferred as these preference weights are used to inform resource allocation, but we were unable to identify any in the literature.

Given that the health-related quality of life in the general population decreases with age, it is important to take this into account in the model. A utility value of 0.83 for age-related utility of a woman aged 65 years is taken from Kind and Dolan[153] and is applied at the start of the model. The utilities for all health states are therefore multiplied by this age-related utility value (0.83) in

TABLE 35 *Utilities for health states*

Health state	Mean	Adjusted by age multiplier	PSA values	How valued	Who valued	Source
DFS	0.94	0.78	β (α = 3.44, β = 0.21)	TTO	Patients	Tengs and Wallace[152]
Contralateral	0.74	0.61	β (α = 1.36, β = 0.48)	TTO	Patients	Tengs and Wallace[152]
LRR	0.74	0.61	See above	See above	See above	See above
Distant metastases	0.5	0.42	β (α = 2.75, β = 2.75)	TTO	Experts	Tengs and Wallace[152]
Remission (following contralateral recurrence and LRR)	0.85	0.71	β (α = 1.97, β = 0.34)	Rating scale	Clinicians	CEA Analysis, Harvard School of Public Health[113]

TTO, time trade-off.

TABLE 36 *Utilities for adverse events*

Adverse event	Mean	PSA values	How valued	Who valued	Source
Endometrial cancer:		β (α = 48.37,		Authors	CEA Analysis, Harvard
Year 1	0.80	β = 12.09)			School of Public Health[113]
Year 2+	0.80				
DVT	0.940	β (α = 19.43, β = 1.24)		Expert opinion	Goodacre *et al.*[141]
Ischaemic cerebrovascular events:		β (α = 281,	SG		
Year 1	0.63	β = 165)			Tengs and Wallace[152]
Year 2+	0.63				Tengs and Wallace[152]
Vaginal bleeding	0.933	β (α = 5.02, β = 0.36)	SG	Patients	ATAC submission

SG, standard gamble.

order to take into account the typical starting age of patients within the trial.

Patients remain in the contralateral disease and LRR health states for 1 year only and then move to remission.

Utility: adverse events

Utility values associated with adverse events in the model are given in *Table 36*.

It is assumed that the utilities values for vaginal bleeding and DVT are 0.933 and 0.94, respectively, in the first year of the AE. Given that these are short-term events, it is assumed that there will be no utility decrement in subsequent years.

Utilities for patients experiencing an AE are used to adjust the utility of patients in different health states, in order to take into account the reduction in utility of patients experiencing a specific AE. For example, patients who experience vaginal bleeding have a utility value of 0.933; this is an absolute reduction of 0.067 (1.000 – 0.933). For patients in a DFS, with a utility of 0.78 (as shown in *Table 35*), who experience vaginal bleeding, their resultant utility is estimated to be 0.713 (the utility of the health state, 0.78, less the absolute reduction in utility for patients experiencing vaginal bleeding, 0.067).

Discounting

The economic analysis assumes that costs and QALYs are discounted at 6% and 1.5% per annum, respectively, in line with current recommendations from the UK Treasury. The impact of using alternative discount rates was explored within the sensitivity analysis, as alternative rates will be implemented within the 11th Wave of NICE technology appraisals.

One-way sensitivity analysis

In order to explore the impact upon the cost-effectiveness results of changes to individual parameters and assumptions, a number of scenario analyses were performed:

- Alternative scenario for extrapolation of recurrence rates beyond the trial period.
- Discount rates – both costs and QALYs were discounted at 3.5% per annum.
- Restricting period of analysis to 10 years.
- Higher cost of recurrence.

Probabilistic sensitivity analysis

PSA was undertaken to demonstrate the impact of uncertainty in the key model parameters and to generate information on the likelihood that each of the interventions is optimal.

The baseline overall survival and DFS curves within the model were described by multivariate normal distributions of the form $X \sim N(m,V)$, where m is the vector of means (the scale and shape parameters of the baseline Weibull survivor function) and V is the covariance matrix of these means. As the standard errors for the HRs between treatments (for both DFS and overall survival) were symmetrical, these were sampled from normal distributions.

Transition probabilities and utility values are modelled using beta distributions and costs are modelled using a gamma distribution.

The PSA was carried out by allowing all of the above parameters to vary according to the uncertainty specified in their probability distributions, with 5000 sets of random numbers used to generate 5000 sets of cost-effectiveness results. These results were then used to derive cost-effectiveness planes and CEACs for each direct treatment comparison.

Budget impact

The total annual cost to the NHS was estimated using the treatment cost estimates from the adjuvant phase for each intervention. This included drug acquisition and administration costs, pharmacy costs, AE management and hospitalisation costs and the costs of diagnostic tests during the adjuvant treatment phase (e.g. CT scans).

ScHARR economic model – results

This section details the results of the health economic model. The cost-effectiveness results of the AIs are presented as marginal estimates when compared against tamoxifen (or placebo, in the case of the extended adjuvant analysis). All results are presented in terms of marginal cost per LYG and cost per QALY gained.

Base-case estimates of cost-effectiveness

All costs are discounted at 6% and benefits at 1.5% unless stated otherwise.

Base case results: primary adjuvant

Two of the AIs have trial evidence in the primary adjuvant setting – anastrozole (ATAC) and letrozole (BIG 1-98). Patients in the ATAC trial have completed the 5-year adjuvant therapy period, with an average follow-up of 68 months. Data from BIG 1-98 are, however, based on a median follow-up of 26 months. Results are presented in *Figures 6* and 7 and *Table 37*.

Cost-effectiveness ratios in the adjuvant setting are higher for anastrozole than for letrozole. This difference is mainly driven by differences in the HRs – in the ATAC trial, the HR for anastrozole compared with tamoxifen for metastatic recurrence is 0.8, whereas in BIG 1-98 the HR for letrozole compared with tamoxifen for metastatic recurrence is 0.75. Approximately 60% of recurrences are metastatic. However, it should be noted that the HR for ATAC is based on an average follow-up of 68 months, whereas that for letrozole is based on an average follow-up of 26 months, but is assumed to remain constant for the full 5-year therapy period. Therefore, there is greater uncertainty around the application of the HR from the BIG 1-98 trial in the economic model

These results are based on the conservative scenario that the benefits of AIs over tamoxifen, in terms of reductions in recurrences, in the 5-year adjuvant therapy period are gradually lost during the following 10 years. A further scenario, "Benefits maintained", is tested in sensitivity analysis. In this scenario, it is assumed that following the treatment period the annual rate of

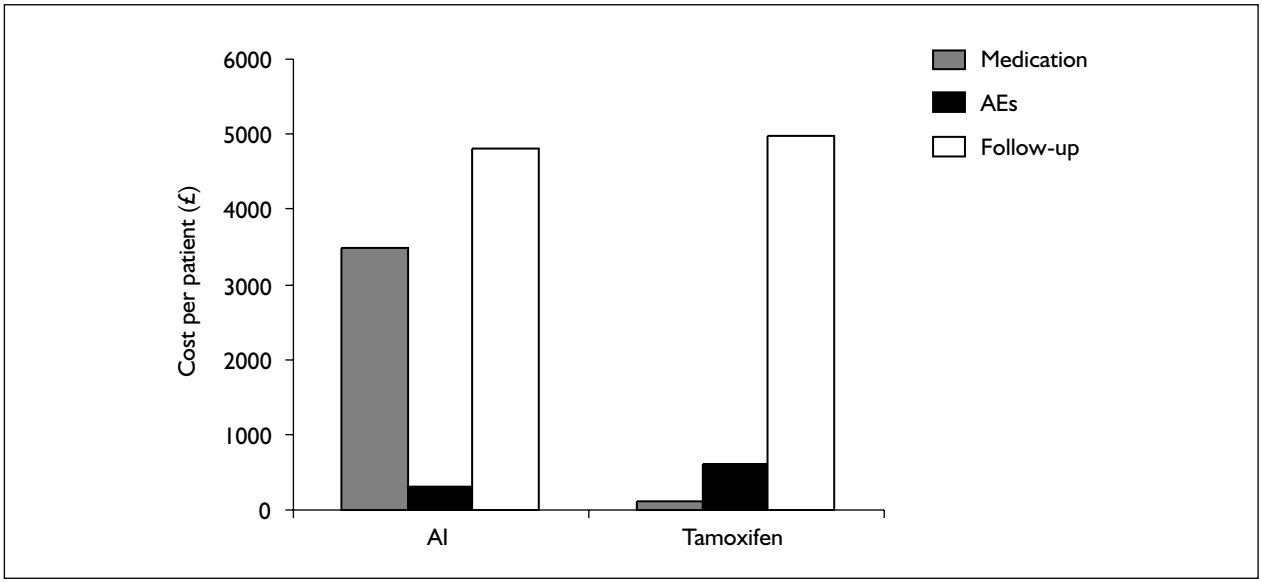

FIGURE 6 *Anastrozole in the primary adjuvant setting: breakdown of discounted costs per patient (35-year analysis)*

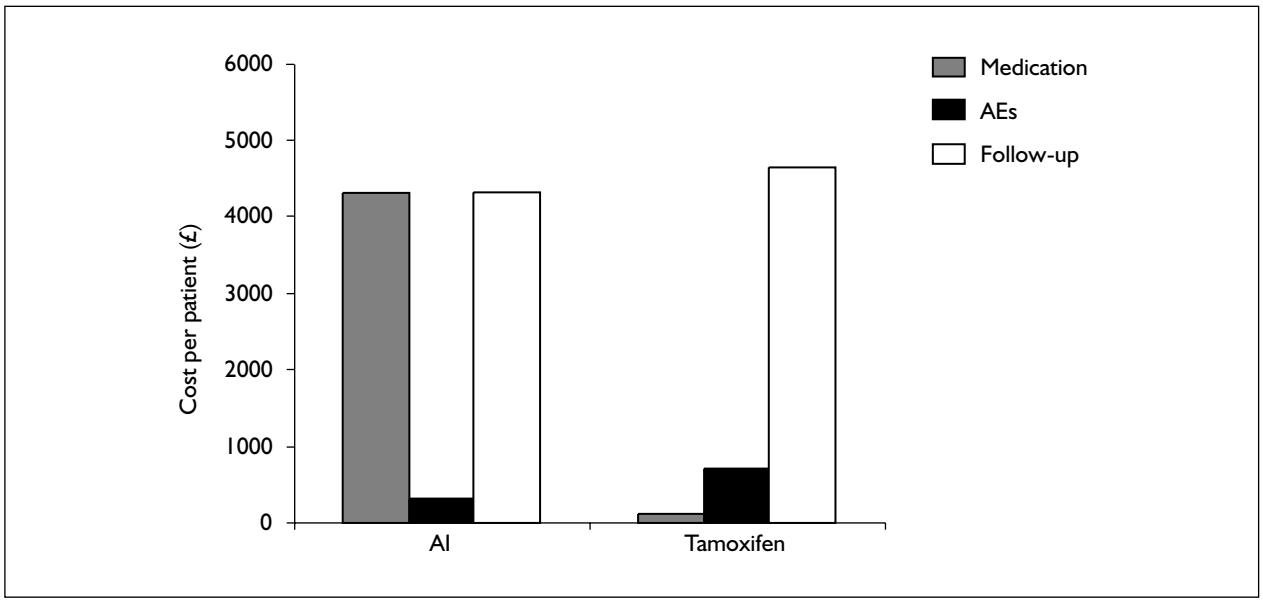

FIGURE 7 *Letrozole in the primary adjuvant setting: breakdown of discounted costs per patient (35-year analysis)*

TABLE 37 *Cost-effectiveness of anastrozole and letrozole in the primary adjuvant setting*

	Anastrozole: primary adjuvant (ATAC)			Letrozole: primary adjuvant (BIG 1-98)		
	Anastrozole	**Tamoxifen**	**Difference**	**Letrozole**	**Tamoxifen**	**Difference**
Costs (£)						
Drug	3,483	117	3,367	4,319	119	4,200
AEs	315	604	–289	336	642	–307
Follow-up costs	4,802	4,981	–180	4,347	4,587	–240
Total costs (£)	8,600	5,702	2,898	9,002	5,348	3,654
Survival (years)						
LYG	12.85	12.77	0.08	14.65	14.48	0.16
QALY	9.78	9.69	0.09	11.12	10.95	0.17
Cost per QALY (£)			31,965			21,580

recurrence in both arms is the same (see the section 'Primary adjuvant', p. 80).

The higher drugs costs associated with AIs are partly offset by lower follow-up costs. Follow-up costs are the costs associated with follow-up and treatment of recurrence and cancer death during a patient's lifetime.

Base-case results – unplanned switch

Two of the AIs have trial evidence in the unplanned switch setting – anastrozole (GABG and Jonat meta-analysis) and exemestane (IES). Patients in the anastrozole trials have completed the 5-year adjuvant therapy period, with an average follow-up of 28 and 36 months for GABG and Jonat, respectively. Data from IES are based on a median follow-up of 37 months. Results are presented in *Figures 8* and *9* and *Table 38*.

Cost-effectiveness results for anastrozole and exemestane in the unplanned switch setting are similar. The treatment costs are lower in this setting than in the primary adjuvant setting given that AI treatment is not given for the full 5-year therapy period.

These results are based on the conservative scenario that benefits of AIs over tamoxifen in the adjuvant therapy period are gradually lost during the following 10 years. This assumption is tested in sensitivity analysis in the 'Unplanned switch' section on p. 80.

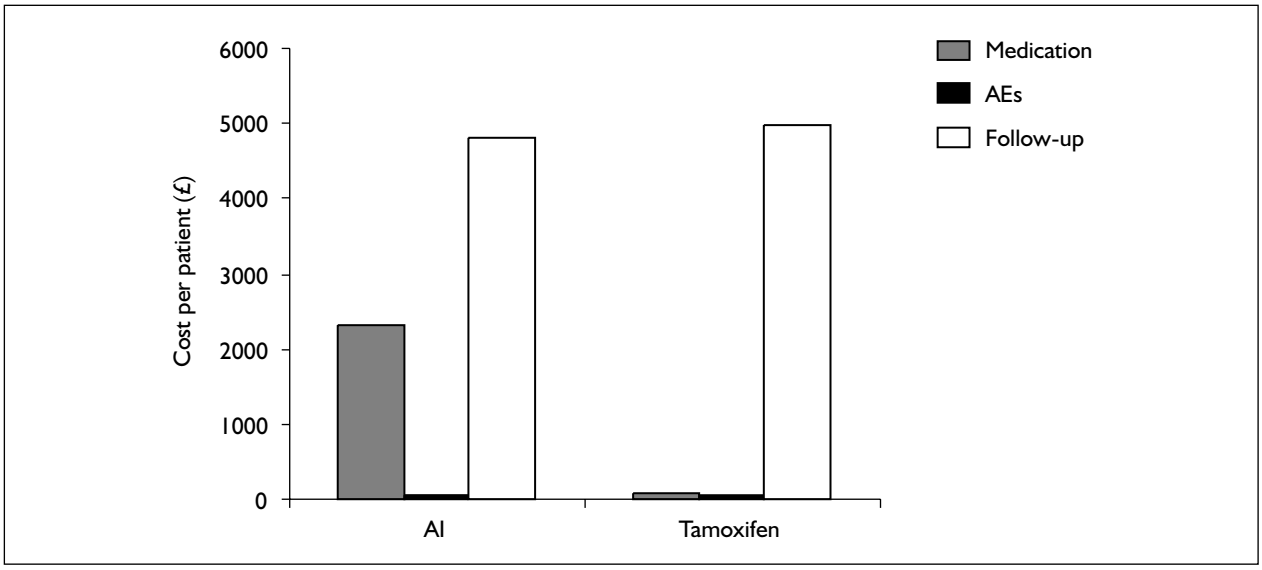

FIGURE 8 *Anastrozole in the switch therapy setting: breakdown of discounted costs per patient (35-year analysis)*

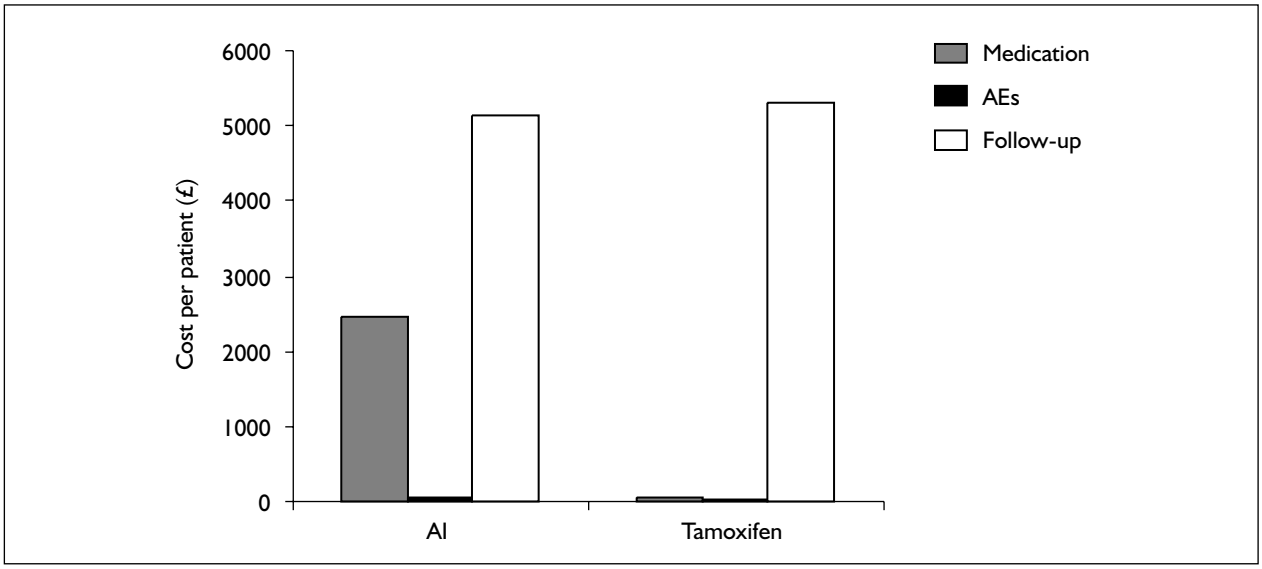

FIGURE 9 *Exemestane in the switch therapy setting: breakdown of discounted costs per patient (35-year analysis)*

TABLE 38 *Cost-effectiveness of anastrozole and exemestane in the unplanned switch setting*

	Anastrozole: unplanned switching (CABG/ITA)			Exemestane: unplanned switching (IES)		
	Anastrozole	**Tamoxifen**	**Difference**	**Exemestane**	**Tamoxifen**	**Difference**
Costs (£)						
Drug	2,330	78	2,252	2,463	67	2,396
AEs	44	57	–13	47	30	17
Follow-up costs	4,809	4,984	–175	5,149	5,314	–165
Total costs (£)	7,183	5,119	2,064	7,659	5,411	2,248
Survival (years)						
LYG	13.80	13.71	0.09	13.02	12.88	0.13
QALY	10.51	10.42	0.09	9.91	9.80	0.12
Cost per QALY (£)			23,215			19,170

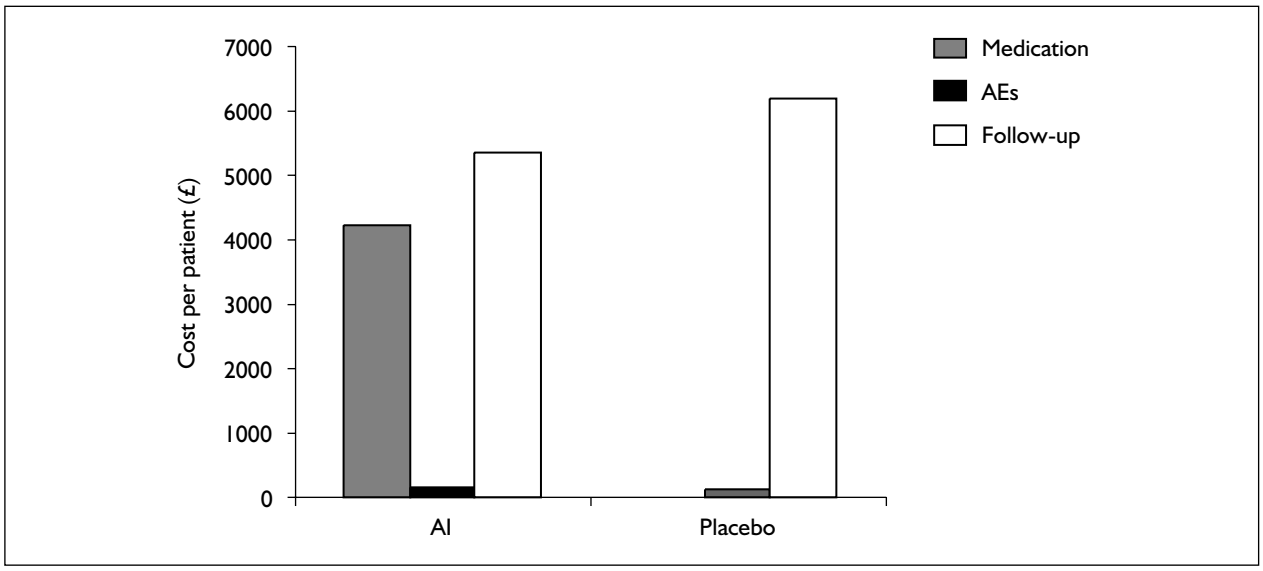

FIGURE 10 *Letrozole in the extended adjuvant setting: breakdown of discounted costs per patient (35-year analysis)*

TABLE 39 *Cost-effectiveness of letrozole in the extended adjuvant setting*

	Letrozole: extended adjuvant (MA 17)		
	Letrozole	**Placebo**	**Difference**
Costs (£)			
Drug	4221	–	4221
AEs	168	143	25
Follow-up costs	5367	6205	–838
Total costs (£)	9757	6348	3409
Survival (years)			
LYG	14.52	14.10	0.42
QALY	11.03	10.68	0.35
Cost per QALY (£)			9760

Base-case results – extended adjuvant
Results for letrozole, based on MA-17, are presented in *Figure 10* and *Table 39*.

In the extended adjuvant setting, the cost per QALY for letrozole, compared with placebo, is estimated to be £9760, based on an analysis over 35 years. This patient group comprises patients who remained disease free following the 5 years of adjuvant therapy on tamoxifen. This group of patients has a better prognosis than the primary adjuvant group given that the majority of recurrences occur within the first 5 years.

These results are based on the conservative scenario that benefits of AIs over tamoxifen in the adjuvant therapy period are gradually lost during the following 10 years. This assumption is tested in sensitivity analysis in the 'Extended adjuvant setting' section below.

Sensitivity analysis results

Primary adjuvant
Results for the primary adjuvant setting are presented in *Tables 40* and *41*.

Unplanned switch
Results for the unplanned switch setting are presented in *Tables 42* and *43*.

Extended adjuvant setting
Results for the extended adjuvant setting are presented in *Table 44*.

The results of univariate sensitivity analysis show that the results are robust to changes in the key parameters.

TABLE 40 *Results of one-way sensitivity analysis for anastrozole in the primary adjuvant setting*

	Costs (£)		QALYs		Cost per QALY (£)
	Anastrozole	**Tamoxifen**	**Anastrozole**	**Tamoxifen**	
Base case	8,600	5,702	9.78	9.69	31,965
Scenarios					
"Benefits maintained" scenario	8,296	5,702	9.90	9.69	12,310
Discount rate: 3.5% costs and benefits	9,809	6,761	8.27	8.18	37,527
10-year analysis time frame	7,022	4,160	5.82	5.74	35,322
Cost of recurrence doubled	12,253	9,502	9.78	9.69	30,346
Start age 75 years (base case = 65 years)	6,812	4,175	6.30	6.23	36,638

TABLE 41 *Results of one-way sensitivity analysis for letrozole in the primary adjuvant setting*

	Costs (£)		QALYs		Cost per QALY (£)
	Letrozole	**Tamoxifen**	**Letrozole**	**Tamoxifen**	
Base case	9,002	5,348	11.12	10.95	21,580
Scenarios					
"Benefits maintained" scenario	8,664	5,348	11.31	10.95	9,325
Discount rate: 3.5% costs and benefits	10,169	6,311	9.20	9.06	26,294
10-year analysis time frame	7,569	3,971	6.02	5.89	29,128
Cost of recurrence doubled	12,078	8,633	11.12	10.95	20,345
Start age 75 years (base case = 65 years)	6,903	3,860	6.11	5.99	26,116

TABLE 42 *Results of one-way sensitivity analysis for anastrozole in the unplanned switch setting*

	Costs (£)		QALYs		Cost per QALY (£)
	Anastrozole	**Tamoxifen**	**Anastrozole**	**Tamoxifen**	
Base case	7,183	5,119	10.51	10.42	23,215
Scenarios					
"Benefits maintained" scenario	6,825	5,119	10.67	10.42	7,016
Discount rate: 3.5% costs and benefits	8,305	6,110	8.79	8.71	26,825
10-year analysis time frame	5,463	3,560	5.95	5.87	22,515
Cost of recurrence doubled	11,010	9,106	10.51	10.42	21,414
Start age 75 years (base case = 65 years)	5,310	3,503	6.20	6.13	24,948

TABLE 43 *Results of one-way sensitivity analysis for exemestane in the unplanned switch setting*

	Costs (£)		QALYs		Cost per QALY (£)
	Exemestane	**Tamoxifen**	**Exemestane**	**Tamoxifen**	
Base case	7,659	5,411	9.91	9.80	19,170
Scenarios					
"Benefits maintained" scenario	7,106	5,411	10.15	9.80	4,793
Discount rate: 3.5% costs and benefits	8,652	6,248	8.33	8.22	22,039
10-year analysis time frame	6,316	4,299	5.73	5.61	16,920
Cost of recurrence doubled	11,736	9,733	9.91	9.80	17,082
Start age 75 years (base case = 65 years)	6,046	4,059	6.07	5.97	20,565

TABLE 44 *Results of one-way sensitivity analysis for letrozole in the extended adjuvant setting*

	Costs (£)		QALYs		Cost per QALY (£)
	Letrozole	Placebo	Letrozole	Placebo	
Base case	9,757	6,348	11.03	10.68	9,760
Scenarios					
"Benefits maintained" scenario	8,857	6,348	11.44	10.68	3,306
Discount rate: 3.5% costs and benefits	11,046	7,324	9.13	8.83	12,475
10-year analysis time frame	8,182	5,196	5.96	5.73	12,835
Cost of recurrence doubled	13,896	11,206	11.03	10.68	7,704
Start age 75 years (base case = 65 years)	7,559	4,747	6.32	6.10	12,499

It should be noted that the base-case results are considered conservative in that they are based on a scenario in which the benefits gained by AIs during the treatment period are gradually lost over the following 10 years. In the "benefits maintained" scenario it is assumed that following the treatment period the annual rate of recurrence in both arms is the same – based on the rate of recurrence between 5 and 15 years from the EBCTCG 2005 paper.[37] In this scenario, the benefits of AIs achieved during the trial period are preserved, with no difference in the rates of recurrence between the two arms after the adjuvant treatment period, and show that the ICERs are typically more than 50% lower under this assumption.

Sensitivity analysis for fracture rates

The impact of risk of fracture is modelled outside the breast cancer model. The impact of treatment with AIs and tamoxifen on fracture rates is assumed to continue for 10 years, 5 years beyond the treatment period. It is assumed that the relative risk of fractures is constant during years 1–5, and then the risk of fracture gradually returns to the normal population rate linearly over the next 5 years. The 10-year costs and QALYs from the osteoporosis model are incorporated into the base-case results from the breast cancer model.

In the base case, the total 10-year costs and benefits associated with AIs compared with tamoxifen are estimated to be a mean cost of £21 and a mean QALY decrement of 0.005 per patient. The impact of this on total costs and QALYs within the breast cancer model is small.

A sensitivity analysis has been undertaken assuming that the fracture risk for AIs is double the risk compared with placebo, a higher relative risk of fracture risk than seen in the trials to date. This produces a 10-year mean cost and QALY decrement estimate of £168 and –0.022, respectively. If it was assumed that the relative risk remained constant over the 10-year period, rather than gradually returning to the normal population rate between years 5 and 10, it is estimated that this would add approximately an extra one-third on to the cost and QALY loss. (Stevenson M, University of Sheffield: personal communication, 2006). When these alternative assumptions on the impact of increased fracture risk and treatment for osteoporosis are included, the cost per QALY gained increases to over £40,000 for anastrozole in the primary adjuvant setting. However, using these assumptions in the "benefits maintained" scenario, the cost per QALY gained remained below £20,000 for all drugs and treatment strategies.

Probabilistic sensitivity analysis results

PSA is used to demonstrate the likely impact of all the uncertainty in the model upon the cost-effectiveness results. The results are presented as cost-effectiveness planes (scatterplots) for each of the treatment comparisons, and subsequently presented as CEACs. The results are based on 10,000 probabilistic model runs.

PSA results: primary adjuvant

The results displayed in *Figures 11–14* show that in most cases anastrozole and letrozole are more costly but more effective than tamoxifen.

Figure 11 demonstrates that in all 10,000 model runs, the anastrozole arm is more costly more than the tamoxifen arm. The results also suggest that, in all but a small number of cases, anastrozole is more effective than tamoxifen in terms of QALYs gained per patient.

Figure 12 shows that in all 10,000 model runs, the letrozole arm is more costly more than the tamoxifen arm, but in all but a small number of cases letrozole is more effective than tamoxifen in terms of QALYs gained per patient.

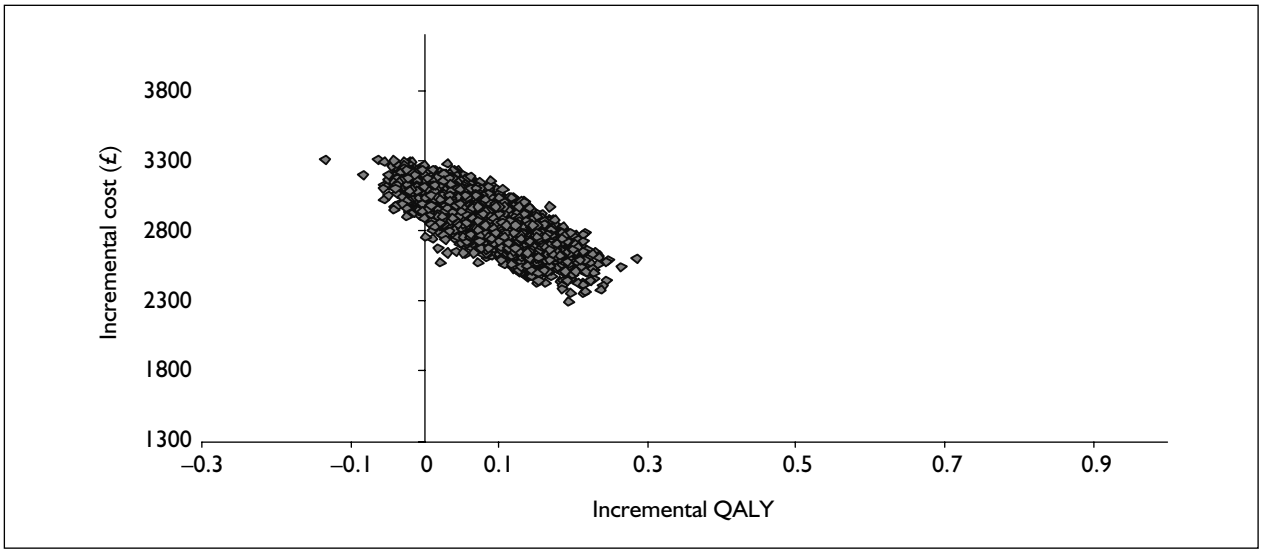

FIGURE 11 *Scatterplot of anastrozole versus tamoxifen in primary adjuvant setting (based on ATAC trial)*

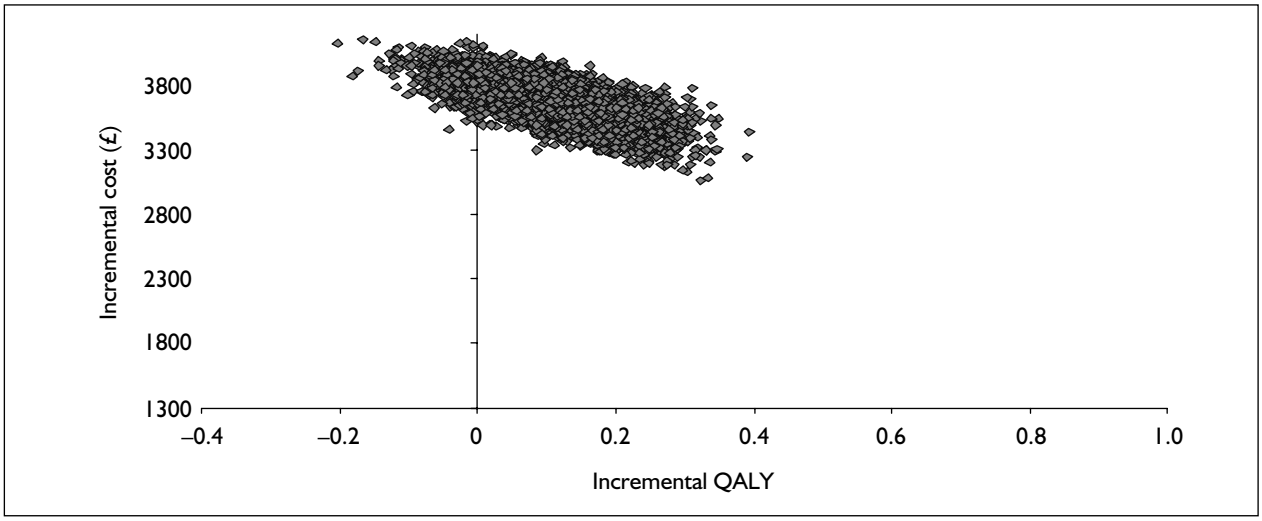

FIGURE 12 *Scatterplot of letrozole versus tamoxifen in primary adjuvant setting (based on Big 1-98 trial)*

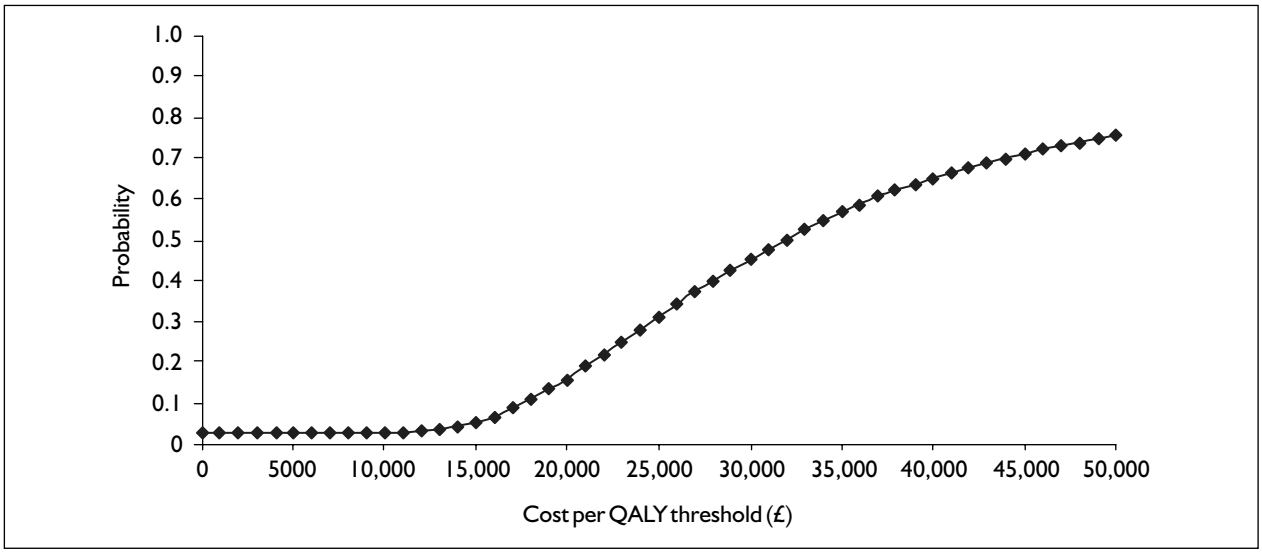

FIGURE 13 *CEAC of anastrozole versus tamoxifen in primary adjuvant setting (based on ATAC trial)*

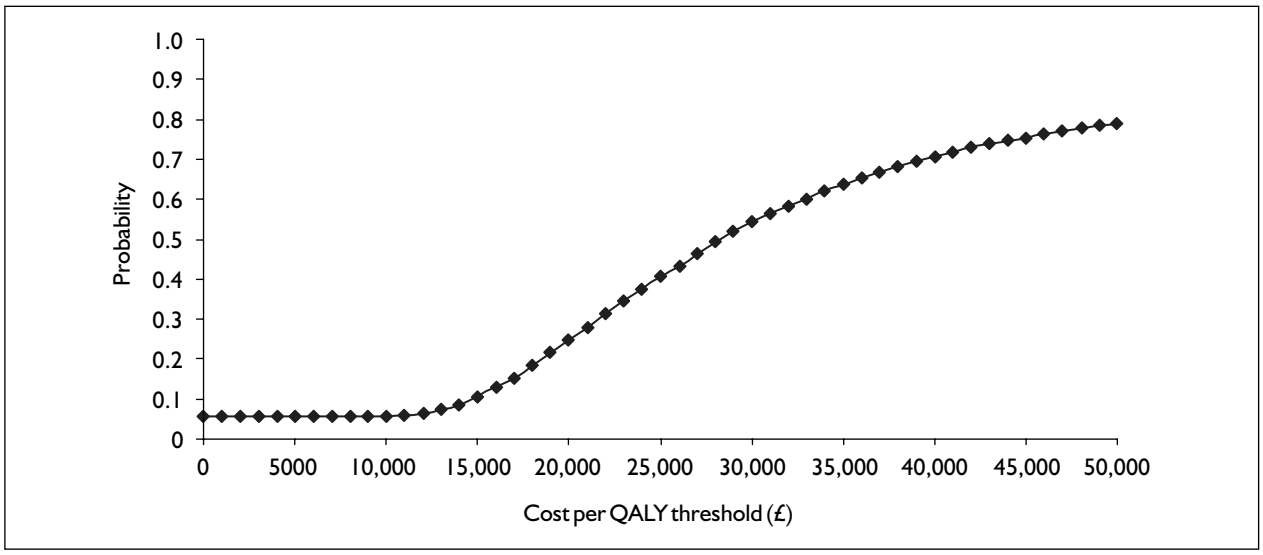

FIGURE 14 *CEAC of letrozole versus tamoxifen in primary adjuvant setting (based on BIG 1-98 trial)*

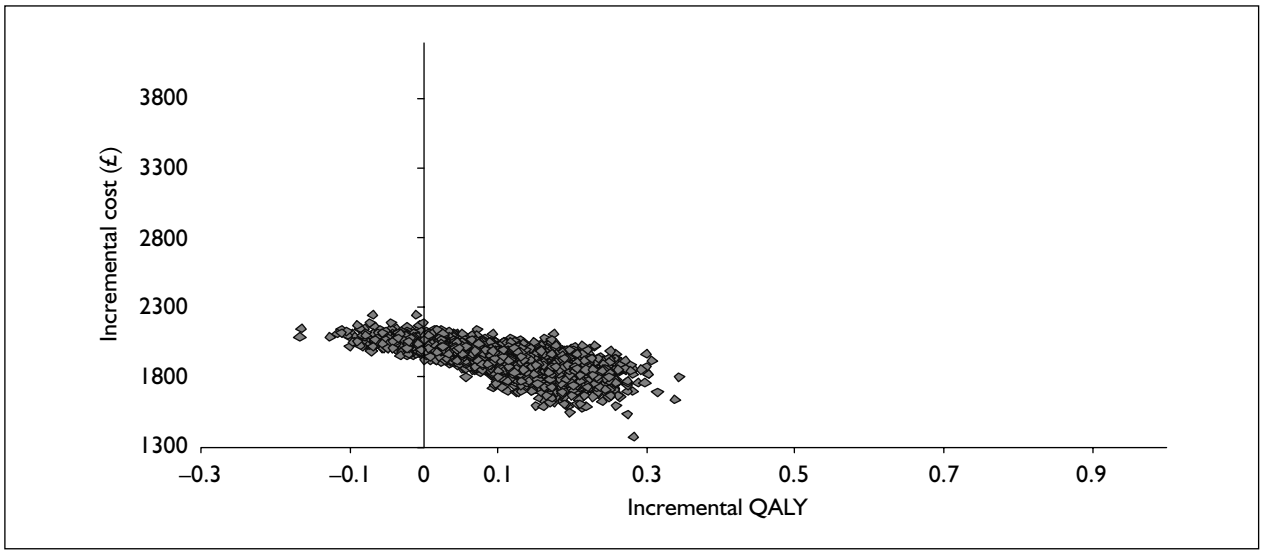

FIGURE 15 *Scatterplot of anastrozole versus tamoxifen in unplanned switch therapy setting (based on GABG trial)*

Figures 13 and *14* present CEACs showing the likelihood that each treatment is cost-effective at each willingness-to-pay threshold.

These plots show that by employing cost-effectiveness thresholds of £30,000, anastrozole and letrozole have around a 50–60% probability of being cost-effective when compared with tamoxifen in the adjuvant setting regimen. It should be noted that these cost-effectiveness results are based on a conservative assumption regarding treatment benefits and it is expected that the cost-effectiveness ratios may well be lower than those presented. In the "benefits maintained" scenario, the cost per QALY for AIs compared with tamoxifen is estimated to be more than 50% lower, at around £10,000–12,000 in the primary adjuvant setting.

PSA results: unplanned switching

Figure 15 demonstrates that in all 10,000 model runs, the anastrozole arm is more costly more than the tamoxifen arm. The results also suggest that, in all but a small number of cases, anastrozole is more effective than tamoxifen in terms of QALYs gained per patient.

Figure 16 shows that in all 10,000 model runs, the exemestane arm is more costly more than the tamoxifen arm. In all but a small number of cases, exemestane is more effective than tamoxifen in terms of QALYs gained per patient.

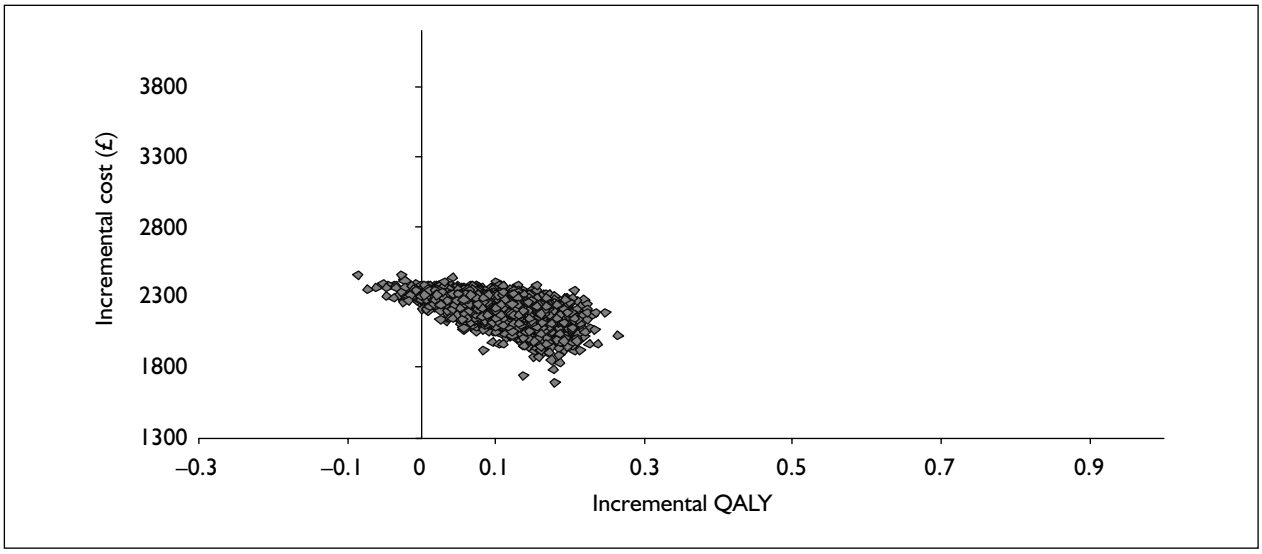

FIGURE 16 *Scatterplot of exemestane versus tamoxifen in unplanned switch therapy setting (based on IES trial)*

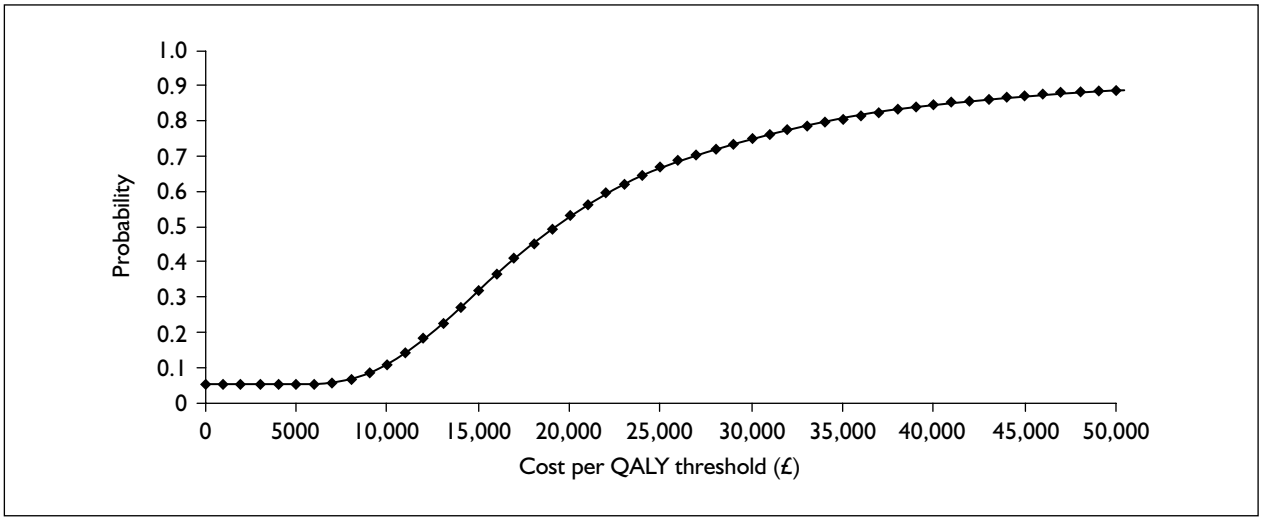

FIGURE 17 *CEAC of anastrozole versus tamoxifen in unplanned switch therapy setting (based on GABG trial)*

Figure 17 shows that by employing a cost-effectiveness threshold of £30,000, anastrozole has a probability of around 70–80% of being cost-effective when compared with tamoxifen in the unplanned switching setting. It should be noted that these cost-effectiveness results are based on a conservative assumption regarding treatment benefits and it is expected that the cost-effectiveness ratios may well be lower than those presented.

Figure 18 shows that by employing a cost-effectiveness threshold of £30,000, exemestane has a probability of around 75% of being cost-effective when compared with tamoxifen in the unplanned switching setting. It should be noted that these cost-effectiveness results are based on a conservative assumption regarding treatment benefits and it is expected that the cost-effectiveness ratios may well be lower than those presented.

Figure 19 shows that in all 10,000 model runs, the letrozole arm is more costly more than the placebo arm, but in all but a small number of cases letrozole is more effective than placebo in terms of QALYs gained per patient.

Figure 20 shows that by employing a cost-effectiveness threshold of £30,000, letrozole has a probability of over 95% of being cost-effective when compared with placebo in the extended

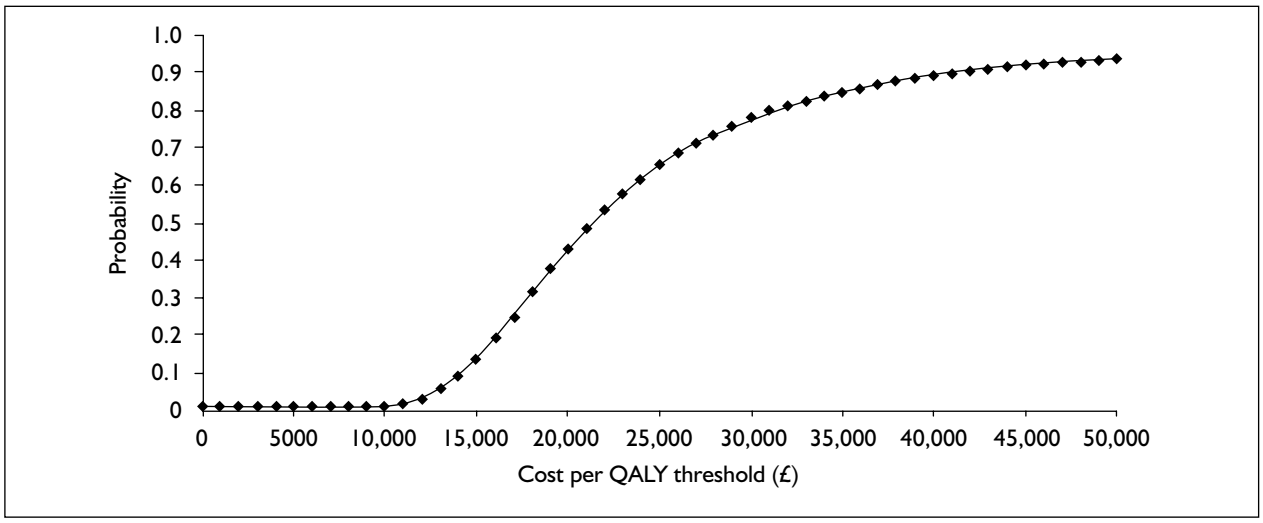

FIGURE 18 *CEAC of exemestane versus tamoxifen in unplanned switch therapy setting (based on IES trial)*

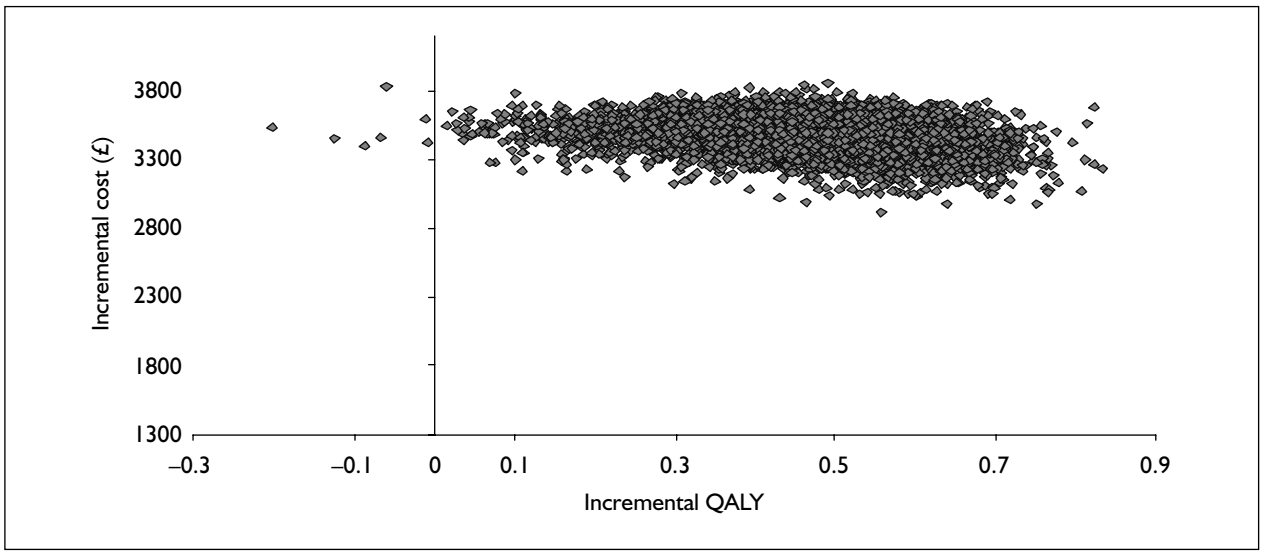

FIGURE 19 *Scatterplot of letrozole versus placebo in extended adjuvant setting (based on MA-17 study)*

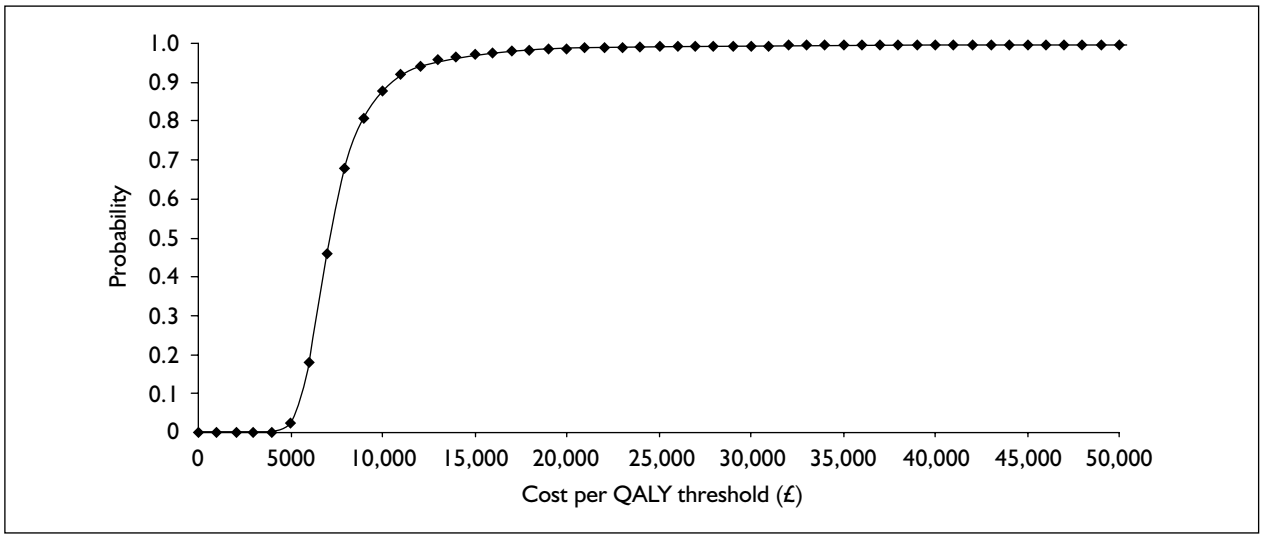

FIGURE 20 *CEAC of letrozole versus placebo in extended adjuvant setting (based on MA-17 study)*

adjuvant setting. It should be noted that these cost-effectiveness results are based on a conservative assumption regarding treatment benefits and it is expected that the cost-effectiveness ratios may well be lower than those presented.

Discussion of cost-effectiveness results

The three treatment strategies – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – are considered separately within the economic analysis. It is not possible to compare directly trials with strategies that randomised patients halfway through or at the end of the standard 5-year adjuvant treatment period with a strategy which randomises patients immediately after surgery.

Based on the results of the ScHARR analysis, the cost per QALY for AIs compared with tamoxifen is estimated to be between £21,600 and £32,000 in the primary adjuvant setting and between £19,200 and £123,200 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £9800.

The base-case results are considered conservative in that they are based on a scenario in which the benefits gained by AIs during the treatment period are gradually lost over the following 10 years. An alternative scenario, "benefits maintained", in which rates of recurrence are the same in both arms after the therapy period is complete, shows that the ICERs are typically over 50% lower under this assumption. In the "benefits maintained" scenario, the cost per QALY for AIs compared with tamoxifen is estimated to be around £12,000 in the primary adjuvant setting and around £5000 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £3000 for the "benefits maintained" scenario. It is plausible, if the AIs are shown to have a 'carry-over' effect similar to that seen with tamoxifen (in which the benefits in terms of reduced recurrence continue beyond the therapy period), that the cost per QALY could be even lower than those presented in the "benefits maintained" scenario. To date, there is early evidence from the 68-month follow-up data from the ATAC trial which shows lower recurrence rates for anastrozole than for tamoxifen continuing after the therapy period.

Key issues

- The assumption regarding the benefits, after the therapy period, in the AI arm relative to the tamoxifen arm has a major influence on the ICER. As discussed above, the base case in the ScHARR model is considered conservative – it assumes that the rate of recurrence in the AI arm is higher than that in the tamoxifen arm after the treatment period, to the extent that after 15 years the number of recurrences in both arms is the same.
- A key influence on cost-effectiveness results is the length of analysis. Drug costs of AIs are high relative to tamoxifen. However, cost offsets for the AI arm are accrued gradually over time, resulting from a lower rate of progression to recurrence and contralateral disease experienced. The model assumes that benefits from reduced recurrence will translate into overall survival benefits in the medium and long term. Restricting the analysis to a period of 10 years reduces the period over which benefits can be accrued and increases the ICER by around 20%.
- The ScHARR model assumes the same rate of progression for patients with contralateral disease and LRR. This may overestimate the benefits of AIs as there is some evidence that patients with contralateral disease have a better prognosis than patients with LRR. In the ScHARR model, these patients will have a worse prognosis and will therefore benefit more, in absolute terms, and this will lower the ICER. However, the proportion of patients who will develop contralateral disease is very low and the impact on results is likely to be small.
- The impact of life-threatening AEs is to increase deaths from other causes, which may offset the reduction in cause-specific deaths. Evidence to date suggests that these AEs do not unduly impact on the predicted ICERs. The largest uncertainty is the potential long-term risk of fracture from AIs. The analysis undertaken suggests that the impact of fracture risk on costs and QALYs within the first 10 years is limited. Further evidence from long-term follow-up is required.

Comparison with industry models

The results from the ScHARR analysis are compared with the results from the industry submissions in *Table 45*.

The ScHARR analyses generally produce a lower QALY gain for the AIs. This is a result of the conservative assumption regarding benefits taken in the ScHARR base case, along with the lower

TABLE 45 *Comparison of results of ScHARR analysis with results from industry submissions*

	Incremental cost (£)	Incremental QALYs	Cost per QALY (£)
Primary adjuvant setting			
Anastrozole			
Industry submission – ATAC	2,400	0.30	7,610
ScHARR – ATAC	2,898	0.09	31,965
Letrozole			
Industry submission – BIG 1-98	3,924	0.38	10,286
ScHARR – BIG 1-98	3,654	0.17	21,580
Unplanned switching			
Anastrozole			
Industry submission – GABG	900	0.36	2,446
ScHARR – GABG	2,064	0.09	23,215
Exemestane			
Industry submission – IES	2,300	0.33	6,970
ScHARR – IES	2,248	0.12	19,170
Extended adjuvant			
Letrozole			
Industry submission – MA-17	3,623	0.469	7,725
ScHARR – MA-17	3,409	0.35	9,760

utility values used in the ScHARR analysis. The AstraZeneca submission assumed that benefits of AIs continue for a further 5 years beyond the treatment period, that is, the rate of recurrence remained lower in the anastrozole arm for 5 years after treatment and the results show the largest variation from the ScHARR results. The Pfizer and Novartis submissions assume that the rate of recurrence in the two treatment arms was the same after the treatment period, equivalent to the ScHARR alternative "benefits maintained" scenario.

The incremental costs in the Pfizer submission are similar to the ScHARR estimates in the IES analysis. In the AstraZeneca submission, the incremental costs are lower than the ScHARR estimates in both settings. In contrast, in the Novartis submission the incremental costs are higher than the ScHARR estimates, particularly in the primary adjuvant setting.

NHS impact

The industry submissions have each presented a predicted budget impact.

AstraZeneca

The budget impact was based on an incidence of 37,719 in 2005, rising to 39,392 by 2009. The key assumptions used to determine the numbers of eligible patients are:

- 80% are postmenopausal.
- 75% are hormone receptor-positive.
- 92% have invasive cancer.
- 93% of these would receive hormonal therapy.

This results in an estimate of 19,363 eligible patients in 2005, rising to 20,222 by 2009.

Budget impact of newly diagnosed patients

The submission estimates the cost of moving from current market prescribing (currently 71% of new patients are prescribed tamoxifen and 29% are prescribed an AI; no source given) to a predicted market share of 40% tamoxifen and 60% AI over a 5-year period. No justification is given for this figure of 60%. The cost impact assumes that the market share between anastrozole (70%) and other AIs (30%) remains the same.

The analysis takes into account the cost of anastrozole and other AIs.

The cost of treatment based on the above assumptions is estimated at £5.65 million in 2005 to £40.78 million in 2009. The cost of maintaining the current market share (71% tamoxifen, 29% AIs) in 2009 is estimated to be £26.6 million, therefore the estimated budget impact is £14.2 million by 2009.

Assuming that around 20,000 eligible patients will be diagnosed per annum, the use of anastrozole instead of tamoxifen would prevent around 700

recurrences in addition to the recurrence prevented by tamoxifen. These cost savings are not taken into account in the analysis.

This budget impact analysis may underestimate the cost impact if the market share for AIs rises above 60%.

Budget impact of patients already receiving tamoxifen (switching scenario)

This analysis considers patients diagnosed since 2000, taking into account the proportion eligible for hormonal therapy treatment, the proportion receiving tamoxifen and the relative survival of patients over time.

It is assumed patients already completing 4 or 5 years of therapy would not be switched, but patients receiving 1, 2 or 3 years of therapy would either continue on tamoxifen or would switch to an AI. The percentage assumed to switch is forecast to rise from 24% in 2005 to 48% in 2009. No justification is given for these values.

The budget impact of the switching scenario in 2005 is £6.14 million, by 2007 this peaks at £14.25 million and it then falls to £5.66 million by 2009 as the number of eligible patients declines.

This budget impact analysis may underestimate the cost impact if the proportion of patients switched to AIs rises above 48%.

Novartis

In the Novartis submission, the projection for incidence of breast cancer in 2005 is 37,376, based on 2002 data. Key assumptions to determine the number of eligible patients are:

- 50 years of age is used as a proxy for the menopause; on this basis, 81% women were postmenopausal.
- 87% of breast cancer patients have early breast cancer at presentation.
- 85% of these have invasive disease.
- 67% are hormone receptor-positive.

This produces an estimate of the number of eligible patients of 12,374, which is low relative to the other submissions.

Budget impact of newly diagnosed patients

[Confidential information removed].

Based on the above assumptions, the impact on the drugs budget is estimated to be £2.8 million in year 1, rising to £14.8 million in year 5. This takes into account the cost of letrozole but not the cost of other AIs. The net overall budget impact is estimated to be £2.7 million in year 1, rising to £13.4 million in year 5.

Budget impact of sequential treatment

The assumptions are:

- 83% of patients will be alive and disease free after 5 years of tamoxifen treatment.
- 9.5% discontinue tamoxifen due to AEs and 17% of patients will stop treatment in the first 2 years.

This results in an estimated 62% of patients who started tamoxifen treatment eligible for letrozole treatment after 5 years.

[Confidential information removed].

Based on the above assumptions, the impact on the drugs budget is estimated to be £4 million in year 1, rising to £19 million in year 5. The net overall budget impact is estimated to be £3.9 million in year 1, rising to £19 million in year 5.

Pfizer

The Pfizer submission considers the impact of replacing 5 years of tamoxifen therapy with a strategy involving switching to exemestane after an initial 2 years of tamoxifen treatment. In total, 10 separate patient cohorts are simulated; five of the cohorts constitute patients who develop primary breast cancer during the period after exemestane introduction (years 1–5). The remaining five cohorts are patients who have previously been diagnosed with breast cancer up to 5 years before exemestane introduction (years –1 to –5). All patient cohorts are followed until 5 years after exemestane introduction.

Key assumptions to determine the number of eligible patients are:

- 80% of women are postmenopausal.
- 96% of women have early breast cancer.
- 70% of these women are ER positive.
- the annual growth rate of incidence of breast cancer is 1.75%.

Calculations are carried out separately for three age groups in order to estimate mortality rates more accurately and thereby the number of patients remaining on treatment.

The budget impact analysis compares a tamoxifen only strategy with a strategy taking into account the introduction of exemestane.

The percentage of women treated on tamoxifen is given as 78% in 2004. It is assumed to be falling gradually each year: 65, 57, 27, 35, 25% and reaching 17% by 2010. This takes into account the introduction of other AIs into the adjuvant setting. The annual uptake of exemestane is 15% in 2004. It is assumed to rise from 21% in 2006 to 28% in 2012. These estimates take into account the introduction of other adjuvant therapies.

This results in an estimate of 19,363 eligible patients in 2005, rising to 20,222 by 2009.

The additional annual drug budget implications are estimated to be £2.8 million in 2006, peaking at £12.1 million in 2008 and falling to £3.6 million by 2012.

The net budget impact, taking into account a reduction in treatment cost relating to breast cancer recurrence in the first year, is estimated to be £2.5 million in 2006, peaking at £10.7 million in 2008 and falling to £2.9 million by 2012.

The budget impact would be less than this if the adopted strategy was to receive 3 years rather than 2 years of tamoxifen before switching.

ScHARR estimates

Methods

Newly diagnosed patients: primary adjuvant therapy

The numbers of eligible patients each year from 2006 to 2010 are taken from the section 'Current service cost' (p. 6) along with an annual growth of 2.3% per annum based on average growth between 1998 and 2003.

It is assumed that all eligible patients will start on AI treatment from 2006. Compliance is assumed to be 100%. Each year a new cohort of patients starts the 5-year therapy.

The budget impact is the difference between 100% tamoxifen strategy and 100% AI strategy.

Switching strategy

It is assumed that patients who have had 2 years of tamoxifen treatment and remain disease free are eligible for switching (to either anastrozole or exemestane, but not letrozole). Patients newly diagnosed in 2004 will be ready to switch in 2006 and patients diagnosed in 2005 will be ready to switch in 2007. No further patients will be eligible to switch, as it is assumed that all newly diagnosed patients are put on to AIs and so will not become eligible for switching.

The budget impact is estimated as the difference between 100% on 5 years of tamoxifen strategy and 100% on 2 years of tamoxifen/3 years of AI strategy.

Extended adjuvant

Patients newly diagnosed in 2001 will complete 5 years of tamoxifen treatment and become eligible for 5 years of letrozole treatment in 2006. Patients in 2002 and 2003 will become eligible in 2007 and 2008, respectively. It is assumed that no further patients will be eligible to switch, given that all newly diagnosed patients are assumed to go on to AIs from 2006 and so will not become eligible for extended treatment and patients who have had 2 years of tamoxifen are eligible for switching, so patients diagnosed in 2004 and 2005 are not eligible for extended adjuvant therapy.

The budget impact is the difference between 100% of eligible patients on 5 years of letrozole and 100% of patients on 5 years of placebo strategy

Results

The estimated impact on AIs on the NHS drugs budget is given in *Table 46*.

This budget impact is the difference between a 100% tamoxifen strategy and a 100% AI strategy. It is therefore considered to be a worst-case scenario. It is unlikely that all patients will be switched over to AIs immediately. The potential cost savings in terms of avoided recurrences achieved by AIs over and above tamoxifen are not taken into account in the analysis.

TABLE 46 *Impact of aromatase inhibitors on the NHS drugs budget (£ million)*

	2006	2007	2008	2009	2010
Primary adjuvant	21.8	41.1	57.9	72.5	84.7
Unplanned switching	18.9	35.9	29.1	16.0	–
Extended adjuvant	16.1	30.0	42.5	38.1	29.1
Total	56.8	106.9	129.5	126.6	113.8

Chapter 5

Factors relevant to the NHS and other parties

Implications for other parties

Women prescribed either tamoxifen or an AI will have similar requirements in terms of attending outpatient appointments and collecting prescriptions, which will entail transport costs. It may also involve time away from paid employment, as would periods of feeling unwell. Employers may be liable for statutory sick pay. Women incapable of paid employment for 28 weeks or more may be eligible for Incapacity Benefit. Those on low income may receive help with the cost of prescriptions (http://www.breastcancercare.org.uk/docs/benefits_factsheet_0.pdf).

Prescription of either tamoxifen or an AI will mean stopping HRT for those women who had been previously been taking HRT. This will mean the return of unwanted menopausal symptoms.

Family and friends may be affected by patients' serious AEs, in terms of hospital visits.

Factors relevant to the NHS

Clinical staff time

There will be similar NHS requirements for those prescribed tamoxifen or AIs in terms of providing outpatient and pharmacy services. If women are to be given choice between treatments, then clinical staff time will be needed for providing information to patients and discussing treatment options.

Impact of adverse events

Endometrial cancers, fractures, ischaemic cerebrovascular events and venous thromboembolic events are AEs occurring at different rates in those taking tamoxifen than in those taking AIs, as indicated in the economic model. Of these, fractures may have implications for the NHS in terms of diagnosis and treatment of osteoporosis. If patients prescribed AIs are to be screened for osteoporosis, this will require the NHS to invest in the scanning equipment and staff necessary for diagnosis.

Adjusting for risk factors

The patient group within the trials encompasses patients with a range of risks, depending on tumour size and grade and nodal status. For instance, patients with node-positive cancer with three or more nodes will have a higher probability of relapse than patients with node-negative cancer or less than three positive nodes.

Trial evidence, from ATAC,[59] suggests that the benefit of AIs, expressed in terms of the HR for recurrence, does not vary according to patient characteristics and tumour type. Those patients with a higher probability of recurrence will therefore benefit more from treatment with AIs in absolute terms than patients with a lower probability. This will in turn influence the cost-effectiveness – it will be more cost-effective to treat the higher risk subgroups within the early breast cancer population.

Chapter 6
Discussion

Principal findings

Effectiveness

No individual study reported a significant difference in overall survival between any AI and tamoxifen (or placebo in the extended adjuvant setting), although it is worth noting that one anastrozole switching study, with a much worse prognosis population (all node-positive) than the others, demonstrated a considerably higher ARR (0.027) than the rest (all <0.01), despite being underpowered. A meta-analysis of three trials did find a significant difference in overall survival when an unplanned anastrozole switching strategy was compared with 5 years' tamoxifen (details are academic-in-confidence).

Compared with 5 years' tamoxifen, disease-free survival (disease recurrence or death from any cause) was significantly improved: in the primary adjuvant setting with anastrozole (68 months' follow-up: HR 0.87, 95% CI 0.78 to 0.97; ARR 0.024) and letrozole (26 months' follow-up: HR 0.83, 95% CI 0.73 to 0.94; ARR 0.019) and with an exemestane switching strategy (31 months' follow-up: HR 0.68, 95% CI 0.56 to 0.82; ARR 0.035). Other trials did not report this outcome.

Breast cancer recurrence (censoring death as an event) was significantly improved with: primary adjuvant anastrozole (68 months' follow-up: HR 0.79, 95% CI 0.70 to 0.90; ARR 0.031) and letrozole (26 months' follow-up: HR 0.74, 95% CI 0.64 to 0.87; ARR 0.021) anastrozole switching (28 months' follow-up: HR 0.59, 95% CI 0.44 to 0.81; ARR 0.027); extended adjuvant anastrozole (60 months' follow-up: HR 0.64, 95% CI 0.41 to 0.99; ARR 0.042) or letrozole (30 months' follow-up: HR 0.58, 95% CI 0.45 to 0.76; ARR 0.024).

The AIs and tamoxifen have different side-effect profiles with tamoxifen responsible for small but statistically significant increases in endometrial cancer and, sometimes, thromboembolic events and stroke. AIs show a trend towards increases in osteoporosis, the statistical significance of which increases with follow-up time. The absence of tamoxifen treatment also increases the risk of hypercholesterolaemia and cardiac events in women of this age (see the section 'Current service provision', p. 5).

There was no significant difference in overall health-related quality of life between standard treatment and either primary adjuvant anastrozole and extended adjuvant letrozole strategies.

Cost-effectiveness

The three treatment strategies – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – are considered separately within the economic analysis. Based on the results of the ScHARR analysis, the cost per QALY for AIs compared with tamoxifen is estimated to be between £21,600 and £32,000 in the primary adjuvant setting and between £19,200 and £23,200 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £9800.

The base-case results are considered conservative in that they are based on a scenario in which the benefits gained by AIs during the treatment period are gradually lost over the following 10 years. An alternative scenario, in which rates of recurrence are the same in both arms after the therapy period is complete, shows that the ICERs are typically at least 50% lower under this assumption, resulting in ICERs of around £12,000 or below in all three settings.

One-way sensitivity analyses and PSAs show that these results are robust. A key influence on cost-effectiveness results is the length of analysis. The drug costs of AIs are high relative to tamoxifen during the therapy period. However, cost offsets for the AI arm are accrued gradually over time, resulting from the lower rate of progression to recurrence and contralateral disease. The model assumes that benefits from reduced recurrence will translate into overall survival benefits in the medium and long term. Restricting the analysis to a period of 10 years reduces the period over which benefits can be accrued and increases the ICER by around 20–30%.

The assumption regarding the benefits after the completion of therapy in the AI arm relative to the tamoxifen arm has a major influence on the ICER. As discussed above, the base case in the ScHARR model is considered conservative – it assumes that the rate of recurrence in the AI arm is higher than that in the tamoxifen arm after the treatment period, to the extent that after 15 years the number of recurrences in both arms is the same. This is considered to be a worst-case scenario. There is limited evidence to date, from the ATAC trial, to suggest that absolute differences in recurrence rates between the anastrozole and tamoxifen arms occurred beyond the 5-year therapy period, suggesting that there may be a carry-over effect for anastrozole similar to that observed for tamoxifen compared with placebo, at least in the short term.

The ScHARR model assumes the same rate of progression for patients with contralateral disease and LRR. This may overestimate the benefits of AIs as there is some evidence that patients with contralateral disease have a better prognosis than patients with LRR. In the ScHARR model, these patients will have a worse prognosis and will therefore benefit more, in absolute terms, and this will lower the ICER. However, the proportion of patients who will develop contralateral disease is very low and the impact on results is likely to be small.

The impact of life-threatening AEs is to increase deaths from other causes, which may offset the reduction in cause-specific deaths. The largest uncertainty is the potential long-term risk of fracture from AIs. The analysis to date suggests that the impact of fracture risk on costs and QALYs is limited within the first 10 years. Further evidence from long-term follow-up is required.

Limitations of the assessment

Heterogeneity of trial design, especially with regard to the point of randomisation, makes it impossible to compare the relative effectiveness of different treatment programmes due to the loss of information early in the adjuvant period. The three patient groups with the adjuvant setting – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – are therefore considered separately within the economic analysis.

Uncertainties

The disease-specific benefits of AIs are demonstrable early on, but their harmful effects are realised more slowly, meaning that benefits may conceivably be reduced or cancelled out with longer follow-up. The median follow-up of some of the primary studies on which this report is based does not exceed the length of the individual treatment programmes, and understanding of long-term treatment effects is incomplete.

Due to the length of follow-up to date, the long-term impact of AIs is not known with certainty. The economic model, however, considers costs and benefits over the lifetime of a patient. Extrapolation of benefits and costs was therefore required.

AE profiles vary across the trials. The largest uncertainty relates to the future risk of fracture in the period following adjuvant therapy, as the population gets older

Further research

Randomisation of populations at any point other than the start of treatment programmes should be strongly discouraged in future trials as it limits the utility of the resulting dataset. In the present case, this means randomising at the start of, not halfway through or at the end of the adjuvant period, because the objective is the same from successful surgery until relapse or death.

Data on the impact of AIs on survival is awaited from the majority of the trials to confirm whether or not the benefits seen in DFS and recurrence rates are translated into overall survival benefit in the medium to long term.

Additional follow-up data on key AEs, including cholesterol levels, cardiovascular events and fracture rates, are awaited. The long-term implications for the costs and benefits of AIs and tamoxifen will need to be reviewed as and when new information becomes available.

Chapter 7
Conclusions

Clinical effectiveness

No individual study reported a difference in overall survival between any AI and tamoxifen (or placebo in the extended adjuvant setting). An unpublished meta-analysis of individual patient data from three trials did find a significant difference in overall survival when unplanned anastrozole switching strategy was compared with 5 years' tamoxifen. Compared with 5 years' tamoxifen, DFS (absence of disease recurrence or death from any cause) was significantly increased in the primary adjuvant setting (using anastrozole or letrozole) and the unplanned switching strategy (using anastrozole or exemestane). Breast cancer recurrence (censoring death as an event) was significantly improved with primary adjuvant anastrozole or letrozole, an anastrozole or exemestane unplanned switching strategy and an extended adjuvant anastrozole or letrozole strategy. There is no evidence that AIs confer any advantage in overall health-related quality of life. On the basis of the current data and within their licensed indications, AIs can be considered clinically effective compared with standard tamoxifen treatment. However, their long-term effects, in terms of both benefits and harms, remain unclear.

Cost-effectiveness

Three treatment strategies for AIs – primary adjuvant therapy, unplanned switch therapy and extended adjuvant therapy – were considered separately within the economic analysis. Under the conservative assumption that benefits gained by AIs during the treatment period are gradually lost over the following 10 years, the cost per QALY for AIs compared with tamoxifen is estimated to be between £21,000 and £32,000 in the primary adjuvant setting and around £20,000 in the unplanned switch setting. The cost per QALY for AIs compared with placebo in the extended adjuvant setting is estimated to be around £10,000. Under the less conservative assumption that rates of recurrence are the same in both arms after the therapy period is complete, the ICERs are typically at least 50% lower, suggesting that AIs are likely to be considered cost-effective in all three settings.

Understanding of the long-term treatment effects on cost-effectiveness is, however, incomplete. The economic model considers costs and benefits over the lifetime of a patient, requiring extrapolation of these costs and benefits well beyond the time frame of the reported trial outcomes to date. Data on the impact of AIs on survival are awaited from the majority of the trials to confirm whether or not the benefits seen in DFS and recurrence rates are translated into overall survival benefit in the medium to long-term. Potential long-term AEs that may impact on the ICER include the potential increase in the long-term risk of fracture for patients in the period following adjuvant therapy with AIs, as this population gets older.

Acknowledgements

Ian Monypenny, Consultant Surgeon, Cardiff and Vale NHS Trust and Breast Test Wales, and Gill Lawrence, Director, West Midlands Cancer Intelligence Unit, provided unpublished summary statistics which informed the budget impact statement. Rob Coleman, Professor of Medical Oncology, University of Sheffield, and Alan Gillespie, Consultant Gynaecologist, Sheffield Teaching Hospitals NHS Trust, provided guidance on the interpretation and modelling of adverse events data. Keith Abrams, Professor of Medical Statistics, University of Leicester, provided advice on behalf of the NICE Decision Support Unit on the design and conduct of a primary study discussed in this report. Rob Coleman, John Robertson, Professor of Surgery, University of Nottingham, Ron Akehurst, Professor of Health Economics, University of Sheffield, Dr Eva Kaltenthaler, Senior Research Fellow, University of Sheffield, and Dr Elisabeth George, Technical Lead, NICE, commented on a draft version of the report. The authors wish to thank all of the above.

The authors also wish to thank Gill Rooney for her help in preparing and formatting the report.

Contribution of authors

Danny Hind (Research Fellow) coordinated the review. Chris Carroll (Information Officer) developed the search strategy and undertook searches. Danny Hind, Emma Simpson (Research Fellow), Sue Ward (Senior Research Fellow) and Enrico De Nigris (Research Associate) screened the search results. Danny Hind, Emma Simpson, Sue Ward and Enrico De Nigris screened retrieved papers against inclusion criteria, appraised the quality of papers and abstracted data from papers. Danny Hind wrote to authors of papers for additional information.

Danny Hind, Emma Simpson, Sue Ward and Enrico De Nigris analysed the data. Danny Hind, Emma Simpson and Lynda Wyld wrote the background section. Danny Hind and Emma Simpson wrote the section on clinical effectiveness. Sue Ward and Enrico De Nigris wrote the section on cost-effectiveness. Sue Ward and Enrico De Nigris undertook the economic evaluation.

This report was commissioned by the NHS R&D HTA Programme. The views expressed are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

None of the authors have any pecuniary relationship, direct or indirect, specific or non-specific, with the sponsors. A member of ScHARR staff, who is not part of the ScHARR Technology Assessment Group, has been involved in the development of a cost-effectiveness model for letrozole. His involvement began before he joined ScHARR and has continued in a private (non-university) role. The individual has licensed his modelling work to a third party. The member of staff concerned has in no way been involved with the team responsible for the hormonal therapies for breast cancer assessment report.

References

1. Office for National Statistics. *Cancer: number of new cases 2002, by sex and age*. London: Office for National Statistics; 2005.
2. Welsh Cancer Intelligence and Surveillance Unit (WCISU). *Cancer incidence in Wales 2002*. WCISU; 2004. http://www.wales.nhs.uk/sites/documents/242/CancerIncidence2002%5FV2%2E.pdf
3. Quinn M, Babb M, Brock A, Kirby L, Jones J. *Cancer trends in England and Wales 1950–1999*. Studies in Medical and Population Subjects No. 66. 2001. London: The Stationery Office.
4. McPherson K, Steel CM, Dixon JM. Breast cancer – epidemiology, risk factors and genetics. *BMJ* 2000;**321**:624–8.
5. Evans DGR, Fentiman IS, McPherson K, Asbury D, Ponder BAJ, Howell A. Familial breast cancer. *BMJ* 1994;**308**:183–7.
6. Antoniou AC, Pharoah PD, McMullan G, Day NE, Ponder BA, Easton D. Evidence for further breast cancer susceptibility genes in addition to BRCA1 and BRCA2 in a population based study. *Genet Epidemiol* 2001;**21**:1–18.
7. Longnecker MP, Bernstein L, Paganini-Hill A, Enger SM, Ross RK. Risk factors for *in situ* breast cancer. *Cancer Epidemiol Biomarkers Prev* 1996;**5**:961–5.
8. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 without breast cancer from 54 epidemiological studies. *Lancet* 1996;**347**:1713–27.
9. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 without breast cancer. *Lancet* 1997;**350**:1047–59.
10. Willett WC. Diet and cancer: one view at the start of the millennium. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:3–8.
11. Smith-Warner SA, Spiegelman D, Yaun S, van den Brandt PA, Folsom AR, Goldbohm RA, *et al.* Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;**279**:535–40.
12. Gandini S, Merzenich H, Robertson C, Boyle P. Meta-analysis of studies on breast cancer risk and diet: the role of fruit and vegetable consumption and the intake of associated micronutrients. *Eur J Cancer* 2000;**36**:636–46.
13. Shephard RJ, Futcher R. Physical activity and cancer: how may protection be maximized? *Crit Rev Oncog* 1997;**8**:219–72.
14. National Institute for Clinical Excellence. *Improving outcomes in breast cancer: manual update*. London: NICE; 2002.
15. Union Internationale Contre le Cancer. *TNM classification of malignant tumours*. 4th ed. Union Internationale Contre le Cancer. Berlin: Springer; 1987. pp. 80–9.
16. Sainsbury JRC, Anderson TJ, Morgan DAL. Breast cancer. *BMJ* 2000;**321**:745–50.
17. Fitzgibbons PL, Page DL, Weaver D, Thor AD, Allred DC, Clark GM, *et al*. Prognostic factors in breast cancer. College of American Pathologists Consensus Statement 1999. *Arch Pathol Lab Med* 2000;**124**:966–78.
18. Atkinson EN, Brown BW, Montague ED. Tumor volume, nodal status, and metastasis in breast cancer in women. *J Natl Cancer Inst Cancer Spectrum* 1986;**76**:171–8.
19. Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status, and survival in 24,740 breast cancer cases. *Cancer* 1989;**63**:181–7.
20. Hilsenbeck SG, Ravdin PM, de Moor CA, Chamness GC, Osborne CK, Clark GM. Time-dependence of hazard ratios for prognostic factors in primary breast cancer. *Breast Cancer Res Treat* 1998;**52**:227–37.
21. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 1996;**14**:2738–46.
22. Office for National Statistics. *Breast cancer survival, England and Wales, 1991–2003*. URL: http://www.statistics.gov.uk. Accessed 10 October 2005.
23. Yarnold JR, Bliss JM, Brunt M, Earl H, Kaye S, Mason M, *et al*. Management of breast cancer. Refer women to multidisciplinary breast clinics. *BMJ* 1994;**308**:714a–15.
24. Miller AB, Rozenberg S, Carly B, Liebens F, Ham H, Baum, *et al*. Effect of screening programme on mortality from breast cancer. *BMJ* 2000;**321**:1527a.
25. Office for National Statistics. *Deaths, 2001 registrations: death by age, sex and underlying cause (England and Wales)*. Office for National Statistics; 2005. http://www.statistics.gov.uk/STATBASE/ssdataset.asp?vlnk=8986
26. Kruijshaar ME, Barendregt JJ, European Disability Weights Group. The breast cancer related burden

of morbidity and mortality in six European countries: *The European Disability Weights project. Eur J Public Health* 2004;**14**:141–6.

27. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary 50*. London: BMA; 2005.

28. Bergman L, Beelen MLR, Gallee MPW, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. *Lancet* 2000;**356**:881–7.

29. Nordenskjold B, Rosell J, Rutqvist LE, Malmstrom PO, Bergh J, Bengtsson NO, *et al.* Coronary heart disease mortality after 5 years of adjuvant tamoxifen therapy: results from a randomized trial. *J Natl Cancer Inst Cancer Spectrum* 2005;**97**:1609–10.

30. Love RR, Wiebe DA, Feyzi JM, Newcomb PA, Chappell RJ. Effects of tamoxifen on cardiovascular risk factors in postmenopausal women after 5 years of treatment. *J Natl Cancer Inst* 1994;**86**:1534–9.

31. Cushman M, Costantino JP, Tracy RP, Song K, Buckley L, Roberts JD, *et al*. Tamoxifen and cardiac risk factors in healthy women: Suggestion of an anti-inflammatory effect. *Arterioscler Thromb Vasc Biol*. 2001;**21**:255–61.

32. Grey AB, Stapleton JP, Evans MC, Reid IR. The effect of the anti-estrogen tamoxifen on cardiovascular risk factors in normal postmenopausal women. *J Clin Endocrinol Metab* 1995;**80**:3191–5.

33. Rutqvist LE, Mattsson A. Cardiac and thromboembolic morbidity among postmenopausal women with early-stage breast cancer in a randomized trial of adjuvant tamoxifen. *J Natl Cancer Inst* 1993;**85**:1398–406.

34. Love RR. Bone density and cardiovascular risk factor changes in postmenopausal women treated with tamoxifen. *B J Cancer* 1990;**62**:3.

35. Wittliff JL, Pasic R, Bland KI. Steroid and peptide hormone receptors: methods, quality control and clinical use. In Bland KI, Copeland EM III, editors. *The breast: comprehensive management of benign and malignant diseases*, Chapter 25. Philadelphia, PA: Saunders; 1998. pp. 458–98.

36. Wittliff JL, Miseljic S, Cummins JA, Pasic R. Does menopausal status influence sex-steroid receptor content and specific-binding capacity? *J Clin Ligand Assay* 1996;**19**:203–7.

37. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;**365**:1687–717.

38. Health and Social Care Information Centre, Department of Health. *Prescription Cost Analysis: England 2004*. London: Department of Health; 2005.

39. Wyld L, Garg DK, Kumar ID, Brown H, Reed MW. Stage and treatment variation with age in postmenopausal women with breast cancer: compliance with guidelines. *Br J Cancer* 2004;**90**: 1486–91.

40. Monypenny I. *UK Symptomatic breast audit 1.4.2002–31.3.2003*. London: British Association of Surgical Oncology; 2003.

41. Office for National Statistics. Cancer statistics registrations: registrations of cancer diagnosed in 2003, England. London: Office for National Statistics, 2005.

42. Welsh Cancer Intelligence and Surveillance Unit (WCISU). *Triennial report: cancer incidence, mortality and survival in Wales*. WCISU; 2005. http://www.wales.nhs.uk/sites/documents/242/CancerIncidence2002_V2.pdf

43. Golledge J, Wiggins JE, Callam MJ. Effect of surgical subspecialization on breast cancer outcome. *Br J Cancer* 2000;**87**:1420–5.

44. Northern and Yorkshire Cancer Registry and Information Service. *Northern and Yorkshire Cancer Networks: a report on incidence and management for the main sites of cancer, 1999*. 2002. http://www.nycris.org.uk/reports/netwks99/netwks99.pdf

45. Patnick J. *Changing lives: NHS breast screening programme. Annual Review 2004*. Sheffield: NHS Breast Screening Programme; 2004.

46. Bardou VJ, Arpino G, Elledge RM, Osborne CK, Clark GM. Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. *J Clin Oncol* 2003;**21**:1973–9.

47. Horwitz KB, McGuire WL, Pearson OH, *et al*. Predicting response to endocrine therapy in human breast cancer. Science 1975;**189**:726–7.

48. Satariano WA, Ragland DR. The effect of comorbidity on 3-year survival of women with primary breast cancer. *Ann Intern Med* 1994; **120**:104–10.

49. Hunt KE, Fry DE, Bland KI. Breast carcinoma in the elderly patient: an assessment of operative risk, morbidity and mortality. *Am J Surg* 1980;**140**: 339–42.

50. Ramesh HS, Pope D, Gennari R, Audisio RA. Optimising surgical management of elderly cancer patients. *World J Surg Oncol* 2005;**23**:1–17.

51. Hind D, Wyld L, Beverley C, Reed M. Surgery versus primary endocrine therapy for operable primary breast cancer in elderly women (70 years plus). *Cochrane Database Syst Rev* 2006;CD004272.

52. NHS. *An audit of screen detected breast cancers for the year of screening April 2003 to March 2004*. London: NHS Breast Screening Programme and Association of Breast Surgery at BASO; 2005.

53. Njar VC, Brodie AM. Comprehensive pharmacology and clinical efficacy of aromatase inhibitors. *Drugs* 1999:**58**:233–55.

54. Santen RJ, Harvey HA. Use of aromatase inhibitors in breast carcinoma. *Endocrine-Related Cancer* 1999;**6**:75–92.

55. AstraZeneca UK Limited. Arimidex 1 mg film-coated tablet. *Electronic Medicines Compendium*. URL: http://emc.medicines.org.uk. Accessed 2005.

56. Novartis Pharmaceuticals UK Ltd. Femara. *Electronic Medicines Compendium*; URL: http://emc.medicines.org.uk/. Accessed 2005.

57. Pharmacia Limited. Aromasin. E*lectronic Medicines Compendium*. URL: http://emc.medicines.org.uk. Accessed 2005.

58. Moher D, Cook DJ, Eastwood S, *et al*. Improving the quality of reports of meta-analyses of randomised controlled trials: the Quorom Statement. *Lancet* 1999;**354**:1896–900.

59. Schulz KF, Chalmers I, Hayes RJ, Altman D. Empirical evidence of bias. Dimensions of methodological quality associated with estimates of treatment effects in controlled trials. *JAMA* 1995;**273**:408–12.

60. Gill TM, Feinstein AR. A critical appraisal of the quality of quality of life measurements. *JAMA* 1994;**272**:619–26.

61. Sanders C, Egger M, Donovan J, Tallon D, Frankel S. Reporting on quality of life in randomized controlled trials: bibliographic study. *BMJ* 1998;**317**:1191–4.

62. Naito M, Nakayama T, Fukuhara S. Quality of life assessment and reporting in randomized controlled trials: a study of literature published from Japan. *Health Qual Life Outcomes* 2004;**2**:31.

63. Pildal J, Chan AW, Hrobjartsson A, Forfang E, Altman DG, Gotzsche PC. Comparison of descriptions of allocation concealment in trial protocols and the published reports: cohort study. *BMJ* 2005;**330**:1049.

64. FDA. *Guidance for industry: clinical trial endpoints for the approval of cancer drugs and biologics*. Washington, DC: US Food and Drug Administration; 2005.

65. Altman DG, Andersen PK. Calculating the number needed to treat for trials where the outcome is time to an event. *BMJ* 1999;**319**:1492–5.

66. Altman DG, Bland JM. Statistics notes: interaction revisited: the difference between two estimates. *BMJ* 2003;**326**:219.

67. The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;**359**:2131–9.

68. Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, *et al*. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003;**98**:1802–10.

69. The ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;**365**:60–2.

70. Howell, A. 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial: completed treatment analysis (PowerPoint presentation). Presented at the San Antonio Breast Cancer Symposium, 2004.

71. The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *New England J Med* 2006;**353**:2747–57.

72. Thürlimann B. Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. *ASCO presentation*, 2005.

73. Jakesz R, Jonat W, Mittlboeck M. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;**366**: 455–62.

74. Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary Results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol* 2005;**23**: 5138–47.

75. Jonat W. Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer: a meta-analysis of ARNO 95, ABCSG8, and the ITA trials. Presentation to SABCS meeting on behalf of all investigators of the GABG, the ABCSG and the ITA Trial Group, 2005.

76. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, *et al*. The Intergroup Exemestane Study: a randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer [published erratum appears in *N Engl J Med*. 2004;**351**:2461]. *N Engl J Med* 2004;**350**:1081–92.

77. Jakesz R, *et al*. The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

78. Schmid M, Jakesz R, Samonigg H, Kubista E, Gnant M, Menzel C, *et al*. Randomized trial of tamoxifen versus tamoxifen plus aminoglutethimide as adjuvant treatment in postmenopausal breast cancer patients with hormone receptor-positive disease: Austrian breast and colorectal cancer study group trial 6. *J Clin Oncol* 2003;**21**:984–90.

79. Jakesz R. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). *2005 ASCO Annual Meeting, Abstract No. 527*; 2005.

80. Asmar L. A planned comparison of menopausal symptoms during the first year in 1,000 patients receiving either exemestane or tamoxifen in a double-blind adjuvant hormonal study. *J Clin Oncol* 2004;**22**:516.

81. Jones S, Vukelja S, Cantrell J, O'Shaughnessy J, Pippen J, Brooks R, *et al*. A planned comparison of menopausal symptoms during year 1 in patients receiving either exemestane or tamoxifen in a double-blind adjuvant hormonal study. *San Antonio Breast Cancer Symposium 2003, Abstract 141*; 12005.

82. Markopoulos C, Polychronis A, Farfarelos C, Zobolas V, Bafaloukos D, Papadiamantis J, *et al*. The effect of exemestane (Aromasin®) on the lipidemic profile of breast cancer patients: preliminary results of the TEAM trial Greek sub-study. *Breast Cancer Res Treat* 2003;**82**:S105, Abstract 440.

83. Markopoulos C. The effect of exemestane on the lipidemic profile of breast cancer patients: preliminary results of the TEAM trial Greek sub-study. *J Clin Oncol* 2004;**22**:799.

84. Takatsuka, Y. Phase III randomized adjuvant study of tamoxifen alone versus sequential tamoxifen and anastrozole in hormone-responsive postmenopausal breast cancer patients (National Surgical Adjuvant Study of Breast Cancer (NSAS BC) 03). *Breast* 2003;**12**:S44.

85. NIH. Exemestane in treating postmenopausal women with resected Stage I, Stage II, or Stage IIIA breast cancer who have completed 5 years of tamoxifen. Current Controlled Trials Database; 2005. http://www.controlled-trials.com/isrctn/search.html

86. Kudachadkar R, O'Regan RM. Aromatase inhibitors as adjuvant therapy for postmenopausal patients with early stage breast cancer. *CA Cancer J Clin* 2005;**55**:145–63.

87. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, *et al*. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst Cancer Spectrum* 2005;**97**:1262–71.

88. Moher D, Schulz KF, Altman DG. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomised trials. *Lancet* 2001;**357**:1191–4.

89. Coombes RC, Hall E, Snowdon CF, Bliss JM. A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen (PowerPoint presentation). Presented at the San Antonio Breast Cancer Symposium, 2004.

90. Thurlimann BJ. BIG 1-98: randomized double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. *2005 ASCO Annual Meeting, Abstract No. 511*; 2005.

91. Buzdar AU. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial: an update. *Clin Breast Cancer* 2004;**5**(Suppl 1):S6–12.

92. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, *et al*. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003;**349**:1793–802.

93. Fallowfield L, Cella D, Cuzick J, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004;**22**:4261–71.

94. Cella DF, Tulsky DS, Gray G, Sarafian B, Linn E, Bonomi A, *et al*. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol* 1993;**11**: 570–9.

95. Fallowfield LJ, Leaity SK, Howell A, Benson S, Cella D. Assessment of quality of life in women undergoing hormonal therapy for breast cancer: validation of an endocrine symptom subscale for the FACT-B. *Breast Cancer Res Treat* 1999;**55**: 189–99.

96. Brady MJ, Cella DF, Mo F, Bonomi AE, Tulsky DS, Lloyd SR, *et al*. Reliability and validity of the Functional Assessment of Cancer Therapy – Breast quality-of-life instrument. *J Clin Oncol* 1997;**15**: 974–86.

97. Fallowfield LJ, Price MH, Hall E, Coombes RC, Bliss JM. Intergroup exemestane study: results of the quality of life sub-protocol. *Breast Cancer Res and Treat* 2004;**88**:S8 (Abstract 4).

98. Whelan TJ, Goss PE, Ingle JN, Pater JL, Tu D, Pritchard K, *et al*. Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women. *J Clin Oncol* 2005;**23**:6931–40.

99. Hunt SM, Mcewen J, Mckenna SP. Measuring health-status – a new tool for clinicians and epidemiologists. *J R Coll Gen Pract* 1985;**35**:185–8.

100. Hilditch JR, Lewis J, Peter A, vanMaris B, Ross A, Franssen E, *et al*. A menopause-specific quality of

life questionnaire: development and psychometric properties. *Maturitas* 1996;**24**:161–75.

101. Ware JE, Sherbourne CD. The Mos 36-Item Short-Form Health Survey (SF-36). 1. Conceptual-framework and item selection. *Med Care* 1992;**30**:473–83.

102. McHorney CA, Ware JE, Raczek AE. The Mos 36-Item Short-Form Health Survey (SF-36). 2. Psychometric and clinical-tests of validity in measuring physical and mental-health constructs. *Med Care* 1993;**31**:247–63.

103. Schulz KF, Grimes DA. Sample size slippages in randomised trials: exclusions and the lost and wayward. *Lancet* 2002;**359**:781–5.

104. Abrams KR. Monitoring randomised controlled trials. *BMJ* 1998;**316**:1183–4.

105. Bryant J, Wolmark N. Letrozole after tamoxifen for breast cancer – what is the price of success? *N Engl J Med* 2003;**349**:1855–7.

106. Twombly R. Critics question price of success in halted clinical trial of aromatase inhibitor letrozole. *J Nat Cancer Inst* 2003;**95**:1738–9.

107. Baum M. Current status of aromatase inhibitors in the management of breast cancer and critique of the NCIC MA-17 trial. *Cancer Control* 2004;**11**: 217–21.

108. Whitehead JR. Stopping clinical trials by design. *Nat Rev Drug Discov* 2004;**3**:973–7.

109. Houghton J. Using anastrozole as initial adjuvant treatment prevents early recurrences and reduces adverse events: updated data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. *2005 ASCO Annual Meeting, Abstract No: 582*; 2005;

110. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL. *Methods for the economic evaluation of health care programmes*, 3rd ed. Oxford: Oxford University Press; 2005.

111. Hillner BE. Benefit and projected cost-effectiveness of anastrozole versus tamoxifen as initial adjuvant therapy for patients with early-stage estrogen receptor-positive breast cancer. *Cancer* 2004;**101**:1311–22.

112. Chang J, Clark G, Allred DC, Chamness GC, Elledge RM. Survival of patients with metastatic breast carcinoma. *Cancer* 2003;**97**:545–53.

113. Harvard School of Public Health; *CEA registry catalog of preference score*s. Harvard Center for Risk Analysis. 2005. http://www.hsph.harvard.edu/cearegistry/data/phaseIIpreferenceweights.pdf

114. Kamby C, Sengelov L. Pattern of dissemination and survival following isolated locoregional recurrence of breast cancer. *Breast Cancer Res and Treat* 1997;**45**:181–92.

115. Stockler M, Wilcken NRC, Ghersi D, Simes RJ. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. *Cancer Treat Rev* 2000;**26**:151–68.

116. Stevenson M, Lloyd-Jones M, De-Nigris E. A systematic review and economic evaluation of alendronate, etidronate, risedronate, raloxifene and teriparatide for the prevention and treatment of postmenooausal osteoporosis. *Health Technol Assess* 2005;**9**(22).

117. Sorensen SV, Locker GY. An economic evaluation of anastrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer from a US health care perspective. *Value Health* 2004;**7**:250.

118. Coyle D, Small N, Ashworth A, Hennessy S, Jenkins-Clarke S, Mannion R, *et al*. Costs of palliative care in the community, in hospitals and in hospices in the UK. *Crit Rev Oncol Hematol* 1999;**32**:71–85.

119. Goss PE, *et al*. Updated analysis of NCIC CTG MA.17 (letrozole vs. placebo to letrozole vs placebo) post unblinding. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

120. Early Breast Cancer Trialists' Collaborative Group. Polychemotherapy for early breast cancer: an overview of the randomised trials. *Lancet* 1998;**352**:930–42.

121. Department of Health. *NHS reference costs 2004*. *National schedule of reference costs 2004*. London: Department of Health; 2005.

122. Kanis JA, Brazier JE, Stevenson M. Treatment of established osteoporosis: a systematic review and cost–utility analysis. *Health Technol Assess* 2002;**6**(29).

123. Brown R, Benedict A, Mansel R, Cost-utility analysis of anastrozole versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer: a UK national health service perspective. ISPOR 7th Annual European Congress, 24–26 October 2004, Hamburg, Germany.

124. Dolan P, Torgerson DJ, The cost of treating osteoporotic fractures in the United Kingdom female population, *Osteoporos Int* 1998;**8**:611–17.

125. Palmer S, Sculpher M, Philips Z, Robinson M, Ginnelly L, Bakhai A, *et al.* A cost-effectiveness model comparing alternative management strategies for the use of glycoprotein IIb/IIIa antagonists in non-ST-elevation acute coronary syndrome. NICE Appraisal Report; 2002.

126. Coombes RC, Hall E, Snowdon CF, Bliss JM. The Intergroup Exemestane Study: a randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen updated survival analysis. *Breast Cancer Res Treat* 2004;**88**:S7.

127. Abner AL, Recht A, Eberlein T, Come S, Shulman L, Hayes DF, *et al*. Prognosis following salvage mastectomy for recurrence in the breast after

conservative surgery and radiation therapy for early-stage breast cancer. *J Clin Oncol* 1993;**11**:44–8.

128. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary (BNF) 49*; 2005. http://www.bnf.org/bnf/
129. Scottish Intercollegiate Guidelines Network. Guideline No 61. Investigation of post-menopausal bleeding. 2002. http://www.sign.ac.uk/guidelines/fulltext/61/index.html
130. Scottish Intercollegiate Guidelines Network. Guideline No 51 Investigation of unstable angina. 2001. http://www.sign.ac.uk/guidelines/fulltext/51/index.html
131. Moran MS, Haffty BG. Local-regional breast cancer recurrence: prognostic groups based on patterns of failure. *Breast J* 2002;**8**:81–7.
132. Doyle T, Schultz DJ, Peters C. Long-term results of local recurrence after breast conservation treatment for invasive breast cancer. *Int J Radiat Oncol Biol Phys* 2001;**51**:74–80.
133. Haylock BJ, Coppin CML, Jackson J. Locoregional first recurrence after mastectomy: prospective cohort studies with and without immediate chemotherapy. *Int J Radiat Oncol Biol Phys* 2000;**46**:355–62.
134. Schmoor C, Sauerbrei W, Bastert G. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. *J Clin Oncol* 2000;**18**:1696–708.
135. Borner MM, Bacchi M, Goldhirsch A. First isolated locoregional recurrence following mastectomy for breast cancer: results of a phase III multicenter study following mastectomy for breast cancer: results of a phase III multicenter study comparing systemic treatment with observation after excision and radiation. *J Clin Oncol* 1994;**12**:2071–7.
136. Toonkel LM, Fix I, Jacobson LH. The significance of local recurrence of carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 1983;**9**:33–9.
137. Guidance on Commissioning Cancer Services; Improving Outcomes in Breast Cancers. *Manual Update* http://www.nice.org.uk/pdf/improving outcomes breastcancer manual.pdf; 2002.
138. Department of Health. *NHS reference costs 2003*. *National schedule of reference costs 2003*. London: Department of Health; 2004.
139. Remak E, Brazil L. Cost of managing women presenting with stage IV breast cancer in the United Kingdom. *Br J Cancer* 2004;**91**:77–83.
140. Ward SE, Lloyd-Jones M, Pandor A, Holmes M, Ara R, Rees A. *Statins for the prevention of cardiovascular events*. NICE Technology Assessment Review. London: NICE; 2004.
141. Goodacre S, Sampson F, Stevenson M, Wailoo A, Sutton A, Thomas S, *et al*. Measurement of the clinical and cost-effectiveness of non-invasive diagnostic testing strategies for deep vein thrombosis. 2005.
142. Morales L, Timmerman D, Neven P, Konstantinovic ML, Carbonez A, Huffel S, *et al*. Third generation aromatase inhibitors may prevent endometrial growth and reverse tamoxifen-induced uterine changes in postmenopausal breast cancer patients. *Ann Oncol* 2005;**16**:70–4.
143. Bundred NJ. The effects of aromatase inhibitors on lipids and thrombosis. *Br J Cancer* 2005;**93**:S23–27.
144. Elisaf MS, Bairaktari ETh, Nicolaides C. Effect of lipid profile in postmenopausal women with breast cancer. *Eur J Cancer* 2001;**37**:1510–13.
145. Winer EP, Hudis C, Burstein HJ. American Society of Clinical Oncology Technology Assessment on the use of aromatase inhibitors as adjuvant therapy for post-menopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005;**23**:619–29.
146. Dennis M, Bamford J, Sandercock P, Warlow C. Prognosis of transient ischemic attacks in the Oxfordshire Community Stroke Project. *Stroke* 1990;**21**:848–53.
147. Douketis JD, Kearon C, Bates S, Duku EK, Ginsberg JS. Risk of fatal pulmonary embolism in patients with treated venous thromboembolism. *JAMA* 1998;**279**:458–62.
148. Anderson FA Jr, Wheeler HB, Goldberg RJ, Hosmer DW, Patwardhan NA, Jovanovic B, *et al*. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med* 1991;**151**:933–8
149. Kniffin WD Jr, Baron JA, Barrett J, Birkmeyer JD, Anderson FA Jr. The epidemiology of diagnosed pulmonary embolism and deep venous thrombosis in the elderly. *Arch Intern Med* 1994;**154**:861–6.
150. Fisher B, Costantino JP, Wickerham DL. Tamoxifen for prevention of breast cancer. Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst Cancer Spectrum* 1998;**90**:1371–88.
151. Eastell R. Results of the Arimidex (anastrozole, A), tamoxifen (T), alone or in combination (C) (ATAC) trial: effects on bone mineral density (BMD) and bone turnover (ATAC Trialists, Group). *Ann Oncol* 2002;**13**:S32, Abstract 158.
152. Tengs T, Wallace A. One thousand health-related quality of life estimates. *Med Care* 2000;**38**: 583–637.
153. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a UK national questionnaire survey. *BMJ* 1998;**316**: 736–46.

Appendix 1

QUOROM checklist

Heading	Subheading	Descriptor	Reported? (Y/N)	Section
Title		Identify the report as a meta-analysis [or systematic review] of RCTs	Y	Title page
Abstract		Use a structured format		
		Describe:		
	Objectives	The clinical question explicitly		
	Data sources	The databases (i.e. list) and other information sources		
	Review methods	The selection criteria (i.e. population, intervention, outcome and study design): methods for validity assessment, data abstraction and study characteristics and quantitative data synthesis in sufficient detail to permit replication		
	Results	Characteristics of the RCTs included and excluded; qualitative and quantitative findings (i.e. point estimates and CIs); and subgroup analyses		
	Conclusions	The main results		
		Describe:		
Introduction		The explicit clinical problem, biological rationale for the intervention and rationale for review	Y	Chapter 2
Methods	Searching	The information sources, in detail (e.g. databases, registers, personal files, expert informants, agencies, handsearching) and any restrictions (years considered, publication status, language of publication)		'Search strategy' (p. 15); see also Appendix 2
	Selection	The inclusion and exclusion criteria (defining population, intervention, principal outcomes and study design)		'Inclusion and exclusion criteria' (p. 15)
	Validity assessment	The criteria and process used (e.g. masked conditions, quality assessment and their findings)		'Validity assessment' (p. 16)
	Data abstraction	The process or processes used (e.g. completed independently, in duplicate)	Y	'Data abstraction' (p. 16)
	Study characteristics	The type of study design, participants' characteristics, details of intervention, outcome definitions, etc., and how clinical heterogeneity was assessed	Y	'Inclusion and exclusion criteria' (p. 15); 'Analysis' (p. 16)
	Quantitative data synthesis	The principal measures of effect (e.g. relative risk), method of combining results (statistical testing and CIs), handling of missing data; how statistical heterogeneity was assessed; a rationale for any *a priori* sensitivity and subgroup analyses; and any assessment of publication bias	Y	'Analysis' (p. 16)
Results	Trial flow	Provide a meta-analysis profile summarising trial flow	Y	'Results', *Figure 3* (p. 18)
	Study characteristics	Present descriptive data for each trial (e.g. age, sample size, intervention, dose, duration, follow-up period)	Y	Throughout

continued

Heading	Subheading	Descriptor	Reported? (Y/N)	Section
	Quantitative data synthesis	Report agreement on the selection and validity assessment; present simple summary	Y	Throughout
Discussion		Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in the light of the totality of available evidence; describe potential biases in the review process (e.g. publication bias); and suggest a future research agenda	Y	Chapter 6, pp. 93–4

Appendix 2

MEDLINE search strategy

Clinical search strategy

Database: Ovid MEDLINE 1966 to May Week 4 2005

1 exp Breast Neoplasms/ (121922)
2 exp NEOPLASMS/ (1584391)
3 exp CARCINOMA/ (315268)
4 exp ADENOCARCINOMA/ (182745)
5 exp BREAST/ (19428)
6 or/2-4 (1584391)
7 5 and 6 (10652)
8 (carcinoma adj3 breast$).tw. (18501)
9 (neoplas$ adj3 breast$).tw. (1846)
10 (adenocarcinoma adj3 breast$).tw. (1064)
11 (cancer$ adj3 breast$).tw. (86198)
12 (tumour$ adj3 breast$).tw. (3088)
13 (tumor$ adj3 breast$).tw. (11486)
14 (malignan$ adj3 breast$).tw. (4947)
15 or/8-14 (105355)
16 1 or 7 or 15 (140766)
17 exp Aromatase Inhibitors/ (3127)
18 anastrozole.mp. or arimidex.af. (539)
19 letrozole.mp. or femara.af. (493)
20 exemestane.mp. or aromasin.af. (244)
21 or/17-20 (3458)
22 randomized controlled trial.pt. (200369)
23 controlled clinical trial.pt. (68191)
24 Randomized Controlled Trials/ (36877)
25 Random Allocation/ (52955)
26 Double-Blind Method/ (81287)
27 Single-Blind Method/ (8887)
28 or/22-27 (340576)
29 clinical trial.pt. (404235)
30 exp Clinical Trials/ (164401)
31 (clin$ adj25 trial$).ti,ab. (108817)
32 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (80519)
33 PLACEBOS/ (23630)
34 placebos.ti,ab. (1095)
35 random.ti,ab. (78778)
36 Research Design/ (40429)
37 or/29-36 (644944)
38 28 or 37 (673850)
39 16 and 21 and 38 (700)
40 from 39 keep 1-700 (700)

Cost-effectiveness search strategy

Database: Ovid MEDLINE1966 to May Week 4 2005

1 exp Breast Neoplasms/ (121922)
2 exp NEOPLASMS/ (1584391)
3 exp CARCINOMA/ (315268)
4 exp ADENOCARCINOMA/ (182745)
5 exp BREAST/ (19428)
6 or/2-4 (1584391)
7 5 and 6 (10652)
8 (carcinoma adj3 breast$).tw. (18501)
9 (neoplas$ adj3 breast$).tw. (1846)
10 (adenocarcinoma adj3 breast$).tw. (1064)
11 (cancer$ adj3 breast$).tw. (86198)
12 (tumour$ adj3 breast$).tw. (3088)
13 (tumor$ adj3 breast$).tw. (11486)
14 (malignan$ adj3 breast$).tw. (4947)
15 or/8-14 (105355)
16 1 or 7 or 15 (140766)
17 exp Aromatase Inhibitors/ (3127)
18 anastrozole.mp. or arimidex.af. [mp=title, original title, abstract, name of substance word, subject heading word] (539)
19 letrozole.mp. or femara.af. [mp=title, original title, abstract, name of substance word, subject heading word] (493)
20 exemestane.mp. or aromasin.af. [mp=title, original title, abstract, name of substance word, subject heading word] (244)
21 or/17-20 (3458)
22 ECONOMICS/ (23838)
23 exp "Costs and Cost Analysis"/ (115324)
24 "Value of Life"/ (4431)
25 exp Economics, Hospital/ (13307)
26 exp Economics, Medical/ (9634)
27 Economics, Nursing/ (3664)
28 Economics, Pharmaceutical/ (1463)
29 exp Models, Economic/ (4190)
30 exp "Fees and Charges"/ (21489)
31 exp BUDGETS/ (8770)
32 ec.fs. (197518)
33 (Costs or cost or costed or costly or costing$).tw. (145664)

34 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (72791)
35 Quality-Adjusted Life Years/ (2149)
36 economic burden.tw. (981)
37 "Cost of Illness"/ (6880)
38 exp quality of life/ (46341)
39 Quality of Life.tw. (46330)
40 life quality.tw. (1467)
41 hql.tw. (55)
42 (Sf36 or sf36 or sf thirtysix or sf thirty six or short form 36 or short term thirty six or short form thirtysix or shortform 36).tw. (1744)
43 Qol.tw. (4598)
44 (Euroqol or eq5d or eq 5d).tw. (589)
45 Qaly$.tw. (1137)
46 Quality adjusted life year$.tw. (1369)
47 Hye$.tw. (344)
48 Health$ year$ equivalent$.tw. (30)
49 Health utilit$.tw. (282)
50 HUI.tw. (251)
51 Quality of wellbeing$.tw. (2)
52 Qwb.tw. (95)
53 Quality of well being.tw. (512)
54 (Qald$ or qale$ or qtime$).tw. (34)
55 or/22-54 (445207)
56 16 and 21 and 55 (94)
57 from 56 keep 1-94 (94)

Appendix 3

Citations for included studies

ABCSG-6a

Jakesz R. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). *2005 ASCO Annual Meeting Abstract No. 527*; 2005.

Jakesz R. Extended adjuvant treatment with anastrozole: results from the ABCSG trial 6a. ASCO presentation, 2005.

ABCSG-8

Jakesz R. The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

Jakesz R. The benefits of sequencing adjuvant tamoxifen and anastrozole in postmenopausal women with hormone-responsive early breast cancer: 5 year-analysis of ABCSG Trial 8: sequencing data from the ABCSG 8 Trial. Presented at the Vienna Medical School, SABCS meeting, 2005.

ATAC

ATAC-Trialists'-Group. Erratum: anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal woman with early breast cancer: first results of the ATAC randomised trial (*Lancet* (June 22) (2131)). *Lancet* 2002;**360**:1520.

ATAC-Trialists'-Group. Breast surgery in the 'Arimidex, Tamoxifen Alone or in Combination' (ATAC) trial: American women are more likely than women from the United Kingdom to undergo mastectomy. *Cancer* 2004; **101**:735–40.

ATAC-Trialists'-Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer: commentary. *Obstet Gynecol Surv* 2005; **60**:307–9.

ATAC Trialists' Group. Update on ATAC. *Eur J Cancer* 2003;**39**:269.

Baum M. Anastrozole (A) is superior to tamoxifen (T) in treatment of postmenopausal (PM) women with early breast cancer (EBC) – first results of the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial (on behalf of the ATAC Trialists' Group). *Ann Oncol* 2002;**13**:32.

Baum M. An exploration of relapse data by hazard rate as a means of developing biological insights into the natural history and treatment of breast cancer: Data from the 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial and the Milan Institute database. *2005 ASCO Annual Meeting, Abstract No. 612*; 2005.

Baum M, Buzdar A, Cuzick J, Forbes J, Houghton J, Howell A, *et al*. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early-stage breast cancer: results of the ATAC (Arimidex, Tamoxifen Alone or in Combination) trial efficacy and safety update analyses. *Cancer* 2003;**98**:1802–10.

Baum M. The ATAC (Arimidex(trademark), Tamoxifen, Alone or in Combination) adjuvant breast cancer trial in postmenopausal patients: Factors influencing the success of patient recruitment. *Eur J Cancer* 2002;**38**:1984–6.

Buzdar A. Anastrozole as adjuvant therapy for early-stage breast cancer: implications of the ATAC trial. *Clin Breast Cancer* 2003;**4**:S42–8.

Buzdar AU. 'Arimidex' (anastrozole) versus tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer – efficacy overview. *J Steroid Biochem Mol Biol* 2003;**86**:399–403.

Buzdar AU. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial: an update. *Clin Breast Cancer* 2004;**5** Suppl 1:S6–12.

Calderdale and Huddersfield NHS Trust. *Adjuvant trial in post menopausal breast cancer (Arimidex, Tamoxifen Alone or in Combination – ATAC)*. Northern/Yorkshire Regional Office: NRR Participating Centres for Multi-Centre Projects; 2005.

Cambridge Consortium – Addenbrookes. *A randomised, double blind trial comparing Arimidex alone with Nolvadex (tamoxifen) alone with Arimidex and Nolvadex (tamoxifen) in combination, as adjuvant treatment in postmenopausal women with breast cancer*. Cambridge: NRR Participating Centres for Multi-Centre Projects; 2005.

Cella D, Fallowfield L. Five-year quality of life (QOL) follow-up of adjuvant endocrine therapy for postmenopausal women in the Arimidex (A), Tamoxifen (T), Alone or in Combination (ATAC) Trial. *2005 ASCO Annual Meeting, Abstract No. 577*; 2005.

Coleman R. Association between prior chemotherapy and the adverse event profile of adjuvant anastrozole and tamoxifen: a retrospective analysis of data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial on behalf of the ATAC Trialists, Group. *Ann Oncology* 2004;**15**: Abstract 243P.

De Castro Jr G, Del Mastro L, Venturini M, Howell A. ATAC trial update (1) (multiple letters). *Lancet* 2005; **365**:1225–6.

Duffy S. Fewer endometrial abnormalities with anastrozole than tamoxifen: Endometrial subprotocol results from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) early breast cancer (EBC) trial in postmenopausal (PM) patients (pts) (on behalf of the ATAC Trial). *Ann Oncol* 2002;**13**: Abstract 139P.

Duffy SR, Jackson TL. The ATAC ('Arimidex', tamoxifen, alone or in combination) early breast cancer (EBC) trial in postmenopausal (PM) patients: endometrial sub-protocol results. *Proc Am Soc Clin Oncol* 2002; Abstract 158.

Duffy S, Jackson TL, Lansdown M, Philips K, Wells M, Pollard S, *et al*. The ATAC adjuvant breast cancer trial in postmenopausal women: baseline endometrial subprotocol data. *BJOG* 2003;**110**:1099–106.

Eastell R. Results of the 'Arimidex' (anastrozole, A), tamoxifen (T), alone or in combination (C) (ATAC) trial: effects on bone mineral density (BMD) and bone turnover (ATAC Trialists' Group). *Ann Oncol* 2002; **13**:S32 Abstract 113PD.

Fallowfield L. Assessing the quality of life of postmenopausal women randomized into the ATAC ("arimidex", tamoxifen, alone or in combination) adjuvant breast cancer trial. *Breast* 2003;**12**:S42.

Fallowfield L, Cella D, Cuzick J, Francis S, Locker G, Howell A. Quality of life of postmenopausal women in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Adjuvant Breast Cancer Trial. *J Clin Oncol* 2004; **22**:4261–71.

Fisher MD, Shaughnessy J, Sparano JA. Anastrozole may be superior to tamoxifen as adjuvant treatment for postmenopausal patients with breast cancer. *Clin Breast Cancer* 2002;**2**:269–71.

Fodor J, Borrego MR. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial (2002;**359**:2131). *Lancet* 2002; **360**:1520.

Houghton J. Using anastrozole as initial adjuvant treatment prevents early recurrences and reduces adverse events: updated data from the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. *2005 ASCO Annual Meeting, Abstract No. 582*; 2005.

Howell A. 'Arimidex', Tamoxifen, Alone or in Combination (ATAC) trial: completed treatment analysis (PowerPoint presentation). Presented at the San Antonio Breast Cancer Symposium, 2004.

Howell A. The anastrozole, tamoxifen, alone or in combination (ATAC) adjuvant breast cancer trial in post-menopausal women: regional variation in knowledge of hormone receptor status prior to randomisation into the trial. The ATAC Trialists' Group. *Ann Oncol* 2000; **11**:76P.

Howell A. The ATAC trial in postmenopausal women with early breast cancer – updated efficacy results based on a median follow-up of 5 years. *Breast Cancer Res Treat* 2004;**88**:S7.

ISRCTN Register. *A randomised double-blind trial comparing Arimidex alone with Nolvadex alone with Arimidex and Nolvadex in combination, as adjuvant treatment in post-menopausal women with breast cancer (ATAC)*. Curr Control Trials Database; 2005. http://www.controlled-trials.com/isrctn/trial/|/0/18233230.html

Klijn J. The ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial – an efficacy update, focusing on breast cancer (BC) events, based on a median follow-up of 47 months. *2003 ASCO Annual Meeting, Abstract No. 338*; 2003.

Locker GY. The time course of bone fractures observed in the ATAC ('Arimidex', Tamoxifen, Alone or in Combination) trial. *2003 ASCO Annual Meeting, Abstract No. 98*; 2003.

Locker GY, Sainsbury JR, Cuzick J, ATAC Trialists' Group. Breast surgery in the 'Arimidex, Tamoxifen Alone or in Combination' (ATAC) trial: American women are more likely than women from the United Kingdom to undergo mastectomy. *Cancer* 2004; **101**:735–40.

NHS Grampian. *A randomised, double-blind trial comparing Arimidex alone with Nolvadex alone with Arimidex and Nolvadex in combination as adjuvant treatment in post-menopausal women with breast cancer*. Aberdeen: NRR Single-Centre Projects; 2005.

NHS Grampian. *A randomised, double-blind parallel-group trial to assess quality of life with Arimidex alone, Nolvadex alone or Arimidex and Nolvadex in combination when used as adjuvant treatment for breast cancer in postmenopausal women*. Aberdeen: NRR Participating Centres for Multi-Centre Projects; 2005.

NHS Grampian. *Lipids sub-protocol of the ATAC trial*. Aberdeen: NRR Participating Centres for Multi-Centre Projects; 2005.

NHS Lothian – University Hospitals Division and NHS LO. *A randomised double-blind parallel group trial to assess quality of life with Arimidex alone, Nolvadex alone, or Arimidex and Nolvadex in combination, when used as adjuvant treatment for breast cancer in postmenopausal women*. Edinburgh: NRR Participating Centres for Multi-Centre Projects; 2005.

Northern General Hospital NHS Trust. *A randomised double-blind trial to assess the effects of bone mineral density and metabolism of Arimdex alone, Nolvadex alone, or Arimdex and Nolvadex in combination when used as an adjuvant treatment for breast cancer in postmenopausal women*. Sheffield: NRR Participating Centres for Multi-Centre Projects; 2005.

Royal Marsden. *A randomised double blind trial of tamoxifen 20 mg daily, Arimidex 1 mg daily, or the combination of tamoxifen 20 mg daily plus Arimidex 1 mg daily for 3 months*

prior to surgical excision in post menopausal patients. London: NRR Single-Centre Projects; 2005.

Royal Marsden. *Adjuvant trial in post-menopausal breast cancer: Arimidex, Tamoxifen Alone or in Combination (ATAC trial)*. London: NRR Single-Centre Projects; 2005.

Royal Marsden. *Pharmacological studies of Arimidex + tamoxifen in association with a multinational adjuvant study in operable breast cancer*. London: NRR Single-Centre Projects; 2005.

Rugo HS. ATAC follow-up continues to show DF survival benefit from anastrozole. *Oncology Report* 2005(spring edition);23–4.

Salford Royal Hospitals NHS Trust. *A randomised double-blind trial comparing Arimidex alone with Nolvadex alone with Armidex and Nolvadex in combination, as adjuvant treatment in post-menopausal women with breast cancer (ATAC)*. NRR Participating Centres for Multi-Centre Projects; 2005.

Sheffield Teaching Hospitals NHS Foundation Trust. *A randomised, double-blind trial to assess the effects on bone mineral density and metabolism of Arimidex alone, Nolvadex alone, or Arimidex and Nolvadex in combination when used as adjuvant treatment for breast cancer in post menopausal women*. NRR Participating Centres for Multi-Centre Projects; 2005.

Sheffield Teaching Hospitals NHS Foundation Trust. *Adjuvant trial in post menopausal breast cancer Arimidex, tamoxifen alone or in combination (ATAC)*. NRR Participating Centres for Multi-Centre Projects; 2005.

Shrewsbury and Telford Research and Development Consortium. *ATAC – A study comparing Arimidex alone with Nolvodex alone with Arimidex and Novaldex in combination, as adjuvant treatment in post-menopausal women with breast cancer*. NRR Participating Centres for Multi-Centre Projects; 2005.

South Bro Taf R&D Consortium. *A randomised, double-blind, parallel-group trial to assess quality of life with Arimidex alone, Nolvadex alone, or Arimidex and Nolvadex in combination, when used as adjuvant treatment for breast cancer in postmenopausal women*. NRR Participating Centres for Multi-Centre Projects; 2005.

South Bro Taf R&D Consortium. *Randomised, double-blind trial to assess effects on bone mineral density and metabolism of Arimidex alone, Nolvadex alone, Arimidex and Nolvadex combined, compared to control, when used as adjuvant treatment for breast cancer in postmenopausal women*. NRR Participating Centres for Multi-Centre Projects; 2005.

St George's Healthcare NHS Trust. *Adjuvant trial in post-menopausal breast cancer Arimidex (Anastrozole) Tamoxifen Alone or in Combination – the ATAC trial*. NRR Participating Centres for Multi-Centre Projects; 2005.

The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;**359**:2131–9.

The ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;**365**:60–2.

The Mid Yorkshire Hospitals NHS Trust. *ATAC Study. Arimidex, Tamoxifen alone or in Combination Study. Endometrial sub protocol of the ATAC study 98/14*. NRR Participating Centres for Multi-Centre Projects; 2005.

The North and South Bank Research and Development Consortium. *Endometrial sub-protocol of the ATAC trial (Arimidex tamoxifen, alone or in combination as adjuvant treatment for breast cancer)*. NRR Single-Centre Projects; 2005.

United Bristol Healthcare NHS Trust. *ATAC: a randomised double-blind trial comparing Arimidex alone with Nolvadex alone with Arimidex and Nolvadex in combination as adjuvant treatment in post-menopausal women with breast cancer*. NRR Single-Centre Projects; 2005.

Whittington Hospital NHS Trust. *A randomised, double-blind trial comparing Arimidex alone with Nolvadex (tamoxifen) alone with Arimidex and Nolvadex (tamoxifen) in combination, as adjuvant treatment in post-menopausal women with breast cancer*. NRR Participating Centres for Multi-Centre Projects; 2005.

BIG 1-98

Christie Hospital NHS Trust. *A Phase III study to evaluate letrozole as adjuvant endocrine therapy for post-menopausal women with receptor (ER and/ or PgR) positive tumours*. NRR Single-Centre Projects; 2005.

NIH. *Letrozole or tamoxifen in treating postmenopausal women with breast cancer*. Current Controlled Trials Database; 2005. http://controlled-trials.com/mrct/trial/LETROZOLE/1059/60489.html

North Middlesex Hospital NHS Trust. *An international, multicenter, double blind, double dummy, phase III, 2-arm adjuvant trial comparing letrozole 2.5 mg versus tamoxifen 20 mg in postmenopausal women with operable breast cancer*. NRR Single-Centre Projects; 2005.

Royal Marsden. *An international, multicentre, double blind, double dummy, Phase III, 2-arm adjuvant trial comparing letrozole 2.5 mg versus tamoxifen 20 mg in postmenopausal women with operable breast cancer*. NRR Lead Centres for Multi-Centre Projects; 2005.

The Breast International Group (BIG) 1-98 Collaborative Group. A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 2006;**353**:2747–57.

Thurlimann BJ. BIG 1-98: randomized double-blind phase III study to evaluate letrozole (L) vs. tamoxifen (T) as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. *2005 ASCO Annual Meeting, Abstract No, 511*; 2005.

Thürlimann B. Letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. *ASCO presentation*, 2005.

Thürlimann B. Letrozole vs. tamoxifen as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer, BIG 1-98: a prospective randomized double-blind Phase III study. *Breast* 2005; **14**:(supplement 1):S3.

GABG

Jakesz R. Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial. *Breast Cancer Res Treat* 2004; **88**:S7.

Jakesz R, Jonat W, Mittlboeck M. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;**366**:455–62.

IES

Bertelli G, Hall E, Bliss JM, Snowdon CF, Coombes RC. Intergroup Exemestane Study: results of the endometrial sub-protocol. *San Antonio Breast Cancer Symposium, 2004*; 2005, Abstract 402.

Coleman RE, Banks LM, Hall E, Price D, Girgis S, Bliss JM, *et al*. Intergroup Exemestane Study: 1 year results of the bone sub-protocol. *San Antonio Breast Cancer Symposium, 2004*; 2005, Abstract 401.

Coleman RE. Skeletal effect of exemestane in the Intergroup Exemestane Study (IES) 2 year bone mineral density (BMD) and bone biomarker data. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

Coombes RC, Hall E, Snowdon CF, Bliss JM. A randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen (PowerPoint presentation). Presented at the San Antonio Breast Cancer Symposium, 2004.

Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, *et al*. The Intergroup Exemestane Study: a randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. [published erratum appears in *N Engl J Med* 2004;**351**:2461]. *N Engl J Med* 2004; **350**:1081–92.

Coombes RC. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer (vol 350, pg 1081, 2004) [Erratum]. *N Engl J Med* 2004; **351**:2461.

Coombes RC, Bliss JM, Hall E. Safety of exemestane in the Intergroup Exemestane Study. *J Clin Oncol* 2005; **23**:3171–2.

Coombes RC. The Intergroup Exemestane Study (IES) – design and patient characteristics. *2002 ASCO Annual Meeting, Abstract No. 1986*; 2002.

Coombes RC, Hall E, Snowdon CF, Bliss JM. The Intergroup Exemestane Study: a randomized trial in postmenopausal patients with early breast cancer who remain disease-free after two to three years of tamoxifen updated survival analysis. *Breast Cancer Res Treat* 2004; **88**:S7.

Fallowfield LJ, Price MH, Hall E, Coombes RC, Bliss JM. Intergroup exemestane study: results of the quality of life sub-protocol. *San Antonio Breast Cancer Symposium 2004*, Abstract 1066; 2004.

Fallowfield LJ, Price MH, Hall E, Coombes RC, Bliss JM. Intergroup exemestane study: results of the quality of life sub-protocol. *Breast Cancer Res Treat* 2004; **88**:S8 (Abstract 4). http://www.controlled-trials.com/isrctn/trial/|/0/11883920.html

ISRCTN Register. *A randomised double-blind trial in post-menopausal women with primary breast cancer who have received adjuvant tamoxifen for 2–3 years, comparing subsequent adjuvant exemestane treatment with further tamoxifen*. Current Controlled Trials Database; 2005.

Jassem J, Hall E, Bliss JM, Patel R, Snowdon CF, Coombes RC. Approaches to adjuvant chemotherapy in postmenopausal breast cancer patients in the Intergroup Exemestane Study. *San Antonio Breast Cancer Symposium, 2004*; 2004, Abstract 1066.

Jones SE. The effect of tamoxifen (T) or exemestane (E) on bone mineral density (BMD) after 1 year of adjuvant treatment of postmenopausal women with early breast cancer. *2005 ASCO Annual Meeting, Abstract No. 610*; 2005.

Lonning PE. Changes in bone metabolism after 2 years' treatment with exemestane (E) in postmenopausal women with early breast cancer (EBC) at low risk: follow-up (FU) results of a randomized placebo-controlled study. *2005 ASCO Annual Meeting, Abstract No. 531*; 2005.

UKCCCR. *A randomised double-blind trial in post-menopausal women with primary breast cancer who have received adjuvant tamoxifen for 2–3 years, comparing subsequent adjuvant exemestane treatment with further tamoxifen*. Current Controlled Trials Database; 2005.

ITA

Boccardo F, Rubagotti A, Amoroso D. Anastrozole appears to be superior to tamoxifen in women already receiving tamoxifen treatment. *Breast Cancer Res Treat* 2003;**82**:S6–7.

Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole Trial. *J Clin Oncol* 2005;**23**:5138–47.

Boccardo FM. Switching to anastrozole (ANA) vs continued tamoxifen (TAM) treatment of early breast cancer (EBC). Updated results of the Italian tamoxifen anastrozole (ITA) trial. *2005 ASCO Annual Meeting, Abstract No. 526*; 2005.

Jonat meta-analysis

Jonat W. Switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-responsive early breast cancer:a meta-analysis of ARNO 95, ABCSG8, and the ITA trials. Presented at the SABCS meeting on behalf of all investigators of the GABG, the ABCSG and the ITA trial group, 2005.

MA-17

Abetz L, Barghout V, Thomas S, Arbuckle R. Letrozole did not worsen quality of life relative to placebo in post-menopausal women with early breast cancer: results from the US subjects of the MA-17 study. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

Barghout V, Abetz L, Thomas S, Arbuckle R. Impact of letrozole on quality of life in post-menopausal women with early breast cancer: does age matter? Presented at the 28th San Antonio Breast Cancer Conference, 2005.

Christie Hospital NHS Trust. *NCIC: a phase III randomised double-blind study letrozole versus placebo in women with primary breast cancer*. NRR Single-Centre Projects; 2005.

DeGrendele H. Benefit of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *Clin Breast Cancer* 2003;**4**:311–12.

Goss PE, Ingle JN, Palmer MJ, Shepherd LE, Tu D. Updated analysis of NCIC CTG MA.17 (letrozole vs. placebo to letrozole vs placebo) post unblinding. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, *et al*. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349**:1793–802.

Goss PE, Ingle JN, Martino S, Buzdar AU. Letrozole improved disease-free survival in postmenopausal women after tamoxifen treatment for breast cancer. *Evid Based Obstet Gynecol* 2004;**6**:91–2.

Goss PE. Updated analysis of the NCIC CTG MA.17 randomized placebo (P) controlled trial of letrozole (L) after five years of tamoxifen in postmenopausal women with early stage breast cancer. *2004 ASCO Annual Meeting, Abstract No. 847*; 2004.

Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, *et al*. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst Cancer Spectrum* 2005; **97**:1262–71.

Ingle JN, Goss PE, Tu D. Analysis of duration of letrozole extended adjuvant therapy as measured by hazard ratios of disease recurrence over time for patients on NCIC CTG MA.17. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

NHS Lothian – University Hospitals Division. *Randomised trial comparing a further 5 years of Letrozole vs nil after 5 years' tamoxifen.: EORTC trial 10983*. NRR Participating Centres for Multi-Centre Projects; 2005.

Royal Marsden. *A Phase III randomised double blind study of letrozole versus placebo in women with primary breast cancer completing five or more years of adjuvant tamoxifen (NCIC CTG MA.17)*. NRR Participating Centres for Multi-Centre Projects; 2005.

St George's Healthcare NHS Trust. *A Phase III randomised double-blind study of letrozole vs placebo in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen*. NRR Lead Centres for Multi-Centre Projects; 2005.

Vachon CM, Ingle JN, Scott CG, Olson JE, Goss PE. Pilot study of changes in mammographic density in women treated with letrozole or placebo on NCIC CTG MA17. Presented at the 28th San Antonio Breast Cancer Conference, 2005.

Appendix 4

Statement from NICE DSU

The following is a statement by Professor Keith Abrams concerning the internal validity of the GABG combined analysis[73] (see 'Number and type of studies included', p. 17, and throughout).

"Whilst the entry criteria and the baseline characteristics are stated to be similar, the combination of patients from both trials in this combined analysis does raise a number of issues.

"1. Given that the study was open-label, in ABCSG-8 all patients received tamoxifen during the first 2 years, whilst although patients in ARNO-95 only switched at 2 years post-initial surgery their status post-randomisation would appear to be known [I cannot find a statement to the contrary in Jakesz *et al*., 2005], and thus differences in the use of adjuvant therapies between ABCSG-8 and ARNO-95 could have potentially occurred, though I accept that this is unlikely.

"2. Inclusion of only the data on all patients post-2 years in fact breaks randomisation, since in ABCSG-8 patients were randomised post-surgery and in ARNO-95 they were randomised at points between surgery and 2 years. In both trials a proper ITT analysis to establish the effectiveness of the different treatment policies would use the time of randomisation as the time origin for any analysis. Clearly the combination of the two trials prevents this.

"3. Whilst the inclusion of patients in a combined or pooled analysis recruited into separate trials is often undertaken, and in some senses can be thought of as an extension of a multi-centre trial, it is also common practice to assess whether there are systematic differences between trial or centre. Perhaps more importantly the synthesis of information using a marginal analysis (i.e. by simply pooling the data as is the case here) prevents the inclusion of trial-to-trial variability being included in the final estimate of effect, and thus the level of uncertainty surrounding such effect estimate, in a marginal analysis, could be considerably smaller than that which would have obtained using standard meta-analysis methods. Whilst in terms of establishing whether a treatment policy is superior such technical details may appear superfluous, if the results of such an analysis are to be included in a decision model for instance to assess the implications of different treatment policies in a UK context the reduced level of uncertainty could have an increased effect on the estimates of cost-effectiveness. However, because no results are presented separately for the ABCSG-8 and the ARNO-95 trials, the precise implications are difficult to assess. At the very least a sensitivity analysis should be undertaken so that these implications could be assessed.

"4. In terms of undertaking a meta-analysis of the ABCSG-8 and ARNO-95 trials and other evidence available, it should be noted that meta-analysis of survival data is often complicated by the difficulty in extracting relevant trial-level summary statistics and associated measures of uncertainty, and that in such circumstances an IPD meta-analysis is often considered necessary, especially if interest also focuses upon the effectiveness in subgroups of patients."

Appendix 5

Critical appraisal of quality of life substudies

TABLE 47 *Critical appraisal of quality of life papers*

Criteria	ATAC[93] (full paper)	IES (abstract only)[97]	MA-17[98] (full paper)
1. Did the investigators conceptually identify what they meant by QoL?[60]	No	No	No
2. Did the investigators identify why QoL measurement was introduced into the trial?[61,62]	Toxicities and tolerability of treatments as inferred from clinician-recorded AEs may differ from those reported by patients	No	To evaluate the effects of lowering oestrogen on a population with relatively good QoL
3. Was QoL a primary or secondary end-point of the trial?[61]	A primary end-point of a separate sub-protocol, recruiting only some of the women randomised to the trial	Secondary end-point	Secondary end-point
4. Did the investigators specify the domains they wanted to measure as components of QoL?[60]	Implicit in choice of questionnaires. The Functional Assessment of Cancer Therapy for Breast Cancer (FACT-B) tool[94] (36-item) covers five domains from the Functional Assessment of Cancer Therapy – General (FACT-G) tool (physical, social, emotional and functional well-being, and relationship with the physician) plus additional concerns more specific to women with breast cancer. The trialists also used an additional Endocrine Subscale (ES) questionnaire (18 items)[95]	Implicit in choice of questionnaires, which were the FACT-B and FACT-ES (see left for details)	Implicit in choice of questionnaires. The Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36)[99] contains eight subscales or domains, which are summarised into two global scores: the physical and mental component summary (PCS and MCS) scores. The Menopause Specific QOL (MENQOL) questionnaire[100]
5. Did the investigators give reasons for choosing instruments they used?[60]	No	No	Yes. SF-36: in view of "the relatively healthy population studied with a similar potential for future cancer and non-cancer outcomes"; "MENQOL was chosen specifically to assess symptoms related to menopause or oestrogen depletion that might be worsened by the use of aromatase inhibitors"
6. Was the instrument disease specific or comprehensive?[62]	Disease specific: the FACT-B is a breast cancer-specific tool and the ES is specific to women receiving endocrine therapy	Yes (see left)	SF-36 is comprehensive, generic measure, which can be used across different patient populations. MENQOL is specific to menopause-related symptoms
7. Were established instruments tested for validity?[62]	FACT-B was validated in 1997[96] and the ES in 1999[95]	Yes (see left)	Data on validation were published in 1992–3[101,102] for the SF-36 and in 1996 for MENQOL[100]

continued

TABLE 47 *Critical appraisal of quality of life papers (cont'd)*

Criteria	ATAC[93] (full paper)	IES (abstract only)[97]	MA-17[98] (full paper)
8. Was the modification of established instruments tested for validity?[62]	No modification to established instruments took place	No modification to established instruments took place	No modification to established instruments took place
9. Were instruments original (developed by the investigators themselves)?[62]	D Cella (one trial author) is the principle author on the FACT-B (which was not designed for this trial).[94] L Fallowfield is the principle author of the ES (the paper reporting its design and validation was published in 1999)[95]	L Fallowfield is the principle author of the FACT-ES (see left)	No
10. Did the investigators aggregate the results from multiple items, domains or instruments into a single composite score for QoL?[60]	No. The primary end-point, the trial outcome index (TOI) of the FACT-B questionnaire, aggregates only scores from the physical and functional well-being and the breast cancer subscales	No (see left)	No. This was not presented for either the SF-36 or the MENQOL surveys
11. What was the response rate?[61]	"Approximately 85%" for all time points (every 3–24 months)	"85% available at each post-baseline visit"	"More than 90% for all time points" (6, 12, 24, 36, 48 months)
12. Were patients asked to give their own global rating for QoL?[60]	No	No	No
13. Was overall QoL distinguished from health-related QoL?[60]	Yes. All elements of the FACT-B and ES questionnaires are health-related	Yes (see left)	Yes. All elements of the SF-36 and MENQOL tools are health-related
14. Were patients invited to supplement the items listed in the instrument(s) offered by the investigators?[60]	No. The questionnaires are standardised and require written responses	No (see left)	No
15. If so, were these supplemental items incorporated into the final rating?[60]	Not applicable	Not applicable	Not applicable
16. Were patients asked to indicate which items (either specified by the investigator or added by the patients) were personally important to them?[60]	No	No	No
17. If so, were these importance ratings incorporated into the final rating?[60]	Not applicable		Not applicable

QoL, quality of life.

Appendix 6

Critical appraisal of economic evidence using the Drummond checklist

AstraZeneca

- Primary adjuvant therapy – ATAC
- Extended adjuvant therapy – ARNO/ABCSG-8.

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – NHS perspective
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a do-nothing alternative (be) considered?	No, not required
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Yes. Comparator arm was 5 years' tamoxifen
3.2.	Was effectiveness established through an overview of clinical studies?	*Primary adjuvant*
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Based on the one available study – ATAC, 68 months' follow-up. Weibull functions were used to estimate survival for 10 years. Beyond 10 years, Weibull curve fitted to pooled data and used to extrapolate recurrence rates for both groups, i.e. same time-dependent rates applied to both arms *Unplanned switching* Based on the combined analysis – GABG. Recurrence-free survival, the proportion of DR within first recurrences associated with first 3 years of continued adjuvant treatment taken from trial. Benefits assumed to continue for 5 years beyond therapy period
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, in addition to operating costs, included?	No, not required
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No

continued

6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	Yes
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	Not required
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility – been selected)?	Yes
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Costs 6%, benefits 1.5%
7.2.	Was any justification given for the discount rate used?	In line with current NICE guidance
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Yes
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	No
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	No
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. ICER)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Cost per QALY was used
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	Yes; Discussion of differences was included
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No

Novartis

- Primary adjuvant therapy – Big 1-98
- Extended adjuvant therapy – MA-17.

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – NHS perspective
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a do-nothing alternative (be) considered?	No, not required
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Yes. Comparator arm was 5 years' tamoxifen
3.2.	Was effectiveness established through an overview of clinical studies?	*Primary adjuvant*
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Based on the one available study in each patient setting – BIG 1-98 trial – average 28 months' follow-up. 3- and 5-year aggregate rates used to estimate annual event rates for tamoxifen and hazard ratios for letrozole from BIG 1-98 CSR *Extended adjuvant* Trial data from years 1–4 were used to extrapolate recurrence rates for year 5. Beyond year 5, event rates are assumed to be constant and equivalent in both arms, based on MA-17 recurrence in year 9
4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, in addition to operating costs, included?	No, not required
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	Yes
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No
6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	Yes
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	Not required
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility been selected)?	Yes
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Costs 6%, benefits 1.5%
7.2.	Was any justification given for the discount rate used?	In line with current NICE guidance

continued

8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Yes
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	No
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	No
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. ICER)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Cost per QALY was used
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	No
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No

Pfizer

- Switching therapy – based on IES.

1.	**Was a well-defined question posed in answerable form?**	
1.1.	Did the study examine both costs and effects of the service(s) or programme(s)?	Yes
1.2.	Did the study involve a comparison of alternatives?	Yes
1.3.	Was a viewpoint for the analysis stated and was the study placed in any particular context?	Yes – NHS perspective
2.	**Was a comprehensive description of the competing alternatives given?**	
2.1.	Were any important alternatives omitted?	No
2.2.	Was (should) a do-nothing alternative (be) considered?	No, not required
3.	**Was the effectiveness of the programmes or services established?**	
3.1.	Was this done through an RCT? If so, did the trial protocol reflect what would happen in regular practice?	Yes. Comparator arm was 5 years' tamoxifen
3.2.	Was effectiveness established through an overview of clinical studies?	Based on the one available study – IES
3.3.	Were observational data or assumptions used to establish effectiveness? If so, what are the potential biases in results?	Trial has 36 months' follow-up. Beyond 36 months, it was assumed that exemestane and tamoxifen would have same effect in preventing recurrences

continued

4.	**Were all the important and relevant costs and consequences for each alternative identified?**	
4.1.	Was the range wide enough for the research question at hand?	Yes
4.2.	Did it cover all relevant viewpoints?	Yes
4.3.	Were capital costs, in addition to operating costs, included?	No, not required
5.	**Were costs and consequences measured accurately in appropriate physical units?**	
5.1.	Were any of the identified items omitted from measurement? If so, does this mean that they carried no weight in the subsequent analysis?	No
5.2.	Were there any special circumstances (e.g. joint use of resources) that made measurement difficult? Were these circumstances handled appropriately?	No
6.	**Were costs and consequences valued credibly?**	
6.1.	Were the sources of all values clearly identified?	Yes
6.2.	Were market values employed for changes involving resources gained or depleted?	No
6.3.	Where market values were absent (e.g. volunteer labour) or market values did not reflect actual values (such as clinical space donated at a reduced rate), were adjustments made to approximate market values?	Not required
6.4.	Was the valuation of consequences appropriate for the question posed (i.e. has the appropriate type of analysis – cost-effectiveness, cost–benefit, cost–utility been selected)?	Yes
7.	**Were costs and consequences adjusted for differential timing?**	
7.1.	Were costs and consequences which occur in the future discounted to their present value?	Costs 6%, benefits 1.5%
7.2.	Was any justification given for the discount rate used?	In line with current NICE guidance
8.	**Was an incremental analysis of costs and consequences of alternatives performed?**	
8.1.	Were the additional (incremental) costs generated by one alternative over another compared with the additional effects, benefits or utilities generated?	Yes
9.	**Was allowance made for uncertainty in the estimates of costs and consequences?**	
9.1.	If data on costs or consequences were stochastic, were appropriate statistical analyses performed?	Yes
9.2.	If sensitivity analysis was employed, was justification provided for the ranges of values (for key study parameters)?	No
9.3.	Were study results sensitive to changes in the values (within the assumed range for sensitivity analysis, or within the CI around the ratio of costs to consequences)?	No
10.	**Did the presentation and discussion of study results include all issues of concern to users?**	
10.1.	Were the conclusions of the analysis based on some overall index or ratio of costs to consequences (e.g. ICER)? If so, was the index interpreted intelligently or in a mechanistic fashion?	Cost per QALY was used
10.2.	Were the results compared with those of others who have investigated the same question? If so, were allowances made for potential differences in study methodology?	No
10.3.	Did the study discuss the generalisability of the results to other settings and patient/client groups?	No
10.4.	Did the study allude to, or take account of, other important factors in the choice or decision under consideration (e.g. distribution of costs and consequences, or other ethical issues)?	No
10.5.	Did the study discuss issues of implementation, such as the feasibility of adopting the 'preferred' programme given existing financial or other constraints, and whether any freed resources could be redeployed to other worthwhile programmes?	No

Appendix 7

Table of key model parameters

Costs (£)

Parameters	Comment	Probabilistic	Base case
Tamoxifen (cost per cycle)		30.52	30.52
Anastrozole (cost per cycle)		894.25	894.25
Letrozole (cost per cycle)		1084.00	1084.00
Exemestane (cost per cycle)		1080.40	1080.40
Adverse events (1st year)			
Endometrial		Gamma (61.47, 57.89)	3558
DVT		Gamma (61.47, 12.76)	784
Vaginal bleeding		Gamma (61.47, 17.31)	158
TIA (year 1)		Gamma (61.47, 130.9)	1064
Stroke (year 1)		Gamma (61.47, 20.95)	8046
Cost PE		Gamma (61.47, 20.95)	1288
Adverse events (2nd year)			
Endometrial		Gamma (61.47, 2.64)	162
DVT		0	0
Vaginal Bleeding		0	0
TIA (year 2)		Gamma (61.47, 4.3)	264
Stroke (year 2)		Gamma (6.47, 35.19)	2163
Stroke (fatal)		Gamma (61.47, 114.55)	7041
States			
Ipsilateral recurrence		Gamma (61.47, 70.27)	4319
Contralateral recurrence		As above	4319
Metastatic recurrence		Gamma (61.47, 157.13)	9658
Remission		Gamma (61.47, 10.31)	634
Death breast cancer		Gamma (61.47, 51.18)	3146
DFS 5 years		Gamma (61.47, 2.67)	164

Utilities

Parameters	Comment	Probabilistic	Base case
Adverse events (1st and 2nd years)			
Endometrial cancer		Beta (48.37, 12.09)	0.8
DVT events		Beta (19.43, 1.24)	0.94
Vaginal bleeding		Beta (5.02, 0.36)	0.933
Ischaemic events		Beta (0.02, 281)	0.63
States			
Multiplier (from Kind *et al*., 1998[145])		Beta (10.2, 2.89)	0.83
Disease free		Beta (1.51, 1.089)	0.940 × 0.83
Ipsilateral recurrence		Beta (1.51, 1.089)	0.740 × 0.83
Contralateral recurrence		(As above)	0.740 × 0.83
Metastatic recurrence		Beta (2.20, 3.11)	0.630 × 0.83
Remission		Beta (3.11, 1.29)	0.850 × 0.83

Other common data

Parameters	Comment	Probabilistic	Base case
Tamoxifen yearly rate of recurrence after 5 year		0.027	0.027
15 years rate of recurrence		0.332	0.332
Death probabilities			
Death from endometrial cancer (year 1)		0.15	0.15
Death from endometrial cancer (year 2)		0.1	0.1
Death from hip fracture		0.06	0.06
Death from DVT		0.004	0.004

Trial-based clinical parameters

Primary adjuvant: anastrozole

Based on ATAC.

Parameters	Comment	Probabilistic	Base case
Weibull regression parameters			
Constant Weibull		Multivariate normal distribution	9.172
Anastrozole parameter (1 if anastrozole, 0 if tamoxifen)			0.249
Scale_weib			0.831
Probability of a recurrence for tamoxifen			
Metastatic recurrence		Dirichlet (101, 265, 54)	0.631
Ipsilateral recurrence			0.24
Contralateral recurrence			0.129
Recurrence hazards for anastrozole			
Metastatic	This is the distribution of the log hazard, which is equivalent to saying that hazard has a log-normal distribution	Norm (–0.17, 0.025)	0.84
Ipsilateral		Norm (–0.33, 0.025)	0.713
Contralateral		Norm (–0.75, 0.025)	0.47
Probability of recurring from remission to metastatic state for 5 years:			
rel_tun_meta1		Beta (25, 114)	0.18
rel_tun_meta2		Beta (21, 92)	0.191
rel_tun_meta3		Beta (11, 81)	0.118
rel_tun_meta4		Beta (7.29, 74)	0.089
rel_tun_meta5		Beta (8.68, 65.9)	0.116
Probability of breast cancer death (from metastatic disease)		Beta (129, 216)	0.3733
Adverse events tamoxifen (fatal)			
Total fatal AE (1 year)		Beta (37, 3056)	0.012
Endometrial cancer (5 year)			0.008
Hip fractures (5 year)			0
Ischaemic cerebrovascular events (5 year)			0.028
DVT events (5 year)			0.024
Adverse events tamoxifen (not fatal)			
Vaginal bleeding			0.102
Adverse events anastrozole (fatal)			
Total fatal AE		Beta (23, 3068)	0.008
Endometrial cancer (5 year)			0.002
Hip fractures (5 year)			0
Ischaemic cerebrovascular events (5 year)			0.02
DVT events (5 year)			0.016
Adverse events anastrozole (not fatal)			
Vaginal bleeding			0.054

Primary adjuvant: letrozole

Based on BIG 1-98.

Parameters	Comment	Probabilistic	Base case
Recurrence – 5 years' tamoxifen		Beta (544, 3462)	0.136
Hazard for letrozole	This is the distribution of the log hazard, which is equivalent to saying that hazard has a log-normal distribution	Norm (–0.328, 0.022)	0.720
Recurrence 5 years' letrozole			0.098
Recurrence – 1 year tamoxifen (converted from 5 years)			0.029
Recurrence – 1 year letrozole (converted from 5 years)			0.021
Probability of incurring a recurrence (tamoxifen)			
Metastatic			0.595
Ipsilateral			0.336
Contralateral		Dirichlet (232, 131, 27)	0.069
Recurrence hazards for Letrozole			
Haz_meta	This is the distribution of the log hazard, which is equivalent to saying that hazard has a log-normal distribution	Norm (–0.28, 0.02)	0.753
Haz_ipsi		Norm (–0.25, 0.02)	0.778
Haz_contra		Norm (–0.56, 0.02)	0.571
Adverse events tamoxifen			
Total fatal AE (1 year)	0.012	Beta (46.13, 3960)	0.012
Endometrial cancer (5 year)			0.005
Ischaemic cerebrovascular events (5 year)			0.028
DVT events (5 year)			0.024
Vaginal bleeding			0.104
Adverse events letrozole			
Total fatal AE (1 year)	0.008	Beta (30.65, 3974)	0.008
Endometrial cancer (5 years)			0.002
Ischaemic cerebrovascular events (5 years)			0.020
DVT events (5 years)			0.016
Vaginal bleeding (5 years)			0.045

Unplanned switching: anastrozole

Based on GABG.

Parameters	Comment	Probabilistic	Base case
Recurrence 3 years' tamoxifen		Beta (292, 3714)	0.073
Hazard	This is the distribution of the log hazard, which is equivalent to saying that hazard has a log-normal distribution	Norm (–0.51, 0.022)	0.600
Recurrence 5 years' anastrozole			0.044
Recurrence – 1 year tamoxifen (converted)			0.025
Recurrence – 1 year letrozole (converted)			0.015
Probability of incurring a recurrence			
p.rel_meta			0.642
p.rel_ipsi			0.220
p.rel_contra		Dirichlet (102, 35,22)	0.138
Recurrence hazards for anastrozole			
Metastatic		Norm (–0.57, 0.025)	0.562
Ipsilateral		Norm (–0.69, 0.025)	0.498
Contralateral		Norm (–0.45, 0.025)	0.635
Adverse events tamoxifen			
Total fatal AE (1 year)		Beta (12, 3081)	0.004
Endometrial cancer (3 year)			0.006
Ischaemic cerebrovascular events (3 year)			0.000
DVT events (3 year)			0.006
Vaginal bleeding			0.102
Adverse events anastrozole			
Total fatal AE (1 year)		Beta (3, 3088)	0.001
Endometrial cancer			0.002
Ischaemic cerebrovascular events			0.000
DVT events			0.001
Vaginal bleeding			0.054

Unplanned switching: exemestane

Based on IES.

Parameters	Comment	Probabilistic	Base case
Intercept			–3.455
Log(time)			1.371
Exemestane parameter		Multivariate normal	–0.442
Probability of incurring a recurrence			
p.rel_meta			0.767
p.rel_ipsi			0.145
p.rel_contra		Dirichlet (174, 33,20)	0.088
Recurrence hazards for exemestane			
Haz_ meta	This is the distribution of the log hazard, which is equivalent to saying that hazard has a log-normal distribution	Norm (–0.42, 0.0254)	0.652
Haz_ipsi		Norm (–0.44, 0.0254)	0.640
Haz_contra		Norm (–0.79, 0.0254)	0.452

continued

Parameters	Comment	Probabilistic	Base case
Adverse events tamoxifen			
Total fatal AE (1 year)		Beta (8.77, 2371)	0.004
Endometrial cancer (3 year)			0.005
Hip fractures (3 year)			
Ischaemic cerebrovascular events (3 year)			
DVT events (3 year)			0.006
Vaginal bleeding			0.019
Adverse events exemestane			
Total fatal AE (1 year)		Beta (2.68, 2359)	0.001
Endometrial cancer			0.002
Hip fractures			
Ischaemic cerebrovascular events			
DVT events (3 year)			0.001
Vaginal bleeding			0.010

Extended adjuvant: letrozole

Based on MA-17.

Parameters	Comment	Probabilistic	Base case
Recurrence 5 years' placebo		Beta (897, 3109)	0.224
Hazard		Norm (–0.5, 0.027)	0.603
Recurrence 5 years' letrozole			0.135
Recurrence 1 year placebo (converted)			0.049
Recurrence 1 year letrozole (converted)			0.029
Probability of incurring a recurrence			
p.rel_meta			0.573
p.rel_ipsi			0.231
p.rel_contra		Dirichlet (82, 33, 28)	0.196
Recurrence hazards for letrozole			
Haz_ meta	This is the distribution of the log hazard, which is equivalent to saying that hazard has a log-normal distribution	Norm (–0.45, 0.027)	0.631
Haz_ipsi		Norm (–0.55, 0.027)	0.575
Haz_contra		Norm (–0.49, 0.027)	0.607
Adverse events placebo			
Total fatal AE (1 year)		Beta (5.68, 2571)	0.002
Endometrial cancer (5 year)			0.000
Hip fractures (5 year)			0.003
Ischaemic cerebrovascular events (5 year)			0.006
DVT events (5 year)			0.002
Vaginal bleeding			0.080
Adverse events letrozole			
Total fatal AE (1 year)		Beta (5.15, 2566)	0.002
Endometrial cancer (5 year)			0.000
Hip fractures			0.002
Ischaemic cerebrovascular events			0.007
DVT events			0.001
Vaginal bleeding			0.060

Appendix 8

Methods of extrapolation

Primary adjuvant setting

Anastrozole

Based on ATAC.

The results from the Weibull regression based on patient-level data were used in the ScHARR model for the first 5 years. This was performed by statisticians at AstraZeneca, who provided us with coefficients and a variance–covariance matrix. A multivariate normal distribution is used for the joint distribution of these coefficients which uses as parameters a vector of means of the coefficients and the variance–covariance matrix. Using a Weibull regression allows variable rates of recurrence to be used.

Beyond 5 years, two scenarios are considered, as follows.

Base-case scenario

From year 6 to year 15, the rate of recurrence increases at a level so as to have 33.2% recurrence at 15 years for both of the two arms. This is based on the rate shown in the EBCTCG's (2005) paper[37] for the tamoxifen arm. This assumes that the rate of recurrence in the anastrozole arm is higher than that in the tamoxifen arm during this period.

Parallel scenario

From year 6 to year 15, the tamoxifen arm is assumed to have a constant rate of recurrence so as to reach 33.2% recurrence at 15 years, as before. The anastrozole arm is assumed to have the same rate of recurrence. In other words, the time to recurrence curve for anastrozole arm is parallel to the tamoxifen curve.

Letrozole

Based on BIG 1-98.

For the first 5 years, recurrence in the tamoxifen arm is based on 5 years' rate of recurrence from the trial. The rate of recurrence for anastrozole is estimated by applying the HR from the trial to the 1 year of recurrence for tamoxifen. By doing so, we are making the assumption of proportional hazard, which means that the hazard at 1 year is the same as the hazard at 5 years. These rates are constant for the first 5 years.

The extrapolation from year 6 to year 15 is undertaken in the same fashion as in the ATAC analysis.

Unplanned switching setting

Anastrozole

Based on GABG.

The same methodology is employed as for the BIG 1-98 analysis. However, the median follow-up is 3 years, so the extrapolation is undertaken from year 4 to year 15.

Exemestane

Based on IES.

For the IES trial, a Weibull regression was used, as for the ATAC analysis. There are, however, a number of issues:

- The extrapolation covers the first 3 years, according to the median survival time of patients in the trial.
- The graph available was a DFS graph; therefore, in our calculation, we made an adjustment for the rate of people who died from a non-cancer cause.
- We do not have access to patient-level data, therefore the Weibull regression is made with a rough regression which has survival rate as a dependent variable and time as an independent variable.

The parameterisation is the following:

$$\text{Log}[-\log F(t)] = \text{gamma} * (\log t) + \text{constant} + \text{status} * D$$

where

$$\text{Constant} = \text{gamma} * \log(\text{lambda})$$

Lambda and gamma are the parameters of the Weibull distribution. D is a dummy variable which

takes value one if the patient is in the treatment arm and zero if the patient is in the control arm.

The extrapolation from year 4 to year 15 is the same as for the other analyses.

Extended adjuvant setting

Letrozole

Based on MA-17.

The methodology used is the same as for BIG 1-98. The rate of recurrence for placebo and the hazard rate for letrozole are based on the time to recurrence graph for the first 5 years.

Health Technology Assessment Programme

Prioritisation Strategy Group

Members

HTA Commissioning Board

Members

Current and past membership details of all HTA 'committees' are available from the HTA website (www.hta.ac.uk)

Diagnostic Technologies & Screening Panel

Members

Chair,
Dr Ron Zimmern, Director of the Public Health Genetics Unit, Strangeways Research Laboratories, Cambridge

Ms Norma Armston, Freelance Consumer Advocate, Bolton

Professor Max Bachmann, Professor of Health Care Interfaces, Department of Health Policy and Practice, University of East Anglia

Professor Rudy Bilous Professor of Clinical Medicine & Consultant Physician, The Academic Centre, South Tees Hospitals NHS Trust

Ms Dea Birkett, Service User Representative, London

Dr Paul Cockcroft, Consultant Medical Microbiologist and Clinical Director of Pathology, Department of Clinical Microbiology, St Mary's Hospital, Portsmouth

Professor Adrian K Dixon, Professor of Radiology, University Department of Radiology, University of Cambridge Clinical School

Dr David Elliman, Consultant in Community Child Health, Islington PCT & Great Ormond Street Hospital, London

Professor Glyn Elwyn, Research Chair, Centre for Health Sciences Research, Cardiff University, Department of General Practice, Cardiff

Professor Paul Glasziou, Director, Centre for Evidence-Based Practice, University of Oxford

Dr Jennifer J Kurinczuk, Consultant Clinical Epidemiologist, National Perinatal Epidemiology Unit, Oxford

Dr Susanne M Ludgate, Clinical Director, Medicines & Healthcare Products Regulatory Agency, London

Mr Stephen Pilling, Director, Centre for Outcomes, Research & Effectiveness, Joint Director, National Collaborating Centre for Mental Health, University College London

Mrs Una Rennard, Service User Representative, Oxford

Dr Phil Shackley, Senior Lecturer in Health Economics, Academic Vascular Unit, University of Sheffield

Dr Margaret Somerville, Director of Public Health Learning, Peninsula Medical School, University of Plymouth

Dr Graham Taylor, Scientific Director & Senior Lecturer, Regional DNA Laboratory, The Leeds Teaching Hospitals

Professor Lindsay Wilson Turnbull, Scientific Director, Centre for MR Investigations & YCR Professor of Radiology, University of Hull

Professor Martin J Whittle, Clinical Co-director, National Co-ordinating Centre for Women's and Childhealth

Dr Dennis Wright, Consultant Biochemist & Clinical Director, The North West London Hospitals NHS Trust, Middlesex

Pharmaceuticals Panel

Members

Chair,
Professor Robin Ferner, Consultant Physician and Director, West Midlands Centre for Adverse Drug Reactions, City Hospital NHS Trust, Birmingham

Ms Anne Baileff, Consultant Nurse in First Contact Care, Southampton City Primary Care Trust, University of Southampton

Professor Imti Choonara, Professor in Child Health, Academic Division of Child Health, University of Nottingham

Professor John Geddes, Professor of Epidemiological Psychiatry, University of Oxford

Mrs Barbara Greggains, Non-Executive Director, Greggains Management Ltd

Dr Bill Gutteridge, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sharon Hart, Consultant Pharmaceutical Adviser, Reading

Dr Jonathan Karnon, Senior Research Fellow, Health Economics and Decision Science, University of Sheffield

Dr Yoon Loke, Senior Lecturer in Clinical Pharmacology, University of East Anglia

Ms Barbara Meredith, Lay Member, Epsom

Dr Andrew Prentice, Senior Lecturer and Consultant Obstetrician & Gynaecologist, Department of Obstetrics & Gynaecology, University of Cambridge

Dr Frances Rotblat, CPMP Delegate, Medicines & Healthcare Products Regulatory Agency, London

Dr Martin Shelly, General Practitioner, Leeds

Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool

Dr Richard Tiner, Medical Director, Medical Department, Association of the British Pharmaceutical Industry, London

Therapeutic Procedures Panel

Members

Chair,
Professor Bruce Campbell, Consultant Vascular and General Surgeon, Department of Surgery, Royal Devon & Exeter Hospital

Dr Mahmood Adil, Deputy Regional Director of Public Health, Department of Health, Manchester

Dr Aileen Clarke, Consultant in Public Health, Public Health Resource Unit, Oxford

Professor Matthew Cooke, Professor of Emergency Medicine, Warwick Emergency Care and Rehabilitation, University of Warwick

Mr Mark Emberton, Senior Lecturer in Oncological Urology, Institute of Urology, University College Hospital

Professor Paul Gregg, Professor of Orthopaedic Surgical Science, Department of General Practice and Primary Care, South Tees Hospital NHS Trust, Middlesbrough

Ms Maryann L Hardy, Lecturer, Division of Radiography, University of Bradford

Dr Simon de Lusignan, Senior Lecturer, Primary Care Informatics, Department of Community Health Sciences, St George's Hospital Medical School, London

Dr Peter Martin, Consultant Neurologist, Addenbrooke's Hospital, Cambridge

Professor Neil McIntosh, Edward Clark Professor of Child Life & Health, Department of Child Life & Health, University of Edinburgh

Professor Jim Neilson, Professor of Obstetrics and Gynaecology, Department of Obstetrics and Gynaecology, University of Liverpool

Dr John C Pounsford, Consultant Physician, Directorate of Medical Services, North Bristol NHS Trust

Dr Karen Roberts, Nurse Consultant, Queen Elizabeth Hospital, Gateshead

Dr Vimal Sharma, Consultant Psychiatrist/Hon. Senior Lecturer, Mental Health Resource Centre, Cheshire and Wirral Partnership NHS Trust, Wallasey

Professor Scott Weich, Professor of Psychiatry, Division of Health in the Community, University of Warwick

Disease Prevention Panel

Members

Chair,
Dr Edmund Jessop, Medical Adviser, National Specialist Commissioning Advisory Group (NSCAG), London

Mrs Sheila Clark, Chief Executive, St James's Hospital, Portsmouth

Mr Richard Copeland, Lead Pharmacist: Clinical Economy/Interface, Wansbeck General Hospital, Northumberland

Dr Elizabeth Fellow-Smith, Medical Director, West London Mental Health Trust, Middlesex

Mr Ian Flack, Director PPI Forum Support, Council of Ethnic Minority Voluntary Sector Organisations, Stratford

Dr John Jackson, General Practitioner, Newcastle upon Tyne

Mrs Veronica James, Chief Officer, Horsham District Age Concern, Horsham

Professor Mike Kelly, Director, Centre for Public Health Excellence, National Institute for Health and Clinical Excellence, London

Professor Yi Mien Koh, Director of Public Health and Medical Director, London NHS (North West London Strategic Health Authority), London

Ms Jeanett Martin, Director of Clinical Leadership & Quality, Lewisham PCT, London

Dr Chris McCall, General Practitioner, Dorset

Dr David Pencheon, Director, Eastern Region Public Health Observatory, Cambridge

Dr Ken Stein, Senior Clinical Lecturer in Public Health, Director, Peninsula Technology Assessment Group, University of Exeter, Exeter

Dr Carol Tannahill, Director, Glasgow Centre for Population Health, Glasgow

Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick, Coventry

Dr Ewan Wilkinson, Consultant in Public Health, Royal Liverpool University Hospital, Liverpool

Expert Advisory Network

Members

Professor Douglas Altman, Professor of Statistics in Medicine, Centre for Statistics in Medicine, University of Oxford

Professor John Bond, Director, Centre for Health Services Research, University of Newcastle upon Tyne, School of Population & Health Sciences, Newcastle upon Tyne

Professor Andrew Bradbury, Professor of Vascular Surgery, Solihull Hospital, Birmingham

Mr Shaun Brogan, Chief Executive, Ridgeway Primary Care Group, Aylesbury

Mrs Stella Burnside OBE, Chief Executive, Regulation and Improvement Authority, Belfast

Ms Tracy Bury, Project Manager, World Confederation for Physical Therapy, London

Professor Iain T Cameron, Professor of Obstetrics and Gynaecology and Head of the School of Medicine, University of Southampton

Dr Christine Clark, Medical Writer & Consultant Pharmacist, Rossendale

Professor Collette Clifford, Professor of Nursing & Head of Research, School of Health Sciences, University of Birmingham, Edgbaston, Birmingham

Professor Barry Cookson, Director, Laboratory of Healthcare Associated Infection, Health Protection Agency, London

Dr Carl Counsell, Clinical Senior Lecturer in Neurology, Department of Medicine & Therapeutics, University of Aberdeen

Professor Howard Cuckle, Professor of Reproductive Epidemiology, Department of Paediatrics, Obstetrics & Gynaecology, University of Leeds

Dr Katherine Darton, Information Unit, MIND – The Mental Health Charity, London

Professor Carol Dezateux, Professor of Paediatric Epidemiology, London

Dr Keith Dodd, Consultant Paediatrician, Derby

Mr John Dunning, Consultant Cardiothoracic Surgeon, Cardiothoracic Surgical Unit, Papworth Hospital NHS Trust, Cambridge

Mr Jonothan Earnshaw, Consultant Vascular Surgeon, Gloucestershire Royal Hospital, Gloucester

Professor Martin Eccles, Professor of Clinical Effectiveness, Centre for Health Services Research, University of Newcastle upon Tyne

Professor Pam Enderby, Professor of Community Rehabilitation, Institute of General Practice and Primary Care, University of Sheffield

Professor Gene Feder, Professor of Primary Care Research & Development, Centre for Health Sciences, Barts & The London Queen Mary's School of Medicine & Dentistry, London

Mr Leonard R Fenwick, Chief Executive, Newcastle upon Tyne Hospitals NHS Trust

Mrs Gillian Fletcher, Antenatal Teacher & Tutor and President, National Childbirth Trust, Henfield

Professor Jayne Franklyn, Professor of Medicine, Department of Medicine, University of Birmingham, Queen Elizabeth Hospital, Edgbaston, Birmingham

Dr Neville Goodman, Consultant Anaesthetist, Southmead Hospital, Bristol

Professor Robert E Hawkins, CRC Professor and Director of Medical Oncology, Christie CRC Research Centre, Christie Hospital NHS Trust, Manchester

Professor Allen Hutchinson, Director of Public Health & Deputy Dean of ScHARR, Department of Public Health, University of Sheffield

Professor Peter Jones, Professor of Psychiatry, University of Cambridge, Cambridge

Professor Stan Kaye, Cancer Research UK Professor of Medical Oncology, Section of Medicine, Royal Marsden Hospital & Institute of Cancer Research, Surrey

Dr Duncan Keeley, General Practitioner (Dr Burch & Ptnrs), The Health Centre, Thame

Dr Donna Lamping, Research Degrees Programme Director & Reader in Psychology, Health Services Research Unit, London School of Hygiene and Tropical Medicine, London

Mr George Levvy, Chief Executive, Motor Neurone Disease Association, Northampton

Professor James Lindesay, Professor of Psychiatry for the Elderly, University of Leicester, Leicester General Hospital

Professor Julian Little, Professor of Human Genome Epidemiology, Department of Epidemiology & Community Medicine, University of Ottawa

Professor Rajan Madhok, Consultant in Public Health, South Manchester Primary Care Trust, Manchester

Professor Alexander Markham, Director, Molecular Medicine Unit, St James's University Hospital, Leeds

Professor Alistaire McGuire, Professor of Health Economics, London School of Economics

Dr Peter Moore, Freelance Science Writer, Ashtead

Dr Andrew Mortimore, Public Health Director, Southampton City Primary Care Trust, Southampton

Dr Sue Moss, Associate Director, Cancer Screening Evaluation Unit, Institute of Cancer Research, Sutton

Mrs Julietta Patnick, Director, NHS Cancer Screening Programmes, Sheffield

Professor Robert Peveler, Professor of Liaison Psychiatry, Royal South Hants Hospital, Southampton

Professor Chris Price, Visiting Professor in Clinical Biochemistry, University of Oxford

Professor William Rosenberg, Professor of Hepatology and Consultant Physician, University of Southampton, Southampton

Professor Peter Sandercock, Professor of Medical Neurology, Department of Clinical Neurosciences, University of Edinburgh

Dr Susan Schonfield, Consultant in Public Health, Hillingdon PCT, Middlesex

Dr Eamonn Sheridan, Consultant in Clinical Genetics, Genetics Department, St James's University Hospital, Leeds

Professor Sarah Stewart-Brown, Professor of Public Health, University of Warwick, Division of Health in the Community Warwick Medical School, LWMS, Coventry

Professor Ala Szczepura, Professor of Health Service Research, Centre for Health Services Studies, University of Warwick

Dr Ross Taylor, Senior Lecturer, Department of General Practice and Primary Care, University of Aberdeen

Mrs Joan Webster, Consumer member, HTA – Expert Advisory Network

Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

ISSN 1366-5278