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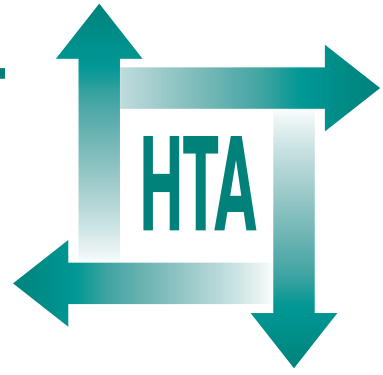

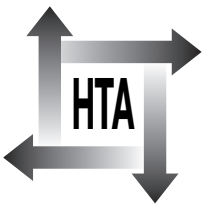

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Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation

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The research reported in this monograph was commissioned by the HTA Programme as project number 06/18/01. The contractual start date was in November 2005. The draft report began editorial review in October 2006 and was accepted for publication in December 2006. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. 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.

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Abstract

Taxanes for the adjuvant treatment of early breast cancer: systematic review and economic evaluation

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Objectives: To estimate the clinical effectiveness and cost-effectiveness of docetaxel and paclitaxel compared with non-taxane, anthracycline-containing chemotherapy regimens, for the adjuvant treatment of women with early-stage breast cancer.

Data sources: Major electronic databases were searched between October 2005 and February 2006.

Review methods: A systematic review of the literature on adjuvant taxane versus anthracycline non-taxane chemotherapy for women with early breast cancer was undertaken. A mathematical model was developed to synthesise the available data on costs, disease-free survival and health-related quality of life (HRQoL) of patients receiving taxane-containing chemotherapy versus non-taxane-containing chemotherapy.

Results: Eight of the 11 selected trials (six docetaxel and five paclitaxel) reported a significant improvement in disease-free survival (DFS) or time to recurrence (TTR) for taxanes over comparator regimens. Docetaxel was associated with more adverse events than paclitaxel, most notably febrile neutropenia. Taxanes produced cardiotoxicity, although this was not reported to be greater than for anthracycline comparator arms in all trials. Treatment-related deaths were uncommon. Where reported, all chemotherapy regimens caused HRQoL to deteriorate during treatment. Following treatment, there were no clinically significant differences between taxane and comparator treatment groups. There were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK. The three trials selected as the basis for the economic analysis were those that used the taxanes in accordance with current UK marketing authorisation and had also reported in full. The estimated incremental cost-effectiveness ratio for docetaxel compared to FAC6, based on the BCIRG 001 study, is £12,000 (£7000–39,000) and for paclitaxel compared with Adriamycin/cyclophosphamide, based on the NSABP B28 and CALGB 9344 studies, is £43,000 (£16,000–dominated) and £39,000 (£12,000–dominated), respectively. However, the comparators used in these trials restrict the generalisability of the results, as they do not conform to current standard care in the UK, typically FEC6 and E4-CMF4. An exploratory indirect comparison shows that the benefits of taxane containing regimens compared to regimens in current use in the UK is subject to large uncertainty due to the lack of direct trial comparisons between these interventions. Assumptions regarding the benefits in the taxane arm after the trial follow-up period and the annual rate of recurrence in this period have the most significant influence on the ICER.

Conclusions: There is a large degree of heterogeneity in the evidence base for the effectiveness of taxane- compared with non-taxane-containing regimens in terms of the interventions, comparators and populations. Eight of the 11 trials providing effectiveness data reported a significant improvement in DFS or TTR for taxanes over comparator regimens. The remaining three trials found no significant differences between the groups in DFS/TTR. The cost-effectiveness results suggest that the cost per quality-adjusted life-year for taxane- compared with non-taxane-containing chemotherapy varies between £12,000 and £43,000, depending on the taxane under consideration and the specific trial used as the basis of the analysis. However, the comparators used in these trials do not conform to current standard care in the UK. More research is needed, comparing taxanes used in line with their current UK marketing authorisation and with anthracycline-containing regimens commonly used in the UK. The on-going TACT trial is expected to provide useful data. There are currently few data on the effectiveness of taxanes for the over-70s. Further research is required into the long-term outcomes of taxane therapy, such as whether there are any long-term adverse events that significantly impact on overall survival or quality of life and whether the increases in DFS will translate into increases in overall survival.

Contents

Glossary and list of abbreviations

Glossary

Adjuvant treatment Treatment given following the main treatment (surgery), usually taking the form of chemotherapy and/or radiation therapy and/or endocrine therapy.

Anthracycline A type of chemotherapy drug that prevents cell division by disrupting the structure of the DNA and terminating its function. Examples of anthracyclines used in breast cancer are doxorubicin and epirubicin.

Arthralgia Joint pain.

Axillary nodes Lymph nodes situated in the axilla (armpit).

Chemotherapy Treatment with cytotoxic drugs that kill cancer cells, or prevent or slow their growth.

Combination chemotherapy Use of more than one cytotoxic drug to kill cancer cells, or prevent or slow their growth.

Contralateral breast cancer Cancer occurring in the opposite breast from the primary tumour.

Cycle A course of chemotherapy followed by a period of recovery.

Disease-free survival Outcome measure defined as the hazard of disease recurrence, second cancer or death from any cause after a given follow-up period, or time from randomisation to first of these events.

Distant recurrence Recurrence of cancer at distant sites.

Dominated Where an intervention costs more and provides less benefit than its comparator it is said to be dominated by its comparator.

GCSF/filgrastim Drug used to promote the growth of white blood cells.

Toxicity grade A measure of the severity of adverse events.

HER2 status Describes whether the tumour is rich in HER2 receptors.

Histological grade Measure of the malignancy of a tumour.

Hormone receptor status Describes whether the tumour is rich in oestrogen receptors (oestrogen receptor positive) and/or progesterone receptors (progesterone receptor positive).

Locoregional recurrence Recurrence of cancer at local or regional sites.

Lymph nodes Small organs that act as filters in the lymphatic system.

Menopause End of menstruation, usually occurring around age 50 years.

Metastases/metastatic cancer Cancer which has spread to distant sites from the primary tumour.

Myalgia Muscle pain.

Neoadjuvant therapy Therapy given before main treatment (surgery).

Neutropenia An abnormal decrease in the number of neutrophils in the blood.

Oestrogen receptor (ER) A protein on breast cancer cells that binds oestrogens.

Overall survival Outcome measure defined as the hazard of death from any cause after a given follow-up period, or time from randomisation to death from any cause.

Polychemotherapy Use of more than one cytotoxic drug to kill cancer cells, or prevent or slow their growth.

Progesterone receptor A protein on breast cancer cells that binds progesterones.

continued

Glossary *continued*

Radiation therapy/radiotherapy Radiation applied locally to kill cancer cells.

Relative dose intensity (RDI) Actual dose intensity/target dose intensity, measure of amount of drug received in relation to amount of drug prescribed.

Scarff–Bloom–Richardson (SBR) grade Measure of how well differentiated a tumour is, ranging from grade 1 to grade 3, with grade 3 being most poorly differentiated and having worst prognosis.

Staging An internationally recognised system for defining a tumour in terms of its size and degree of spread through the body.

Tamoxifen A drug which is a type of hormonal (endocrine) therapy. Tamoxifen is a selective oestrogen receptor modulator, prescribed for women with hormone receptor-positive cancer.

Taxane A class of anticancer drug, including docetaxel and paclitaxel, which may be included in chemotherapy regimens.

List of abbreviations

AE	adverse event
AJCC	American Joint Committee on Cancer
ARR	absolute risk reduction
ASCO	American Society of Clinical Oncology
BNF	British National Formulary
CEAC	cost-effectiveness acceptability curve
CI	confidence interval
DCIS	ductal carcinoma *in situ*
DFS	disease-free survival
ECOG	Eastern Cooperative Oncology Group
EMEA	European Agency for the Evaluation of Medicinal Products
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QLQ BR23	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire specific to breast cancer
ER+/ER–	oestrogen receptor positive/negative status
ESMO	European Society for Medical Oncology
FFP	freedom from progression
G-CSF	granulocyte colony-stimulating factor
HADS	Hospital Anxiety and Depression Scale
HR	hazard ratio
HR+/HR–	hormone receptor positive/negative status
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio

continued

List of abbreviations *continued*

ITT	intention-to-treat
LYG	life-year gained
N+ve/N–ve	nodal status: node positive/node negative
NICE	National Institute for Health and Clinical Excellence
NNTB	number-needed-to-treat to benefit
NRR	National Research Register
OS	overall survival
PR+/PR–	progesterone receptor positive/negative status
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RDI	relative dose intensity
RR	relative risk
SD	standard deviation
TNM	tumour/nodes/metastasis staging system
TTR	time to recurrence
UICC	Union Internationale Contre le Cancer (International Union Against Cancer)

Chemotherapy abbreviations

A	doxorubicin (Adriamycin)
C	cyclophosphamide [Neosar (intravenous) or Cytoxan (oral)]
D	docetaxel (Taxotere)
E	epirubicin (Ellence)
F	fluorouracil (Adrucil)
M	methotrexate (Mexate)
P	paclitaxel (Taxol)

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.

Note

This report is the result of an independent assessment of the clinical and cost-effectiveness of taxanes for the adjuvant treatment of early breast cancer carried out by the authors. This assessment began before the National Institute for Health and Clinical Excellence (NICE) transferred their appraisal of docetaxel and paclitaxel for early breast cancer to the new Single Technology Appraisal (STA) process in November 2005. It has been carried out independently from the NICE STA process but has made use of material from the STA process which is publicly available on the NICE website, such as the Evidence Review Group reports for paclitaxel and docetaxel STAs.

The breast cancer model described in Chapter 4 of this report has been adapted from a model developed by ScHARR to inform the NICE appraisal of hormonal therapies for the adjuvant treatment of early oestrogen receptor-positive breast cancer. ScHARR acted as the Assessment Group in this appraisal and the breast cancer model has been previously described in their assessment report.

Executive summary

Background

Breast cancer is the most common cancer in women. The mainstay of treatment for early stage cancer is surgical removal of the tumour, and is often followed by adjuvant systemic therapy (chemotherapy and/or endocrine therapy) and/or radiotherapy to reduce the risk of recurrence, particularly if the tumour is large or has spread to lymph nodes. Current UK practice recommends an anthracycline-containing chemotherapy regimen. Taxanes are a class of anti-cancer drug (including docetaxel and paclitaxel) that can be used in chemotherapy, and are known to be effective against metastatic breast cancer.

Objectives

The objectives were to estimate the clinical effectiveness and cost-effectiveness of docetaxel and paclitaxel compared with non-taxane, anthracycline-containing chemotherapy regimens, for the adjuvant treatment of women with early-stage breast cancer.

Methods

A systematic review of the literature on adjuvant taxane versus anthracycline non-taxane chemotherapy for women with early breast cancer was undertaken. Literature searches were conducted between October 2005 and February 2006. A mathematical model was developed to synthesise the available data on costs, disease-free survival and health-related quality of life (HRQoL) of patients receiving taxane-containing chemotherapy versus non-taxane-containing chemotherapy. The primary outcome of interest was the cost per quality-adjusted life-year (QALY) gained. The model considered the use of taxanes within current licensed indications only.

Results

Clinical effectiveness

Eleven randomised controlled trials accepted into the clinical review had reported effectiveness data: six docetaxel trials and five paclitaxel trials. An additional seven trials had reported safety or quality of life data. Heterogeneity of interventions, comparators and populations precluded meta-analysis.

Eight of the 11 trials reported a significant improvement in disease-free survival (DFS) or time to recurrence (TTR) for taxanes over comparator regimens. For the four docetaxel trials reporting significant differences in DFS between groups, hazard ratios (HRs) varied from 0.67 to 0.83, with an absolute difference in DFS rates of 5–7%, favouring the docetaxel groups. One docetaxel trial showed no difference in DFS rates between groups and another found a non-significant difference favouring the docetaxel group. Two paclitaxel trials reported a significant improvement in DFS, and two paclitaxel trials a significant improvement in TTR, for the paclitaxel arm over the comparator arms. HRs varied from 0.63 to 0.83, with absolute differences in DFS or TTR rates between trial arms of 4–6% favouring the paclitaxel group. For the paclitaxel trial not finding a significant difference in DFS between groups, the direction of effect favoured paclitaxel.

Docetaxel was associated with more adverse events than paclitaxel, most notably febrile neutropenia. Taxanes produced cardiotoxicity, although this was not reported to be greater than for anthracycline comparator arms in all trials. Treatment-related deaths were uncommon, ranging from 0 to 0.64% across trials. Where reported, all chemotherapy regimens caused HRQoL to deteriorate during treatment. Following treatment, there were no clinically significant differences between taxane and comparator treatment groups.

There were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK. One docetaxel trial and two paclitaxel trials used taxanes in strict accordance with current UK marketing authorisation. Four other trials used comparators that are frequently used in UK practice: two docetaxel and two paclitaxel trials.

Cost-effectiveness

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 QALY gained, associated with taxane-containing chemotherapy versus non-taxane-containing chemotherapy.

The three trials selected as the basis for the economic analysis were those which used the taxanes in accordance with current UK marketing authorisation and had also reported in full. The cost-effectiveness results suggest that the cost per QALY for taxane- compared with non-taxane-containing chemotherapy varies depending on the taxane under consideration and the specific trial used as the basis of the analysis. Docetaxel has a cost per QALY of £12,000 (£7000–39,000) compared with FAC6 based on the regimens used in the BCRIG 001 study, whereas paclitaxel has a cost per QALY of £43,000 (£16,000–dominated) and £39,000 (£12,000–dominated) compared to AC (Adriamycin/cyclophosphamide), based on the regimens used in the NSABP B28 and CALGB 9344 studies, respectively.

The estimated incremental cost-effectiveness ratio (ICER) for taxane- relative to non-taxane-containing chemotherapy is lower for docetaxel based on the BCIRG 001 study than it is for paclitaxel, based on both the NSABP B28 and CALGB 9344 studies. This is partly due to the HR for recurrence, which is lower in BCIRG 001 than in the two paclitaxel trials which have been modelled. In addition, the paclitaxel regimens have a larger number of cycles (four 3-weekly cycles of AC followed by four 3-weekly cycles of paclitaxel) than the comparator arm (four 3-weekly cycles of AC only) and therefore the period on treatment is 12 weeks longer in the intervention arm in the first year of the model. It is assumed that the quality of life of patients is lower during chemotherapy and this loss of quality of life for patients receiving a longer period of therapy on paclitaxel reduces the QALY benefits for the paclitaxel arm.

The assumption regarding the benefits in the taxane arm relative to the comparator arm, after the current follow-up period of 5 years, has a major influence on the cost-effectiveness ratio. The basecase for the ScHARR model assumes that the benefits in terms of rates of recurrence are the same in both arms after the first 5 years. Assuming that the benefits of taxanes continue for 10 years with recurrence rates the same in both arms thereafter decreases the cost per QALY by around 50% for docetaxel and by around 70% for paclitaxel.

The assumption regarding the long-term risk of recurrence after the follow-up period also has a major influence on the ICER. The basecase for the ScHARR model estimates the risk after the trial period from the risk seen during the trial period, but this may have overestimated the long-term risk and therefore underestimated the cost-effectiveness of taxanes. A sensitivity analysis was carried out to assess the extent to which the cost per QALY decreases when the long-term risk of recurrence is assumed to be at its lowest reasonable value. Decreasing the annual rate of recurrence after the trial follow-up period by 50% lowered the cost per QALY for docetaxel by around 20% and the cost per QALY for paclitaxel by around 40%.

Univariate and probabilistic sensitivity analysis suggests that these results are robust to other changes in the key model parameters.

The comparators used by the trials restrict the generalisability of the results, as they do not conform to current standard care in the UK. The comparators in these trials – FAC6 and AC4 – may be less effective than other regimens more commonly used within standard care in the UK, such as FEC6 and E4-CMF4. For this reason, an indirect comparison was undertaken to allow a comparison of taxanes against FEC6 and E4-CMF4. The indirect comparison has many limitations and can therefore only be considered an exploratory analysis showing the minimum uncertainty in the cost-effectiveness achievable with the current evidence base. This exercise does suggest that the ICERs may be higher than those estimated for taxanes compared to FAC6 and AC and that there is a high degree of uncertainty in the benefit of taxanes compared with current standard practice. This suggests that the cost-effectiveness of taxanes relative to current standard care is unproven at this time.

Discussion

The major weakness of this analysis is that there is a lack of data on the effectiveness of taxanes relative to regimens in common use in the UK and this restricts the generalisability of the trial evidence. Also, due to the rapid advance of technologies and the very wide range of potential

comparator therapies, there is little RCT evidence comparing the range of regimens used in the UK from which to construct reliable indirect comparisons.

Assumptions regarding the benefits in the taxane arm after the trial follow-up period and the annual rate of recurrence in this period have the most significant influence on the ICER. Longer term follow-up is required to determine the potential impact of any long-term adverse events, such as cardiotoxicity and severe gastrointestinal toxicity. It should also be noted that the benefits of taxanes in terms of overall survival have not yet been confirmed due to the relatively short follow-up data available. The model assumes that benefits from reduced recurrence in the first 5 years will translate into overall survival benefits in the medium and long term. There is as yet no long-term evidence to support this as the maximum follow-up from the published trials is currently 69 months.

Conclusions

There is a large degree of heterogeneity in the evidence base for the effectiveness of taxane- compared with non-taxane-containing regimens in terms of the interventions, comparators and populations. Eight of the 11 trials providing effectiveness data reported a significant improvement in DFS or TTR for taxanes over comparator regimens. The remaining three trials found no significant differences between the groups in DFS/TTR. However, there were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK.

The cost-effectiveness results suggest that docetaxel-containing chemotherapy has a cost per QALY of £12,000 (£7000–39,000) compared with non-taxane-containing chemotherapy based on the regimen used in the BCRIG 001 study, whereas paclitaxel-containing chemotherapy has a cost per QALY of £43,000 (£16,000–dominated) compared with non-taxane-containing chemotherapy based on the regimens used in the NSABP B28 study and a cost per QALY of £39,000 (£12,000–dominated) based on the regimens used in the CALGB 9344 study. However, the comparators in these trials do not reflect the regimens currently used in the UK. The use of indirect comparison demonstrates that there is a high degree of uncertainty in the effectiveness of taxane-containing regimens relative to regimens in common use in the UK and therefore the cost-effectiveness of taxanes compared with current standard practice is considered to be unproven at this time. The cost-effectiveness of taxanes will need to be reconsidered as further data become available from ongoing trials comparing taxanes with standard UK regimens. Of particular interest will be the TACT trial, which compares four cycles of FEC followed by four cycles of docetaxel with two regimens used in the UK – eight cycles of FEC or four cycles of EMF, followed by four cycles of CMF. This trial is expected to report efficacy data in the next year or two.

Suggested research priorities

More research is needed, comparing taxanes used in line with their current UK marketing authorisation, with anthracycline-containing regimens commonly used in the UK. The ongoing TACT trial is expected to provide useful data. There are currently few data on the effectiveness of taxanes for the over-70s. Further research is required into the long-term outcomes of taxane therapy, such as whether there are any long-term adverse events that significantly impact on overall survival or quality of life and whether the increases in DFS will translate into increases in overall survival.

Chapter 1
Background

Description of health problem

Incidence/prevalence

Breast cancer is by far the most common cancer in women, accounting for 30% of all new cases. The lifetime risk of developing breast cancer for women is almost 11% (one in nine).[1] Approximately one-third of new breast cancer cases are diagnosed in patients aged 70 years or over. Incidence data are given in *Table 1*.

Aetiology

The aetiology of breast cancer is not fully understood; however, genetic and hormonal risk factors have been identified. The likelihood of diagnosis increases with age and, following the menopause, risk increases with age but at slower rate.[1]

Approximately 5–10% of breast cancers are thought to have a genetic cause. Carriers of the BRCA1 or BRCA2 mutations have an increased risk of developing breast cancer. Family history is a risk factor, with a relative risk (RR) of up to 2.1 for those with a first-degree relative with breast cancer and 1.5 for those with a second-degree relative.[4]

Several hormonal risk factors have been identified, which are more predictive when combined, indicating that a measure of lifetime oestrogen exposure may be responsible for the risk.[4]

Risk factors associated with endogenous (originating in the body) oestrogen include early menarche, late natural menopause, nulliparity or lower (rather than higher) number of full-term pregnancies, later age at first full-term pregnancy and never breastfeeding.[4] There is a protective effect of oophorectomy before age 40 years.[5]

Risk factors associated with exogenous (taken into the body) oestrogen include oral-contraceptive use (small increase in risk), oestrogen replacement therapy and combined hormone replacement therapy.[4]

Markers of oestrogen exposure associated with increased risk include plasma oestradiol, breast density and bone density.[4]

Factors which may be mediating factors for hormonal risk include a body mass index of 25+ in postmenopausal women, moderate to heavy alcohol intake, sedentary lifestyle and central adiposity.[6] There is inconclusive evidence regarding dietary factors.

Other risk factors include history of breast cancer and radiation exposure.[4]

Pathology, clinical staging and prognosis

Breast cancer develops in the cells lining the ends of the milk-producing glands (the lobules) and in the thin tubes that carry milk to the nipple (the ducts). Breast cancer is classified into clinical stages according to tumour size, spread of cancer to lymph nodes and distant metastases.

The tumour/nodes/metastasis (TNM) staging system was developed and is maintained by the American Joint Committee on Cancer (AJCC) and the Union International Contre le Cancer (UICC).[7] It defines tumour stage (*Table 2*) according to tumour size, lymph nodes and metastases, as follows:.

T tumour stage
Tx cannot be assessed
T0 no evidence of primary tumour
Tis carcinoma *in situ*

TABLE 1 *Breast cancer: incidence by age (2003)*

	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

Sources: Office for National Statistics (2005)[2] and Welsh Cancer Intelligence and Surveillance Unit (2005).[3]

T1 tumour <2 cm in greatest dimension
T2 tumour 2–5 cm
T3 tumour >5 cm
T4 tumour of any size with direct extension to skin or chest wall

N lymph node stage
Nx cannot be assessed
N0 no nodal metastases
N1 metastasis to mobile ipsilateral nodes
N2 metastasis to ipsilateral nodes that are fixed to one another or other structures
N3 metastasis to ipsilateral supraclavicular or infraclavicular nodes

M metastasis stage
Mx cannot be assessed
M0 no distant metastasis
M1 distant metastasis.

Alternatively, staging can take into account number of positive axillary lymph nodes, rather than location of lymph nodes. The summary of stages presented below is from the American Cancer Society:[8]

- Stage 0: Ductal carcinoma *in situ* (DCIS) – cancer cells are located within a duct and have not invaded the surrounding fatty breast tissue.
- Stage I: The tumour is 2 cm or less in diameter and has not spread to lymph nodes or distant sites.
- Stage IIA: No tumour is found in the breast but it is in 1–3 axillary lymph nodes, or the tumour is less than 2 cm and has spread to 1–3 axillary lymph nodes or found by sentinel node biopsy as microscopic disease in internal mammary nodes but not on imaging studies or by clinical examination, or the tumour is larger than 2 cm in diameter and less than 5 cm but has not spread to axillary nodes. No metastasis.
- Stage IIB: The tumour is larger than 2 cm in diameter and less than 5 cm and has spread to 1–3 axillary lymph nodes or found by sentinel node biopsy as microscopic disease in internal mammary nodes or the tumour is larger than 5 cm and does not grow into the chest wall and has not spread to lymph nodes. No metastasis.
- Stage IIIA: The tumour is smaller than 5 cm in diameter and has spread to 4–9 axillary lymph nodes or found by imaging studies or clinical examination to have spread to internal mammary nodes, or the tumour is larger than 5 cm and has spread to 1–9 axillary nodes or to internal mammary nodes. No metastasis.
- Stage IIIB: The tumour has grown into the chest wall or skin and may have spread to no lymph nodes or as many as nine axillary nodes. It may or may not have spread to internal mammary nodes. No metastasis.
- Stage IIIC: The tumour is any size, has spread to 10 or more nodes in the axilla or to one or more lymph nodes under the clavicle (infraclavicular) or above the clavicle (supraclavicular) or to internal mammary lymph nodes, which are enlarged because of the cancer. All of these are on the same side as the breast cancer. No metastasis.
- Stage IV: The cancer, regardless of its size, has spread to distant organs such as bone, liver or lung, or to lymph nodes far from the breast.

TABLE 2 *TNM staging*

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
IIA	T0	N1	M0
	T1	N1	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N(any)	M0
	T(any)	N3	M0
IV	T(any)	N(any)	M1

TABLE 3 *Survival at 5 years according to stage of breast cancer.*

Stage	Proportion of women diagnosed at this stage living for at least 5 years (%)
I	90
IIA	75
IIB	75
IIIA	42
IIIB	42
IV	14

Source: Cancer Research UK.[10]

Stage is an indicator of prognosis. Approximately 50% of women with early breast cancer (Stages 1 and 2) will eventually relapse and develop metastatic or advanced disease.[9] Survival data at 5 years are given in *Table 3*.

Other factors are associated with prognosis. Clinicians may use a prognostic index (such as the Nottingham Prognostic Index[11] or Adjuvant Online[12]). These indices take into account a

TABLE 4 *Breast cancer: mortality*

Mortality	England	Wales
Number	10,609	731
Crude rates per 100,000	41.9	48.7

Sources: Office for National Statistics (2005)[2] and Welsh Cancer Intelligence and Surveillance Unit (2005).[3]

combination of factors such as tumour grade, tumour size, lymph node status, age and hormonal receptor status. Good prognosis is associated with small tumour size, node-negative (N–ve) status, younger age, oestrogen receptor positive (ER+) and progesterone receptor positive (PR+) status. HER2 overexpression is associated with poor prognosis. Recurrence occurred within 10 years of adjuvant chemotherapy for early breast cancer in 60–70% of node-positive women and 25–30% of node N–ve women.[13]

Impact of health problem

Approximately 86% of patients present with early-stage disease at diagnosis.[14] Around 11,500 women died from breast cancer in England and Wales in 2002, a rate of 30 per 100,000 women. It is the most common cause of cancer death in women.[2] Metastatic breast cancer is currently incurable.[9] Mortality data are given in *Table 4*.

Survival rates are improving. The survival rate for patients diagnosed between 1993 and 1995 was 93% at 1 year and 76% after 5 years. Among women whose cancer was diagnosed by screening in 1994–5, over 93% were still alive 5 years later.[1]

Current service provision

The mainstay of treatment for early-stage cancer is surgical removal of the tumour. Adjuvant therapy with chemotherapy agents may be indicated, based on the patient's age and prognosis. For instance, women are more likely to receive chemotherapy if the primary cancer in the breast is large, or if the lymph nodes contain breast cancer cells. The aim of adjuvant therapy is to kill off any cancer cells that have broken away from the tumour in the breast and spread before it was removed. It therefore reduces the risk of the cancer coming back. Endocrine therapy and/or radiation therapy may also be indicated.

Current chemotherapy treatment recommended by the National Institute for Health and Clinical Excellence (NICE) is as follows:[1] women at intermediate or high risk of recurrence, who have not had neoadjuvant chemotherapy, should normally be offered four to eight cycles of multiple-agent chemotherapy which includes anthracyclines. High-dose chemotherapy is not recommended.

Treatment in the UK varies widely, but commonly used regimens are FEC6 or E4-CMF4 (chemotherapy abbreviations are given at the end of the 'List of abbreviations' and full interventions are explained in *Tables 5* and *6*, pp. 12–15). It is unusual for only four cycles to be used, although AC4 may be chosen for patients aged over 50 years at lower risk, as determined by a prognostic index such as the Nottingham Prognostic Index or Adjuvant Online, or for oestrogen receptor-negative (ER–) patients aged 70 years or over. Prognosis is strongly influenced by nodal status, with nearly all patients having more than three positive nodes being at high risk. Most patients with 1–3 positive nodes with tumours of grade 2 or higher are at intermediate, or higher, risk. Age is an important factor, with many oncologists prescribing chemotherapy to all patients aged under 35 years. Patients aged over 70 years with ER+ tumours are generally not given chemotherapy.

Chemotherapy with CMF has been found to be less effective than that with some anthracycline-containing regimens[1,15,16] such as FEC, FAC and E-CMF.[15–17] It has been reported that more than six cycles of CMF or anthracycline-containing polychemotherapy does not substantially improve outcomes.[18]

Although there have been many trials of chemotherapy agents, investigations comparing the many drug combinations of polychemotherapy regimens and doses have not been exhaustive. Little evidence is available on effectiveness of chemotherapy for women aged 70 years or over. Health-related quality of life (HRQoL) is significantly lower in patients treated with systemic chemotherapy than with local therapy only.[19]

The taxanes have UK marketing authorisation for the adjuvant treatment of patients with operable and node-positive (N+ve) breast cancer. Of the 38,884 patients who present with breast cancer each year in England and Wales (see *Table 1*), around 86% present with early-stage disease at diagnosis.[14] Approximately 30% of this group, around 12,000 patients, are assumed to be N+ve.[20] The majority of this group will currently receive anthracycline-based chemotherapy. FEC6 and E4-CMF4 are the most common regimens in

the UK and market research has reported that the split between the two drugs is around 75:25.[21] Based on costs of FEC6 and E4-CMF4 of £2755 [average of FEC6(50) and FEC6(100)] and £2863, respectively (see the section 'Chemotherapy costs', p. 37) the estimated cost of current provision is around £33 million.

Description of technology under assessment

Intervention

The taxanes are a class of anti-cancer drugs. The goal of taxane therapy in breast cancer is to prevent cell division, resulting in cell death. Taxanes are chemotherapy drugs which may be included as part of a chemotherapy regimen, alone or in combination with anthracycline. In some instances, the taxane may be substituted for one or more drugs generally administered in the regimen. Both docetaxel and paclitaxel are administered by intravenous infusion.

Docetaxel and paclitaxel prevent the growth of cancer cells by affecting cell structures called microtubules, which play an important role in cell functions. In normal cell growth, microtubules are formed when a cell starts dividing. Once the cell stops dividing, the microtubules are broken down or destroyed. Taxanes stop the microtubules from breaking down; cancer cells become so clogged with microtubules that they cannot grow and divide. The goal of taxane therapy in breast cancer is to stop cancerous cells from dividing, thereby preventing the growth and spread of cancer.

Docetaxel (Taxotere, Sanofi Aventis) has a UK marketing authorisation for the adjuvant treatment of patients with operable breast cancer and positive axillary lymph nodes, in combination with doxorubicin and cyclophosphamide.[22] The recommended dose is 75 mg/m^2 administered 1 hour after doxorubicin 50 mg/m^2 and cyclophosphamide 500 mg/m^2 every 3 weeks for six cycles.[22] Docetaxel is currently also licensed in the UK for the treatment of metastatic breast cancer and for non-small cell lung cancer.

Paclitaxel has a UK marketing authorisation for the adjuvant treatment of patients with operable and N+ve breast cancer following anthracycline and cyclophosphamide therapy.[23] The recommended dose is 175 mg/m^2 administered over a period of 3 hours every 3 weeks for four courses, following anthracycline and cyclophosphamide therapy.[23] Adjuvant treatment with paclitaxel should be regarded as an alternative to extended anthracycline and cyclophosphamide therapy. It is manufactured in the UK as Taxol (Bristol-Myers Squibb). Generic paclitaxel is also manufactured by Mayne Pharma and by Teva. Paclitaxel is currently also licensed in the UK for the treatment of other forms of cancer, including metastatic of breast cancer, and specific types of ovarian cancer, small-cell lung cancer and AIDS-related Kaposi's sarcoma.

Docetaxel has a longer half-life and more rapid cellular uptake and longer intracellular retention than paclitaxel.[24] Dose and scheduling may affect tolerability and effectiveness. Paclitaxel is used in a sequential strategy, whereas docetaxel can be used sequentially or in combination with anthracyclines.[25] In metastatic breast cancer, weekly paclitaxel was more effective than 3-weekly paclitaxel, whereas docetaxel had similar effectiveness weekly or 3-weekly.[24] In metastatic breast cancer, docetaxel was more effective than paclitaxel.[24]

Results from a clinical trial (E1199) of Stage 2 and 3 breast cancer comparing paclitaxel and docetaxel found similar effectiveness for both drugs. Docetaxel and paclitaxel also showed similar effectiveness for weekly or 3-weekly administration. There was higher toxicity for docetaxel than for paclitaxel.[26]

Neutropenia is a dose-limiting toxicity for taxanes.[27] Growth factors administered concomitantly with taxanes can reduce the risk of febrile neutropenia and help maintain the scheduled dose delivery,[28] or the prophylactic use of antibiotics after chemotherapy can reduce the incidence of febrile episodes.[29] Like other cytotoxic treatments, taxane-based treatments have an indirect endocrine effect, and so may cause chemotherapy-related amenorrhoea.[17] Docetaxel can cause skin toxicity and nail disorders.[30]

Some adverse events associated with polychemotherapy including a taxane and an anthracycline have long-term implications,[31] with the European Agency for the Evaluation of Medicinal Products (EMEA) highlighting particular concern over cardiotoxicity and severe gastrointestinal toxicity.

Subgroups

Subgroups associated with prognosis following adjuvant therapy include age, nodal status, oestrogen receptor status, progesterone receptor status and HER2 positivity. Prognostic status can

be evaluated by taking into account several of these factors, for example the Nottingham Prognostic Index or St Gallens criteria. The absolute benefit of any regimen of polychemotherapy increases according to number of positive nodes, oestrogen receptor negativity, HER2 positivity and age 35 years or younger.[32] There are improved outcomes following chemotherapy for N+ve patients or for high-risk N–ve patients.[33] Adjuvant chemotherapy is more beneficial in patients aged under 50 years than for older patients.[18] In postmenopausal patients, chemotherapy is more beneficial for ER– than ER+ tumours.[15] Adjuvant chemotherapy does not substantially improve outcomes for postmenopausal women with ER+, HER2–, grade 1 or 2 tumours, given endocrine therapy.[32]

Current usage in the NHS

Taxanes may be used for first-line adjuvant treatment of early-stage breast cancer in the context of clinical trials.[1] Assuming that in the future taxanes are prescribed for all N+ve early breast cancer patients, the cost of chemotherapy will increase for these patients. Based on the cost of DAC6 of £8516 and cost of AC4 + P4 of £7609 (see the section 'Methodology', p. 54), the additional cost of taxanes per patient is estimated to be £5734 or £4827 assuming 100% prescribing of docetaxel or paclitaxel, respectively. The additional expenditure by the NHS, based on 12,000 patients receiving therapy (see the section 'Current service provision', p. 3) is estimated to be between £57.4 million and £68.2 million, depending on the share of the two drugs.

Chapter 2

Definition of the decision problem

Decision problem

The assessment report addresses the following question, in order to assist the production of guidance to NHS commissioners in England and Wales:

> "Are docetaxel and paclitaxel clinically and cost-effective compared with non-taxane-containing chemotherapy regimens including anthracycline agent, for the adjuvant treatment of women with early stage breast cancer?"

1. Interventions

The two main comparisons were:

(a) sequential paclitaxel therapy (paclitaxel following anthracycline therapy) versus anthracycline-based non-taxane therapy
(b) combination docetaxel therapy versus anthracycline-based non-taxane therapy.

The review team also reviewed the clinical effectiveness of adjuvant trials which use taxanes in regimens which fall outside their current marketing authorisation.

Neoadjuvant therapy was not included in the review because women who may be eligible for neoadjuvant therapy may differ from those eligible for adjuvant therapy, and some important outcome measures differ between the two settings.

2. Population including subgroups

Women who have had surgery for early-stage breast cancer (Stages I and II and IIIa of the AJCC system).

Subgroups: age; nodal status; ER+ versus ER– and PR+ versus PR–; HER2 positivity (HER2+); prognostic status (however evaluated).

3. Relevant comparators

Anthracycline-containing chemotherapy regimen: this was not restricted to the more commonly used regimens in the UK. Outside the UK there is much heterogeneity in choice of chemotherapy regimens, including, but not confined to, Ax4-CMF4, ACx4-CMFx3 and FECx3.[27]

4. Outcomes

(a) overall survival (OS)
(b) disease-free survival (DFS)
(c) local and distant recurrence
(d) adverse events (AEs)/toxicity
(e) health-related quality of life (HRQoL).

Overall aims and objectives of assessment

The review focused on the differences in OS, DFS, HRQoL benefits, local and distant recurrence, AEs and toxicity resulting from the use of docetaxel and paclitaxel compared with the current anthracycline-based chemotherapy used to treat patients with early breast cancer. The costs and cost-effectiveness of docetaxel and paclitaxel were assessed from the perspective of the NHS and Personal Social Services.

The objectives of the review were:

1. to evaluate the relative clinical effectiveness of docetaxel and paclitaxel in terms of OS, DFS and HRQoL compared with the current treatment with an anthracycline-based chemotherapy
2. to evaluate the side-effect profiles of docetaxel and paclitaxel
3. to estimate the incremental cost-effectiveness ratio (ICER) of docetaxel and paclitaxel compared with current standard therapies.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

Identification of studies

The search aimed to identify all studies relating to taxanes for the treatment of early-stage breast cancer. The following databases were searched: MEDLINE, EMBASE, CINAHL, BIOSIS, the Cochrane Database of Systematic Reviews (CDSR), the Cochrane Controlled Trials Register (CCTR), the Science Citation Index and the NHS Centre for Reviews and Dissemination databases (DARE, NHS EED, HTA) and OHE HEED. Pre-MEDLINE was also searched to identify any studies not yet indexed on MEDLINE. Current research was identified from database citations through searching the National Research Register (NRR), the Current Controlled Trials register, the MRC Clinical Trials Register and the US National Institute of Health website ClinicalTrials.gov. There was additional searching of the *Proceedings of the American Society of Clinical Oncology* (ASCO), the San Antonio Breast Cancer Symposium and the European Society for Medical Oncology (ESMO). 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 1. References were collected in a database and duplicates removed. Literature searches were conducted between October 2005 and February 2006.

Inclusion and exclusion criteria

Inclusion criteria

Population

- Women who had undergone surgery for early-stage breast cancer (Stages I, II and IIIa of the AJCC system).

Any available data considering the following subgroups separately were sought: age; nodal status; ER+ versus ER– and PR+ versus PR–; HER2+; prognostic status (however evaluated).

Interventions

- Docetaxel or paclitaxel as part of a chemotherapy regimen, alone or in combination with anthracycline, including instances where the taxane was substituted for one or more drugs generally administered in the regimen, administered adjuvant to surgical resection. Trials with patients receiving endocrine therapy were included if its administration was consistent between treatment groups.

Comparator

- Non-taxane, anthracycline-containing, chemotherapy regimen.

Outcomes

- OS, defined as the hazard of death from any cause after a given follow-up period, or time from randomisation to death from any cause
- DFS, defined as the hazard of disease recurrence, second cancer or death from any cause after a given follow-up period, or time from randomisation to first of these events
- type of recurrence as first event – contralateral breast cancer, distant recurrence or local/regional recurrence
- AEs/toxicity – any reported, however defined
- HRQoL measured using any validated HRQoL instrument.

In addition to DFS, time to recurrence (TTR) was accepted as an outcome measure. TTR is defined as the hazard of recurrence after a given follow-up period, and thus differs from DFS in that deaths without disease are not counted as an event. According to the US Food and Drug Administration, DFS is less prone to bias than TTR.[34] TTR "has the potential for bias in the *post hoc* determination of the cause of death" and, because it censors patients at death, it "assumes that the censored patients have the same risk of recurrence as noncensored patients".[34] However, DFS is limited by "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 falsely prolong the DFS estimates in patients who die after a long unobserved period".[34]

Study design

- Randomised controlled trials (RCTs).

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. Evidence was available from RCTs, therefore observational studies were not included. Reviews of primary studies were not included in the analysis, but were retained for discussion.

Exclusion criteria

- Population: Men; women with advanced-stage breast cancer; women receiving neoadjuvant chemotherapy.
- Interventions/comparators: Taxanes administered in the adjuvant setting where the comparator is not anthracycline-containing chemotherapy; taxanes in both/all study arms; taxanes administered as neoadjuvant chemotherapy.
- Study design: Studies considered methodologically unsound.
- Publications in languages other than English were excluded.

Based on the above inclusion/exclusion criteria, study selection was made by one reviewer, with involvement of a second reviewer when necessary.

Data abstraction and critical appraisal strategy

Data were abstracted with no blinding to trial authors or journal. Data were abstracted by one researcher using a standardised form,[35] with a second researcher independently abstracting outcomes data. Any disagreements were resolved by discussion. For time-to-event measures, data on proportions of patients with events in each treatment arm were recorded, as were reported hazard ratios (HRs). Where sufficient data were available, number-needed-to-treat to benefit (NNTB) and absolute risk reduction (ARR) were calculated using the method of Altman and Andersen.[36]

The quality of RCTs was assessed according to criteria based on those proposed by the NHS Centre for Reviews and Dissemination.[35] The purpose of such quality assessment was to provide a narrative account of trial quality for the reader. Use of data from non-randomised studies was not considered as there was sufficient evidence from good-quality RCTs.

Methods of data synthesis

Prespecified outcomes were tabulated and discussed within a descriptive synthesis. Heterogeneity of interventions, comparators and populations precluded meta-analysis.[35] The different combinations and schedules of drugs in the intervention arms, and importantly the variety of comparators, meant that regimens differed in benefits and harms and make meta-analysis inappropriate.

Results

Quantity and quality of research available

The literature search yielded 9041 citations when duplicates had been removed. Of these, 151 were database citations (that is, records of trials giving varying amounts of details of trial protocols, but no reports of data, such as may be found on the NRR). *Figure 1* shows the study selection. There were 43 references accepted into the review, including two citations of a relevant systematic review.[31,37]

There were 41 references of 18 trials meeting inclusion criteria for this review with reporting of effectiveness, toxicity or HRQoL data. These comprised 11 trials of docetaxel and seven trials of paclitaxel.

Of the docetaxel trials, six had reported effectiveness data – BCIRG 001,[38–41] Eastern Cooperative Oncology Group (ECOG) 2197,[42–44] PACS 01,[45–49] USO 9735,[50–52] BIG 2-98[53] and Taxit 216;[54–56] five had reported safety or HRQoL data – TACT,[56,57] GEICAM 9805,[58] RAPP 01,[59,60] PACS 04[61] and GOIM 9902.[62]

Of the paclitaxel trials, five had reported effectiveness data – NSABP B28,[63,64] CALGB 9344[65–69], HCOG,[70,71] ECTO[72] and GEICAM 9906;[73–75] two had reported safety data – Elling Phase II[76] and MIG 5.[77,78]

There were 131 database citations of studies meeting the inclusion criteria – these comprised the 18 reported trials and five ongoing trials. Ongoing trials identified by the search, and excluded studies with reason for exclusion, are presented in Appendix 4.

The studies' most recent results were presented in peer-reviewed journal articles for six of the trials, BCIRG 001, RAPP 01, NSABP B28, CALGB 9344, HCOG and Elling Phase 2, and presented in conference proceedings for 12 of the trials, ECOG 2197, PACS 01, USO 9735, BIG 2-98, Taxit 216, TACT, GEICAM 9805, ECTO, GEICAM 9906, MIG 5, PACS 04 and GOIM 9902.

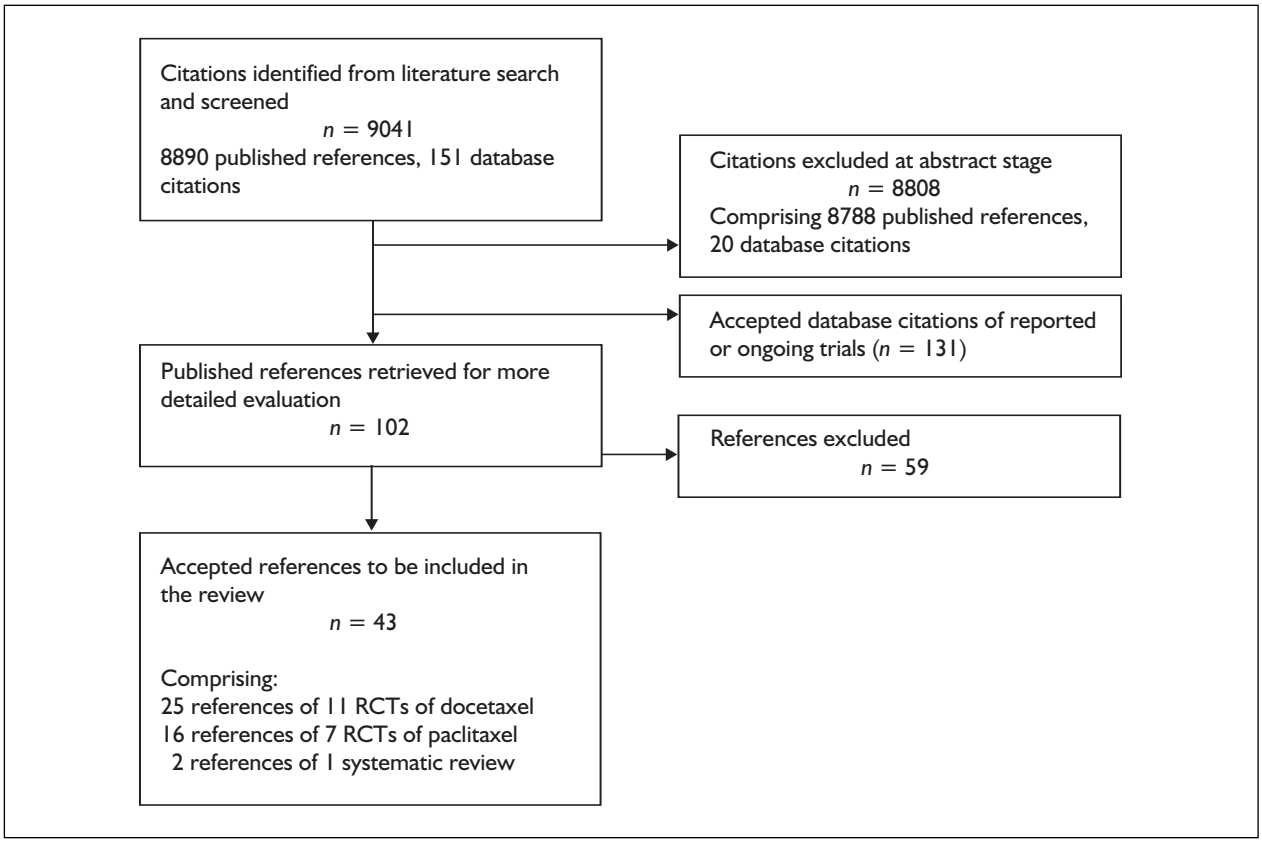

FIGURE 1 *Flow diagram of study selection*

A summary of the interventions studied in included trials is given in *Tables 5* and *6*. Details of concomitant therapy are presented in Appendix 3 (tables of docetaxel concomitant therapy and paclitaxel concomitant therapy).

With one exception (Elling Phase 2), all studies were Phase 3, multi-centre RCTs.

As can be seen from the tables, interventions varied considerably between trials, in the combinations of drugs used and in the incorporation of taxanes either being concurrent or sequential. Some trials had more cycles of chemotherapy in the taxane arm than in the control arm (BIG 2-98, Taxit 216, GOIM 9902, NSABP B28, CALGB 9344, HCOG, GEICAM 9906). Only one of the docetaxel trials, BCIRG 001, used docetaxel in line with current UK marketing authorisation. GEICAM 9805 used docetaxel concurrently with AC in accordance with the licensed chemotherapy regimen, but the trial population were N–ve, whereas marketing authorisation is for N+ve patients. Four of the paclitaxel trials used paclitaxel in line with the licensed regimen (NSABP B28, CALGB 9344, GEICAM 9906, Elling Phase 2), but only two of these complied with recommended dose and frequency (CALGB 9344, Elling Phase 2).

NSABP B28 and CALGB 9344 were the only two trials with reported effectiveness data which had similar interventions. However, they differed in dose of paclitaxel. The trials also differed in that CALGB 9344 used randomisation in a three-by-two factorial design, with one of three doses of doxorubicin, followed by paclitaxel or by no additional chemotherapy. CALGB 9344 found no evidence of doxorubicin dose effect, and this is not reported in effectiveness data (see the section 'Critical review and synthesis of population', p. 16), as anthracycline dose effect is not in the remit of the review.

Two of the paclitaxel trials included additional trial arms which are not in the remit of this review. Elling Phase 2[76] had two trial arms containing vinorelbine, data from which are not reported in this review. ECTO[72] had a trial arm of neoadjuvant therapy containing paclitaxel, and this review does not report the trial results in which neoadjuvant and adjuvant arms were combined. The docetaxel trial PACS 04 data reported here are from the first part of the trial;

the trial has further randomisation to study trastuzumab which would not be relevant to this review.

Population eligibility criteria varied between trials, as can be seen in *Tables 7* and *8*.

Details of quality assessment are presented in Appendix 2. None of the trials were blinded. Blinding of patients and clinicians may have been impossible, for example for trials with different numbers of cycles between intervention and control arms. However, there was no indication

TABLE 5 *Summary of included docetaxel studies*

Trial	No. randomised	Interventions (abbreviated)	Interventions	Effectiveness reported at time of review publication?
BCIRG 001[38]	745	DAC6	Doxorubicin 50 mg/m^2 i.v. infusion for 15 minutes, followed by cyclophosphamide 500 mg/m^2 i.v. for 1–5 minutes, after a 1-hour interval Docetaxel 75 mg/m^2 i.v. infusion for 1 hour. Six 21-day cycles	Yes
	746	FAC6	Doxorubicin 50 mg/m^2, followed by fluorouracil 500 mg/m^2, as i.v. infusion for 15 minutes, then cyclophosphamide 500 mg/m^2 i.v. infusion for 1–5 minutes. Six 21-day cycles	
ECOG 2197[43]	Total 2952	DA4	Docetaxel 60 mg/m^2 and doxorubicin 60 mg/m^2. Four 3-week cycles	Yes
		AC4	Doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Four 3-week cycles	
PACS 01[47]	Total 1999	FEC3-D3	5-Fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2. Three 3-week cycles. Then docetaxel 100 mg/m^2. Three 3-week cycles	Yes
		FEC6	5-Fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2. Six 3-week cycles	
USO 9735[52]	506	DC4	Docetaxel 75 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles	Yes
	510	AC4	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles	
BIG 2-98[53]	Total 2887	DA4-CMF3	Docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2. Four 3-week cycles. Then cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 on two days of three 4-week cycles	Yes
		A3-D3-CMF3	Doxorubicin 75 mg/m^2. Three 3-week cycles. Then docetaxel 100 mg/m^2. Three 3-week cycles. Then cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 on two days of three 4-week cycles	
		AC4-CMF3	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles. Then cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 on two days of three 4-week cycles	

continued

TABLE 5 *Summary of included docetaxel studies (cont'd)*

Trial	No. randomised	Interventions (abbreviated)	Interventions	Effectiveness reported at time of review publication?
		A4-CMF3	Doxorubicin 75 mg/m^2. Four 3-week cycles. Then cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 on two days of three 4-week cycles	
Taxit 216[52]	486	E4-D4-CMF4	Epirubicin 120 mg/m^2. Four 3-week cycles. Then docetaxel 100 mg/m^2. Four 3-week cycles. Then cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2 and fluorouracil 600 mg/m^2 on two days of four 4-week cycles	Yes
	486	E4-CMF4	Epirubicin 120 mg/m^2. Four 3-week cycles. Then cyclophosphamide 100 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 on two days of four 4-week cycles	
TACT[57]	Total 4162	FEC4→D4	5-Fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles. Then docetaxel 100 mg/m^2. Four 3-week cycles	No – HRQoL data reported
		FEC8	5-Fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Eight 3-week cycles	
		E4-CMF4	Epirubicin 100 mg/m^2. Four 3-week cycles. Then cyclophosphamide 600 mg/m^2 (alternatively 100 mg/m^2, 14 days), methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 on two days of four 4-week cycles	
GEICAM 9805[58]	Total 1059	DAC6	Docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2. Six 3-week cycles	No – safety data reported
		FAC6	5-Fluorouracil 500 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2. Six 3-week cycles	
RAPP 01[59]	311	DA4	Docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2. Four 3-week cycles	No – trial terminated due to toxicity
	316	AC4	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles	
PACS 04[61]	1492	DE6	Docetaxel 75 mg/m^2, epirubicin 75mg/m^2. Six 3-week cycles	No – safety data reported
	1518	FEC6	5-Fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2. Six 3-week cycles	
GOIM 9902[62]	376	D4-EC4	Docetaxel 100 mg/m^2. Four 3-week cycles. Then epirubicin 120 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles	No – safety data reported
	374	EC4	Epirubicin 120 mg/m^2, cyclophosphamide 600 mg/m^2, Four 3-week cycles	

TABLE 6 *Summary of included paclitaxel studies*

Trial	No. randomised	Interventions (abbreviated)	Interventions	Effectiveness reported at time of review publication?
NSABP B28[63]	1531	AC4-P4	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles, followed by paclitaxel 225 mg/m^2 3-hour infusion. Four 3-week cycles	Yes
	1529	AC4	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles	
CALGB 9344[68]	1590	AC4-P4	Cyclophosphamide 600 mg/m^2, one of three doses of doxorubicin 60 or 75 or 90 mg/m^2. Four 3-week cycles, followed by paclitaxel 175 mg/m^2. Four 3-week cycles	Yes
	1580	AC4	Cyclophosphamide 600 mg/m^2, one of three doses of doxorubicin 60 or 75 or 90 mg/m^2. Four 3-week cycles	
HCOG[71]	Total 604	E3-P3-CMF3	Epirubicin 110 mg/m^2. Three 2-week cycles, then paclitaxel 250 mg/m^2. Three 2-week cycles, then cyclophosphamide 840 mg/m^2, methotrexate 57 mg/m^2, fluorouracil 840 mg/m^2. Three 2-week cycles	Yes
		E4-CMF4	Epirubicin 110 mg/m^2. Four 2-week cycles, then cyclophosphamide 840 mg/m^2, methotrexate 57 mg/m^2, fluorouracil 840 mg/m^2. Four 2-week cycles	
ECTO[72]	451	PA4-CMF4	Paclitaxel 200 mg/m^2 over 3 hours, doxorubicin 60mg/m^2. Four 3-week cycles, followed by i.v. cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2 days 1 and 8. Four 4-week cycles	Yes
	453	A4-CMF4	Doxorubicin 75 mg/m^2. Four 3-week cycles, followed by i.v. cyclophosphamide 600 mg/m^2, methotrexate 40 mg/m^2, fluorouracil 600 mg/m^2 days 1 and 8. Four 4-week cycles	
		(also has neoadjuvant arm, not relevant to this review)		
GEICAM 9906[75]	614	FEC4-P8	Fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles, then paclitaxel 100 mg/m^2. Eight 1-week cycles	Yes
	634	FEC6	Fluorouracil 600 mg/m^2, epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2. Six 3-week cycles	
Elling Phase 2[76]	15	EV4-P4 (not relevant to this review)	Epirubicin 90 mg/m^2, vinorelbine 25 mg/m2. Four 3-week cycles, then paclitaxel 175 mg/m^2. Four 3-week cycles	No – safety data reported
	15	EV4 (not relevant to this review)	Epirubicin 90 mg/m^2, vinorelbine 25 mg/m^2. Four 3-week cycles	
	15	EC4-P4	Epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles, then paclitaxel 175 mg/m^2. Four 3-week cycles	

continued

TABLE 6 *Summary of included paclitaxel studies (cont'd)*

Trial	No. randomised	Interventions (abbreviated)	Interventions	Effectiveness reported at time of review publication?
	15	EC4	Epirubicin 90 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles	
MIG 5[78]	317	PE4	Epirubicin 90 mg/m^2, paclitaxel 175 mg/m^2 i.v. infusion over 3 hours. Four 3-week cycles	No – safety data reported
	314	FEC6	Fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Six 3-week cycles	

TABLE 7 *Eligibility for docetaxel trials*

Trial	Population description, including tumour stage or size	Nodal status	Other
BCIRG 001[38]	Unilateral, resected breast cancer. Margins of resected specimens histologically free of invasive adenocarcinoma and ductal carcinoma *in situ*	Positive. At least one axillary lymph node positive for cancer on histological examination	Aged 18–70 years; Karnofsky performance scale score 80% or more; primary surgery (mastectomy, tumourectomy, or lumpectomy) with axillary node dissection (sentinel node biopsy was not routine practice). Randomisation within 60 days after surgery. Excluded: history of cancer, motor or sensory neuropathy of grade 2 or more, pregnancy, lactation, any serious illness or medical condition other than breast cancer, prior therapy with anthracyclines or taxanes
ECOG 2197[43]	Either 1–3 nodes positive; or node negative and tumour size more than 1 cm	Positive or negative	NR
PACS 01[47]	Unilateral, localised resected breast cancer	Positive. At least one positive node	Aged 18–65 years, non-pretreated cancer, normal cardiac, hepatic, haematological and renal functions. First chemotherapy no more than 42 days after surgery
USO 9735[52]	Stage 1–3 resected breast cancer	Positive or negative	Aged over 18 years, adequate renal, hepatic and haematological functions; Karnofsky performance scale score 80%. Excluded: other significant illness, malignancy or neoadjuvant chemotherapy, prior chemotherapy or radiation therapy within 3 years of date of diagnosis of breast cancer, pregnancy or lactation
BIG 2-98[53]	Resected early-stage breast cancer	Positive	Aged 18–70 years
Taxit 216[52]	Resected early-stage breast cancer	Positive	NR
TACT[57]	Resected early-stage breast cancer, clear surgical margins	Positive or negative	Surgical axillary staging according to BASO guidelines

continued

TABLE 7 *Eligibility for docetaxel trials (cont'd)*

Trial	Population description, including tumour stage or size	Nodal status	Other
GEICAM 9805[58]	Resected, high-risk (St Gallen, 1998) breast cancer	Negative	Aged 18–70 years
RAPP 01[59]	Unilateral resected breast cancer. Clear surgical margins and axillary node clearance. High-risk node-negative; or limited node-positive disease	Positive or negative	Aged 18–70 years
PACS 04[61]	Unilateral, localised resected breast cancer	Positive	Aged 18–64 years, adequate heart and organ functions
GOIM 9902[62]	T1-3 (tumour any size but no extension to skin or chest wall)	Positive	Aged 18–70 years, normal cardiac function, adequate bone marrow, hepatic and renal function, (ECOG) performance status 0–1

BASO, British Association of Surgical Oncology; ECOG, Eastern Cooperative Oncology Group; NR, not reported.

from any of the trials that outcome assessors were blinded. The method of randomisation was reported and adequate in three docetaxel trials (BCIRG 001, Taxit 216, RAPP 01) and three paclitaxel trials (NSABP B28, HCOG, GEICAM 9906). Allocation concealment was reported and adequate in one docetaxel trial (RAPP 01) and two paclitaxel trials (NSABP B28, HCOG). For studies with effectiveness data, analysis included at least 80% of the participants originally randomised in four docetaxel trials reporting effectiveness data (BCIRG 001, ECOG 2197, PACS 01, USO 9735) and four paclitaxel trials (NSABP B28, CALGB 9344, HCOG, GEICAM 9906).

Assessment of effectiveness

Critical review and synthesis of information

There was a high rate of compliance with therapy and few withdrawals reported (see the tables in the section 'Relative dose intensities' in Appendix 3, (p. 92).

Baseline population characteristics of the trials are shown in *Tables 9* and *10*. Within trials, intervention and control groups were well balanced at baseline, with the exceptions of HCOG groups not being balanced on nuclear grade (the docetaxel group had relatively more patients with nuclear grade 3 and fewer with grade 2 than the control group), and PACS 01 had relatively more ER+ patients in the docetaxel group than the control group. Some of the trials included N–ve patients, for whom taxanes are not currently licensed. Some of the trials had a minority of patients with more than nine positive nodes; it may be considered these patients should have been excluded from the review as being above Stage IIIa; however, data were not available excluding these patients, and it was decided to keep these trials in the review as they only concerned a minority of patients.

Effectiveness data

Overall survival

Overall survival data, where reported, are shown in *Tables 11* and *12*. Median follow-up for studies ranged from 43 to 69 months.

BCIRG 001 reported a significant improvement {HR 0.69 [95% confidence interval (CI) 0.52 to 0.90]} in OS for DAC6 compared with FAC6. PACS 01 reported an improvement in OS for FEC3-D3 compared with FEC6 which had a 4% lower survival rate. No significant difference in OS was found between DA4 and AC4 (ECOG), or between PA4-CMF4 and A4-CMF4 (ECTO), or between DC4 and AC4 (USO 9735).

CALGB 9344 reported a significant improvement in OS for AC4-P4 compared with AC4 [HR 0.82 (95% CI 0.71 to 0.95)]. HCOG reported a 3% higher overall survival rate for E3-P3-CMF3 compared with E4-CMF4. No significant difference in OS was found between AC4-P4 and AC4 (NSABP B28) or between FEC4-P4 and FEC6 (GEICAM 9906).

USO 9735 reported deaths from breast cancer at 36 months: the docetaxel group had 17 deaths (3.4%) from breast cancer, the control group had

TABLE 8 *Eligibility for paclitaxel trials*

Trial	Population description, including tumour stage or size	Nodal status	Other
NSABP B28[63]	Resected breast cancer	Positive. Histologically positive axillary nodes	Excluded: history of breast cancer, prior radiation, chemotherapy, immunotherapy, hormonal therapy
CALGB 9344[68]	Resected breast cancer with clear surgical margins	Positive	Systemic therapy to start within 84 days of patient's last surgery, initial surgical treatment either mastectomy or lumpectomy with axillary lymph node sampling. Radiotherapy for all patients with less than mastectomy, begun after chemotherapy
HCOG[71]	Histologically confirmed epithelial breast cancer; pathological stage T1–3N1M0 or T3N0M0	Positive or negative	ECOG performance status 0–1; normal cardiac function; and adequate bone marrow, hepatic and renal function. Excluded: history of serious cardiac disease, other serious medical illness or inability to comply with the treatment plan and follow-up visits, postmenopausal patients with 1–3 positive axillary nodes and positive hormonal receptor status
ECTO[72]	Resected breast cancer, tumour size >2 cm	Positive or negative	NR
GEICAM 9906[75]	Resected breast cancer, T1–3, pN1, M0	Positive	Age 18–70 years, Karnofsky performance scale score 90%, adequate bone marrow, renal and hepatic function, mastectomy or breast conservation surgery with free margins, axillary dissection with 6+ lymph nodes, adequate cardiac function (normal LVEF)
Elling Phase 2[76]	Histologically proven breast cancer (T1–3)	Positive, 1–3 positive lymph nodes	Complete resection of tumour and dissection and examination of at least 10 axillary lymph nodes, Premenopausal patients ER+/– and PR+/– or postmenopausal (over 52 years) patients ER+/– and PR+/–; aged 18–75 years; ECOG performance status 1 or less; no previous radiation-, chemo-, hormone or immunotherapy for breast cancer; start of chemotherapy no later than 4 weeks after surgery; no clinically detectable neuropathy; normal cardiovascular, haematological, hepatobiliary and renal function
MIG 5[78]	Resected breast cancer	Positive, less than 10 positive nodes	Excluded: patients with pre-existing serious cardiac disease

LVEF, left ventricular ejection fraction.

15 (2.9%). None of the other trials reported deaths from breast cancer.

Disease-free survival

DFS data, where reported, are shown in *Tables 13* and *14*. Two paclitaxel trials, CALGB 9344 and HCOG, report TTR, and one trial, ECTO, reports freedom from progression (FFP), defined as time "from date of randomisation to first evidence of breast cancer progression or relapse", and these are shown in *Table 15*. DFS events were defined by most of the studies as breast cancer recurrence (local, regional or distant relapse), contralateral breast cancer or second cancer, or death. However, trials ECOG 2197, CALGB 9344 and HCOG do not specify second cancer being counted as an event. BCIRG 001 defines second cancer as excluding skin cancer other than melanoma, ductal or lobular carcinoma *in situ* of the breast or carcinoma *in situ* of the cervix.

TABLE 9 *Baseline population characteristics for docetaxel trials*

Trial	No. of patients	Intervention group	Tumour size/stage	Nodal status	Hormone receptor status	Age (median) years)
BCIRG 001	745	DAC6	T1 (up to 2 cm) 39.7%; T2 (2–5 cm) 52.6%; T3 (over 5 cm) 7.7%	N–ve 0%; 1–3 +ve nodes 62.7%; 4+ +ve nodes 37.3%	ER+ or PR+ 76.1%	49
	746	FAC6	T1 (up to 2 cm) 42.9%; T2 (2–5 cm) 51.3%; T3 (over 5 cm) 5.8%	N–ve 0%; 1–3 +ve nodes 61.5%; 4+ +ve nodes 38.5%	ER+ or PR+ 75.7%	49
ECOG 2197	1444 1445	DA4 1445	(Across both groups) median 2.0 cm (range 0.1–12.5 cm)	(Across both groups) N–ve 65%	(Across both groups) ER+ 64%	(Across both groups) 51 (range 24–85)
PACS 01	1003	FEC3-D3	2+ cm 60.9%	N–ve 0%; 1–3 +ve nodes 62.4%; 4+ +ve nodes 37.6%	ER+ 76.3%; ER– PR– 19.1%	50.0 (range 25.2–65.0)
	996	FEC6	2+ cm 65.5%	N–ve 0%; 1–3 +ve nodes 61.3%; 4+ +ve nodes 38.7%	ER + 71.1%; ER– PR– 22.3%	49.8 (range 26.2–66.9)
USO 9735	506	DC4	Stage I 20%, Stage II 74%, Stage III 5%, unknown 1%	N–ve 47%; 1–3 +ve nodes 41%; 4+ +ve nodes 12%	ER+PR+ 59%; ER– PR+ 3%; ER+ PR– 10%; ER– PR– 27%; unknown 1%	(Across both groups) 52 (range 28–78)
	510	AC4	Stage I 22%, Stage II 71%, Stage III 7%, unknown 0%	N–ve 49%; 1–3 +ve nodes 42%; 4+ +ve nodes 9%;	ER+ PR+ 56%; ER– PR+ 4%; ER+ PR– 9%; ER– PR– 31%; unknown <1%	
BIG 2-98	2887 enrolled	DA4-CMF3 A3-D3-CMF3 AC4-CMF3 A4-CMF3	NR	(Across all groups) N–ve 0%; 4+ +ve nodes 46%	NR	NR
Taxit 216	486 486	E4-D4-CMF4 E4-CMF4	NR	(N+ve eligibility criteria)	(Across both groups) ER+ 64.7%; ER unknown 11.3%	(Across both groups) 51.3
TACT	417 (in QoL study) 264 148	FEC4-D4 FEC8 E4-CMF4	NR	NR	NR	(Across both groups) 49 (range 27–70)

continued

TABLE 9 *Baseline population characteristics for docetaxel trials (cont'd)*

Trial	No. of patients	Intervention group	Tumour size/stage	Nodal status	Hormone receptor status	Age (median) years)
GEICAM 9805	530 (in analysis)[a]	DAC6	NR	(N–ve eligibility criteria)	NR	(Range 18–70 eligibility criteria)
	520	FAC6				
RAPP 01	311 (enrolled when study ended)	DA4	Median (range) 2 (0.6–8) cm	N–ve 42.1%; N+ve 57.9%	ER+ or PR+ 80.4%	53 (range 27–70)
	316	AC4	Median (range) 2 (0.3–8) cm	N–ve 44.0%; N+ve 56.0%	ER+ or PR+ 81.3%	52 (range 26–70)
PACS 04	2622 (in analysis)	DE6 FEC6	NR	NR	NR	NR
GOIM 9902	376	D4-EC4	NR	N–ve 0%; 1–3 +ve nodes 48.9%; 4–9 +ve nodes 34.8%; 10+ +ve nodes 16.2%	HR+ 76.9%	Under 50 52.4%
	374	EC4		N–ve 0%; 1–3 +ve nodes 48.7%; 4–9 +ve nodes 34.5%; 10+ +ve nodes 16.8%	HR+ 76.7%	Under 50 49.5%

NR, not reported; N–ve, node negative; N+ve, node positive.
[a] Of whom 416 received GCSF and 114 did not.

DFS was reported to be significantly better for DAC6 compared with FAC6 (BCIRG 001) and in DC4 compared with AC4 (USO 9735), and narrowly reached statistical significance in FEC3-D3 compared with FEC6 (PACS 01) and in A3-D3-CMF3 compared with A4-CMF3 (BIG 2-98), with HRs from 0.71 to 0.83. There was no significant difference in DFS between DA4 and AC4 (ECOG 2197) or between DA4-CMF3 and A4-CMF3 (BIG 2-98), or between E4-D4-CMF4 and E4-CMF4 (Taxit 216). BIG 2-98 also reported a non-significant difference, but with trend favouring sequential (A3-D3-CMF3) compared with concurrent (DA4-CMF3) docetaxel.

NSABP B28 reported a significant improvement in DFS for AC4-P4 compared with AC4, which had a 4% lower DFS rate. GEICAM 9906 reported a significant improvement in DFS for FEC4-P8 compared with FEC6 (HR 0.63). No significant difference in DFS or in TTR was found between E3-P3-CMF3 and E4-CMF4 (HCOG).

TTR was reported to be significantly improved in AC4-P4 compared with AC4 by CALGB 9344 [HR 0.83 (95% CI 0.73 to 0.94)]. FFP was reported to be significantly improved in PA4-CMF4 compared with A4-CMF4 by the ECTO trial (HR 0.65).

Locoregional or distant recurrence or contralateral breast cancer

Type of first event was not reported by most of the trials. Where reported, first events of locoregional and distant recurrences, or contralateral breast cancers, are shown in *Tables 16* and *17*. Significantly fewer first events as distant recurrences were reported in FEC3-D3 compared with FEC6 by PACS 01. Significantly fewer first events as contralateral breast cancer were reported in AC4 than P4 compared with AC4 by NSABP B28.

Disease-free survival – subgroup analyses

Some DFS data were available considering the following subgroups separately: nodal status; ER+ versus ER– and PR+ versus PR–; HER2 positive

TABLE 10 *Baseline population characteristics for paclitaxel trials*

Trial	No. of patients	Intervention group	Tumour size/stage	Nodal status	Hormone receptor status	Age (median) years)
NSABP B28	1531	AC4-P4	2 cm or less 58.4%; 2.1–4 cm 32.5%; over 4 cm 9%	N–ve 0%; 1–3+ve nodes 69.9%; 4–9 +ve nodes 25.9%; 10+ +ve nodes 4.2%	ER+ 65.7%; PR+ 60.5%	(Median not reported) 39 or under 15%; 40–49 36.6%; 50–59 29.8%; 60+ 18.7%
	1528	AC4	2 cm or less 60%; 2.1–4 cm 32.2%; over 4 cm 7.6%	N–ve 0%; 1–3 +ve nodes 70%; 4–9 +ve nodes 26.2%; 10+ +ve nodes 3.9%	ER+ 66.3%; PR+ 62.1%	39 or under 13.5%; 40–49 36.3%; 50–59 31.7%; 60+ 18.5%
CALGB 9344	1570 (in analysis)	AC4-P4	2 cm or less 35%; over 5 cm 13%	N–ve 0%; 1–3+ve nodes 46%; 4–9+ve nodes 42%; 10+ +ve nodes 12%	ER+ 60%; ER+ or PR+ 67%	(Median not reported) under 40 20%; 40–49 41%; 50–59 26%; 60+ 13%
	1551	AC4	2 cm or less 35%; over 5 cm 12%	N–ve 0%; 1–3 +ve nodes 47%; 4–9 +ve nodes 42%; 10+ +ve nodes 12%	ER+ 58%; ER+ or PR+ 66%	Under 40 21%; 40–49 39%; 50–59 28%; 60+ 12%
HCOG	298	E3-P3-CMF3	2 cm or less 29%; 2.1–5 cm 55%; over 5 cm 15%	N–ve 2%; 1–3+ve nodes 24%; 4–9+ve nodes 41%; 9+ +ve nodes 33%	ER+ or PR+ 75%; HR– 23%	50 (range 24–76)
	297	E4-CMF4	2 cm or less 33%; 2.1–5 cm 52%; over 5 cm 16%	N–ve 2%; 1–3+ve nodes 27%; 4–9+ve nodes 42%; 9+ +ve nodes 29%	ER+ or PR+ 76%; HR– 24%	50 (range 22–78)
ECTO	432	PA4-CMF4	4 cm or less 80%; over 4 cm 20%		HR+ 68%; HR– 31%; unknown 1%	Under 50 47%; 50+ 53%
	444	A4-CMF4	4 cm or less 80%; over 4 cm 20%		HR+ 68%; HR– 31%; unknown 1%	Under 50 42%; 50+ 58%
GEICAM 9906	610 in safety analysis	FEC4-P8	1 cm or less 7%; over 1 and up to 2 cm 38%; over 2 cm 55%	N–ve 0%; 1–3 positive nodes 63%; 4+ +ve nodes 37%	ER+ and/or PR+ 82%	50.2 (23–76)
	633	FEC6	1 cm or less 7%; over 1 and up to 2 cm 33%; over 2 cm 60%	N–ve 0%; 1–3 positive nodes 62%; 4+ +ve nodes 38%	ER+ and/or PR+ 79%	50.4 (24–76)
Elling Phase 2	15 in safety analysis	EC4-P4	NR	(N+ve eligibility criteria)	NR	(Across all groups) 53
	13	EC4				

continued

TABLE 10 *Baseline population characteristics for paclitaxel trials (cont'd)*

Trial	No. of patients	Intervention group	Tumour size/stage	Nodal status	Hormone receptor status	Age (median) years)
MIG 5	268 in safety analysis 265	PE4 FEC6	NR	(N+ve eligibility criteria)	NR	(Across both groups) 53 (range 26–70)

TABLE 11 *Overall survival: docetaxel trials*

Trial	Follow-up (median) (months)	Group	No. in analysis	Deaths (No.)	Deaths (%)	OS (%)	HR (95% CI)	ARR	NNTB (95% CI)
BCIRG 001	55	DAC6	745	91	12	88	0.69 (0.52 to 0.90), $p = 0.005$	0.05	20.26 (12.88 to 64.06)
	55	FAC6	746	130	17	83			
ECOG 2197	59	DA4	1444	117	8	92		0.01	100
	59	AC4	1441	125	9	91	1.09 (0.85 to 1.40), $p = 00.49$		
PACS 01	59.7	FEC3-D3	1003	100	10	90	0.77 (0.59 to 1.00), $p = 0.050$[a]	0.04	32.94
	59.7	FEC6	996	135	14	86			
USO 9735	66	DC4	506	55	11	89	0.76, $p = 0.131$	0.03	33.33
	66	AC4	510	71	14	86			
Taxit 216	53	E4-D4-CMF4	486	NR			0.74 (0.51 to 1.07), $p = 0.10$		
	53	E4-CMF4	486		NR				

CI, confidence interval.
[a] Adjusted for age, nodes, tumour size, hormone receptors and SBR grade.

TABLE 12 *Overall survival: paclitaxel trials*

Trial	Follow-up (median) (months)	Group	No. followed up	Deaths (No.)	Deaths (%)	OS (%)	HR (95% CI)	ARR	NNTB (95% CI)
NSABP B28[a]	64.4	AC4-P4	1531	243	16	84	NR	0.01	100
	64.8	AC4	1528	255	17	83			
CALGB 9344	69	AC4-P4	1570	342	20	80	0.82 (0.71 to 0.95)	0.03	26.96 (16.49 to 98.73)
	69	AC4	1551	400	23	77			
HCOG	61.7	E3-P3-CMF3	298	53	18	82		0.03	33.33
	62	E4-CMF4	297	61	21	79	2.42 (1.17 to 4.99), $p = 0.02$		
ECTO	43	PA4-CMF4	451	30	7	93[b]	0.71, $p = 0.16$	0.02	39.63
	43	A4-CMF4	453	41	9	91[b]			
GEICAM 9906	46	FEC4-P8	614	34	6	94	0.74, $p = 0.1391$	0.02	50
	46	FEC6	634	49	8	92			

[a] NSABP B28 reports a non-significant RR of OS for paclitaxel groups versus control of RR 0.93 (95% CI 0.78 to 1.12), $p = 0.46$.
[b] At 5 years.

TABLE 13 *Disease-free survival: docetaxel trials*

Trial	Follow-up (median) (months)	Group	No. followed up	Breast cancer event or death (No.)	Breast cancer event or death (%)	DFS (%)	HR (95% CI)	ARR	NNTB (95% CI)
BCIRG 001	55	DAC6	745	172	23	77	0.71 (0.58 to 0.87), $p < 0.001$	0.07	13.11 (9.07 to 30.10)
	55	FAC6	746	227	30	70			
ECOG 2197	59	DA4	1444	213	15	85		0	Not estimable
	59	AC4	1441	219	15	85	1.03 (0.86 to1.25), $p = 0.70$[a]		
PACS 01	59.7	FEC3-D3	1003	218	22	78	0.83 (0.69 to 0.99), $p = 0.041$[b]	0.05	24.93
	59.7	FEC6	996	264	27	73			
USO 9735	66	DC4	506	NR	14	86	0.67 (0.50 to 0.94), $p = 0.015$	0.06	16.36 (10.59 to 92.74)
	66	AC4	510	NR	20	80			
BIG 2-98 (comparison concurrent D)	62.2	DA4-CMF3	NR	NR	NR	NR	0.93 (0.75 to 1.14), $p = 0.48$[c]		
	62.2	AC4-CMF3	NR	NR	NR	NR			
BIG 2-98 (comparison sequential D)	62.2	A3-D3-CMF3	NR	NR	NR	NR	0.79 (0.64 to 0.98), $p = 0.035$[c]		
	62.2	A4-CMF3	NR	NR	NR	NR			
Taxit 216	53	E4-D4-CMF4	486	NR	NR	74	0.80 (0.62 to 1.03), $p = 0.079$[d]		
	53	E4-CMF4	486	NR	NR	67			

[a] Adjusted.
[b] Adjusted for age, nodes, tumour size, hormone receptors and Scarff–Bloom–Richardson (SBR) grade.
[C] Event-free survival.
[d] 5-year estimate, when adjusted for nodal status, menopausal status and ER, estimated HR 0.78 (95% CI 0.61 to 1.00).

TABLE 14 *Disease-free survival: paclitaxel trials*

Trial	Follow-up (median) (months)	Group	No. followed up	Mortality or recurrence (No)	Mortality or recurrence (%)	DFS (%)	HR (95% CI)	ARR	NNTB (95% CI)
NSABP B28[a]	64.4	AC4-P4	1531	400	26	74	NR	0.04	25.00
	64.8	AC4	1528	463	30	70			
CALGB 9344	60	AC4-P4	1570	NR	30	70	NR		
	60	AC4	1551	NR	35	65			
HCOG	61.7	E3-P3-CMF3	298	NR	NR	70[b]		0.02	50.00
	62	E4-CMF4	297	NR	NR	68[b]	1.16 (0.87 to 1.55), $p = 0.31$		
ECTO	43	PA4-CMF4	451	NR	NR	NR	NR		
	43	A4-CMF4	453	NR	NR	NR	NR		
GEICAM 9906	46	FEC4-P8	614	83	14	86	0.63, $p = 0.0008$	0.06	14.39
	46	FEC6	634	128	20	80			

[a] NSABP B28 reports a significant RR of DFS for paclitaxel with reference control group of 0.83 (95% CI 0.72 to 0.95), $p = 0.006$.
[b] 5-year estimate.

TABLE 15 *Time to recurrence*

Trial	Follow-up (median) (months)	Group	No. followed up	Any breast cancer (1st) event (No.)	Any breast cancer (1st) event (%)	Free from recurrence (%)	HR (95% CI)	ARR	NNTB (95% CI)
NSABP B28	64.4	AC4-P4	1531	NR	NR	NR	NR		
	64.8	AC4	1528	NR	NR	NR	NR		
CALGB 9344	69	AC4-P4	1570	491	31	69	0.83 (0.73 to 0.94)	0.05	19.82 (12.20 to 57.57)
		AC4	1551	563	36	64			
HCOG	61.7	E3-P3-CMF3	298	91	31	69		0.02	50
	62	E4-CMF4	297	98	33	67			
ECTO	43	PA4-CMF4	451	63	14	86[a]	0.65 (0.47 to 0.90), $p = 0.01$	0.06	15.39 (9.96 to 55.40)
	43	A4-CMF4	453	91	20	80[a]			
GEICAM 9906	46	FEC4-P8	530	NR	NR	NR	NR		
	46	FEC6	520	NR	NR	NR	NR		

[a] At 5 years.

TABLE 16 *Recurrences: docetaxel trials*

Trial	Follow-up (median) (months)	Group	No.	First event	Patients with event (%)
BCIRG 001	55	DAC6	745	Locoregional recurrence	3.9
	55	FAC6	746	Locoregional recurrence	5.2
PACS 01	59.7	FEC3-D3	1003	Locoregional recurrence	4.7
	59.7	FEC6	996	Locoregional recurrence	7.1
BCIRG 001	55	DAC6	745	Distant recurrence	15.4
	55	FAC6	746	Distant recurrence	21.2
PACS 01	59.7	FEC3-D3	1003	Distant recurrence	17.7[a]
	59.7	FEC6	996	Distant recurrence	21.8[a]
BCIRG 001	55	DAC6	745	Contralateral	0.9
	55	FAC6	746	Contralateral	1.1
PACS 01	59.7	FEC3-D3	1003	Contralateral	2.4
	59.7	FEC6	996	Contralateral	3

[a] Significant difference between groups, $p = 0.023$.

or negative; age or menopausal status. These are shown in *Tables 18–23*.

BCIRG 001 found that for patients with 1–3 positive nodes there was a significant improvement in DFS for DAC6 compared with FAC6, but no difference between treatment groups for patients with ⩾4 positive nodes. PACS 01 found a borderline significant improvement for FEC3-D3 compared with FEC6 for patients with 1–3 positive nodes, but no difference between treatment groups for patients with ⩾4 positive nodes. USO 9735 found a significant improvement in DC4 compared with AC4 for N+ve patients, but no significant treatment effect for N–ve patients. ECOG 2197 found no significant effect according to nodal status.

BCIRG 001 reported significant improvement in DFS for DAC6 compared with FAC6 for HR+ and HR– patients. ECOG 2197 reported a significant improvement in DA4 compared with AC4 for

TABLE 17 *Recurrences: paclitaxel trials*

Trial	Follow-up (median) (months)	Group	No.	First event	Patients with event (%)
NSABP B28	64.4	AC4-P4	1531	Locoregional recurrence	6.7
	64.8	AC4	1528	Locoregional recurrence	8.2
NSABP B28	64.4	AC4-P4	1531	Distant recurrence	15
	64.8	AC4	1528	Distant recurrence	15.8
NSABP B28	64.4	AC4-P4	1531	Contralateral	1.1[a]
	64.8	AC4	1528	Contralateral	1.9[a]
HCOG	61.7	E3-P3-CMF3	298	Contralateral	0.7
	62	E4-CMF4	297	Contralateral	0

[a] Reported HR 0.53 (95% CI 0.29 to 0.98), $p = 0.039$.

TABLE 18 *Disease-free survival by nodal status: docetaxel trials*

Trial	Follow-up (median) (months)	Group	Population subgroup	No.	Breast cancer event or death (No.)	Breast cancer event or death (%)	HR (95% CI)
BCIRG 001	55	DAC6	1–3 nodes +ve	467	NR	NR	0.61 (0.46 to 0.82)
	55	FAC6	1–3 nodes +ve	459			
	55	DAC6	4+ nodes +ve	278			0.83 (0.63 to 1.08)
	55	FAC6	4+ nodes +ve	287			
PACS01	59.7	FEC3-D3	1–3 nodes +ve	626	NR	NR	0.76 (0.58 to 1.00)[a]
	59.7	FEC6	1–3 nodes +ve	611			
	59.7	FEC3-D3	4+ nodes +ve	377			0.87 (0.68 to 1.11)[a]
	59.7	FEC6	4+ nodes +ve	385			
USO 9735	66	DC4	N–ve	239	NR	NR	0.73 (0.42 to 1.27)
	66	AC4	N–ve	248			
	66	DC4	N+ve	267			0.67 (0.45 to 0.98)
	66	AC4	N+ve	262			

[a]Adjusted.

patients who were ER– and PR+, but no treatment effect for other hormone receptor status patients. Benefit of DC4 over AC4 was of borderline significance for ER– or PR– patients, and for ER+ or PR+ patients, in USO 9735, with point estimates of HRs suggesting a non-significant trend of DA4 to worsen DFS result compared with AC4 for patients with PR– status.

HER2+ patients significantly benefited from DAC6 compared with FAC6, with HER2 negative patients having a borderline significant treatment effect, in BCIRG 001. PACS 01 did not report HRs for HER2 status, but reported that HER2 positivity was not a poor prognostic factor for the FEC3-D3 group, whereas it was for the FEC6 group.

Premenopausal patients showed significant improvement in DAC6 compared with FAC6 in BCIRG 001, with borderline significance for postmenopausal patients. In PACS 01, patients aged 50 years or older significantly benefited from FEC3-D3 compared with FEC6, unlike younger patients. Benefit of DC4 over AC4 was of borderline significance for patients aged under 50 years, or 50+ years, in USO 9735. ECOG 2197 found no significant effect according to age or menopausal status.

Patients with ⩾4 positive nodes significantly benefited from FEC4-P8 compared with FEC6, whereas treatment effect was not significant in patients with 1–3 positive nodes, in GEICAM 9906.

TABLE 19 *Disease-free survival by hormone receptor status: docetaxel trials*

Trial	Follow-up (median) (months)	Group	Population subgroup	No.	Breast cancer event or death (No.)	Breast cancer event or death (%)	HR (95% CI)
BCIRG 001	55	DAC6	HR+	567	NR	NR	0.72 (0.56 to 0.92)
	55	FAC6	HR+	565			
	55	DAC6	HR–	178			0.69 (0.49 to 0.97)
	55	FAC6	HR–	181			
ECOG 2197	59	DA4	ER– PR–	464	86	18.5	1.30 (0.96 to 1.70)
	59	AC4	ER– PR–	468	108	23.1	
	59	DA4	ER– PR+	62	14	22.6	0.30 (0.10 to 0.95)
	59	AC4	ER– PR+	88	8	9.1	
	59	DA4	ER+PR–	182	22	12.1	1.64 (0.96 to 2.80)
	59	AC4	ER+PR–	184	84	45.7	
	59	DA4	ER+PR+	787	91	11.6	0.79 (0.58 to 1.10)
	59	AC4	ER+PR+	770	78	10.1	
USO 9735	66	DC4	ER– /PR–	137	NR	NR	0.64 (0.38 to 1.04)
	66	AC4	ER– /PR–	157			
	66	DC4	ER+ or PR+	369			0.71 (0.47 to 1.08)
	66	AC4	ER+ or PR+	353			

TABLE 20 *Disease-free survival by HER2 status: docetaxel trials*

Trial	Follow-up (median) (months)	Group	Population subgroup	No.	Breast cancer event or death (No.)	Breast cancer event or death (%)	HR (95% CI)
BCIRG 001	55	DAC6	HER2+	319 both groups	NR	NR	0.60 (0.41 to 0.88)
	55	FAC6	HER2+				
	55	DAC6	HER2–	943 both groups			0.76 (0.59 to 1.00)
	55	FAC6	HER2–				
	55	DAC6	HER2 unknown	229 both groups			0.72 (0.45 to 1.17)
	55	FAC6	HER2 unknown				

NSABP B28 reported a significant improvement in DFS for AC4-P4 compared with AC4 for patients with ER+ and/or PR+ status, but no significant treatment effect for HR– patients. There was no significant interaction effect of hormone receptor status and treatment group. GEICAM 9906 found a significant improvement for FEC4-P8 compared with FEC6 for both HR+ and HR– subgroups.

GEICAM 9906 found significant improvement of DFS for FEC4-P8 compared with FEC6 for patients with HER2 negative to 2+, and also for patients with HER2 3+. Postmenopausal patients benefited significantly from FEC4-P8 compared with FEC6, whereas difference between treatment groups did not reach significance for premenopausal patients in GEICAM 9906.

HCOG stated that the treatment effect on the hazard of disease progression was not different according to hormonal receptor status. TTR was reported as an unplanned analysis for CALGB 9344, with a significant improvement of AC4-P4 compared with AC4 for HR– patients, and treatment effect of borderline significance for patients with ER+ and/or PR+ status. There was no significant difference in hormone receptor subgroups when adjusted for multiple comparisons. A subgroup of patients from CALGB 9344 were used in an analysis of ER+ patients given tamoxifen compared with ER– patients, adjusted for menopausal status, number of positive axillary lymph nodes and tumour size, and reported for paclitaxel an RR reduction for recurrence of 25 (95% CI 12 to 36) in

TABLE 21 *Disease-free survival by menopausal status or age: docetaxel trials*

Trial	Follow-up (median) (months)	Group	Population subgroup	No.	Breast cancer event or death (No.)	Breast cancer event or death (%)	HR (95% CI)
BCIRG 001	55	DAC6	Premenopausal	830 both groups	NR	NR	0.66 (0.50 to 0.86)
	55	FAC6	Premenopausal				
	55	DAC6	Postmenopausal	661 both groups			0.79 (0.59 to 1.07)
	55	FAC6	Postmenopausal				
PACS 01	59.7	FEC3-D3	Aged <50 years	499	NR	NR	0.98 (0.77 to 1.25)[a]
	59.7	FEC6	Aged <50 years	505			
	59.7	FEC3-D3	Aged 50+ years	504			0.67 (0.51 to 0.88)[a]
	59.7	FEC6	Aged 50+ years	491			
USO 9735	66	DC4	Aged <50 years	210	NR	NR	0.64 (0.38 to 1.04)
	66	AC4	Aged <50 years	214			
	66	DC4	Aged 50+ years	296			0.73 (0.48 to 1.10)
	66	AC4	Aged 50+ years	296			

[a] Adjusted for age, nodes, tumour size, hormone receptors and SBR grade.

TABLE 22 *Disease-free survival by hormone receptor status: paclitaxel trials*

Trial	Follow-up (median) (months)	Group	Hormone receptor status	Relative risk reduction (95% CI)
NSABP B28	64.4	AC4-P4	HR+ (ER+ and/or PR+)	0.77 (0.65 to 0.92), $p = 0.004$
	64.8	AC4	HR+ (ER+ and/or PR+)	
	64.4	AC4-P4	HR–	0.90 (0.72 to 1.12), $p = 0.33$
	64.8	AC4	HR–	

TABLE 23 *Time to recurrence by hormone receptor status: paclitaxel trials*

Trial	Follow-up (median) (months)	Group	Hormone receptor status	HR (95% CI)
CALGB 9344	69	AC4-P4	HR+ (ER+ and/or PR+)	0.91 (0.78 to 1.07)
	69	AC4	HR+ (ER+ and/or PR+)	
	69	AC4-P4	HR–	0.72 (0.59 to 0.86)
	69	AC4	HR–	

1281 ER– patients, and RR 12 (95% CI –3 to 25) in 1784 ER+ patients.[69]

Three of the paclitaxel trials also considered hormone receptor status in relation to overall survival. NSABP B28 reported non-significant RR reductions for death from any cause, for HR+ (ER+ and/or PR+) patients, RR 0.94 (95% CI 0.74 to 1.21), $p = 0.64$, and for HR– patients, RR 0.90 (95% CI 0.70 to 1.17), $p = 0.44$. HCOG reported HRs for the control group, with reference to the paclitaxel group. There was a non-significant HR 0.96 (95% CI 0.62 to 1.50), $p = 0.87$, for HR+ patients, whereas for HR– patients a beneficial effect of paclitaxel was reported, HR 2.42 (95% CI 1.17 to 4.99), $p = 0.02$. The CALGB 9344 subgroup analysis reported the reduction in RR of paclitaxel was 24 (95% CI 10 to 37) for ER– patients, and RR 11 (95% CI –8 to 26) for ER+ patients given tamoxifen.[69]

Adverse event data

Deaths due to toxicity are shown in *Tables 24* and *25*.

TABLE 24 *Treatment-related deaths: docetaxel trials*

Trial	Follow-up (median) (months)	Group	*N*	Deaths (treatment related) (No.)	Deaths (treatment related) (%)	Deaths (treatment related) (details)
BCIRG 001	55	DAC6	745	2	0.27	1 PE (within 30 days of treatment); 1 cardiac death (>30 days after last treatment cycle)
	55	FAC6	746	3	0.40	1 PE (within 30 days of treatment); 2 cardiac deaths (>30 days after last treatment cycle), both after relapse/second cancer
ECOG 2197	59	DA4	1444	4	0.28	NR
	59	AC4	1445	0	0	
PACS 01	59.7	FEC3-D3	1001	1	0.10	1 cardiac death
	59.7	FEC6	995	1	0.10	1 cardiac death
USO 9735	66	DC4	506	2	0.40	1 cardiac; 1 neutropenic sepsis
	66	AC4	510	0	0	
GEICAM 9805	24	DAC6	530	NR	NR	NR
	24	FAC6	520	NR	NR	NR
RAPP 01	24	DA4	311	2[a]	0.64	1 intestinal obstruction, febrile neutropenia and suspected mesenteric infarction; 1 febrile neutropenia, septic shock and multiorgan failure
	24	AC4	316	0	0	

PE, pulmonary embolism.
[a] 1 additional patient required major surgery for perforative peritonitis and septic shock, but did not die from this toxicity.

With the exception of the RAPP 01 trial, rates of treatment-related deaths ranged from 0 to 0.4%. Overall there were slightly more deaths from toxicity in the taxane-containing arms (17/8829) than in the control arms (11/8819). Cardiac and thromboembolic deaths occurred in taxane and control arms. Neutropenia caused three deaths in patients taking docetaxel and hypersensitivity reaction to paclitaxel caused one death.

Reported AEs are detailed in Appendix 3, comprising haematological, gastrointestinal, neurological, cardiotoxicity and other AEs.

Docetaxel

Docetaxel was associated with significantly more febrile neutropenia/neutropenic fever: DAC6 compared with FAC6 (BCIRG 001); FEC3-D3 during D administration compared with FEC6 (PACS 01); DC4 compared with AC4 (USO 9735); and DE6 compared with FEC6 (PACS 04) (although there was less low-grade neutropenia in the docetaxel groups of trials BCIRG 001 and PACS 01). Significantly more neutropenia was found in DA4 compared with AC4 (RAPP 01). Other haematological AEs occurring significantly more frequently in DAC6 than FAC6 were thrombocytopenia, anaemia and the need for blood transfusions (BCIRG 001).

Docetaxel was associated with significantly less nausea and vomiting or high-grade nausea/vomiting: DAC6 compared with FAC6 (BCIRG 001); FEC3-D3 during docetaxel administration compared with FEC6 (PACS 01); DC4 compared with AC4 (USO 9735); DA4 compared with AC4 (RAPP 01); and DE6 compared with FEC6 in PACS 04. Docetaxel was associated with significantly more stomatitis, DAC6 compared with FAC6 (BCIRG 001), FEC3-D3 compared with FEC6 (PACS 01), and significantly more mucositis or high-grade mucositis, DAC6 [without granulocyte colony-stimulating factor (G-CSF)] compared with FAC6 (GEICAM 9805) and DA4 compared with AC4 (RAPP 01). Docetaxel was associated with significantly more

TABLE 25 *Treatment-related deaths: paclitaxel trials*

Trial	Follow-up (median) (months)	Group	*N*	Deaths (treatment related) (No.)	Deaths (treatment related) (%)	Deaths (treatment related) (details)
NSABP B28	64.4	AC4-P4	1531	2	0.13	1 coronary artery disease; 1 PE
	64.8	AC4	1528	5	0.33	1 PE; 2 CHF; 1 sepsis; 1 seizure
CALGB 9344	69	AC4-P4	1570	2	0.13	1 hypersensitivity reaction; 1 brain infarction
	69	AC4	1551	1	0.06	1 death during AC therapy (not necessarily control group) respiratory and cardiac failure
HCOG	61.7	E3-P3-CMF3	298	0	0	
	62	E4-CMF4	297	0	0	
GEICAM9906	46	FEC4-P8	610	2	0.33	2 myocardial infarction/sudden death of possible cardiac origin
	46	FEC6	633	1	0.16	1 myocardial infarction/sudden death of possible cardiac origin
Elling phase II	?	EC4-P4	15	0	0	
	?	EC4	13	0	0	
MIG 5	92% of patients more than 12 months	PE4	268	0	0.00	
	92% of patients more than 12 months	FEC6	265	0	0	

CHF, congestive heart failure.

diarrhoea or high-grade diarrhoea: DAC6 compared with FAC6 (BCIRG 001); DAC6 without GCSF compared with FAC6 (GEICAM 9805); and DA4 compared with AC4 (RAPP 01).

There were significantly more neurosensory effects in the DAC6 group compared with the FAC6 group (BCIRG 001). BCIRG 001 reported significantly more mild to severe congestive heart failure for DAC6 as compared with FAC6. However, PACS 01 reported significantly less cardiotoxicity for FEC3-D3 compared with FEC6.

Nail disorders were more prevalent in docetaxel: DAC6 compared with FAC6 (BCIRG 001); and FEC3-D3 during docetaxel administration compared with FEC6 (PACS 01). BCIRG 001 also reported significantly more skin toxicity in the docetaxel group.

Docetaxel was associated with significantly more chemotherapy-related amenorrhea: DAC6 compared with FAC6 (BCIRG 001); and DA4 compared with AC4 (RAPP 01). Docetaxel was associated with significantly more arthralgia, myalgia or asthenia: DAC6 compared with FAC6 (BCIRG 001); DC4 compared with AC4 (USO 9735); and DAC6 without G-CSF compared with FAC6 (GEICAM 9805). Oedema was more common in DAC6 compared with FAC6 (BCIRG 001); FEC3-D3 during docetaxel administration compared with FEC6 (PACS 01); DC4 compared with AC4 (USO 9735).

RAPP 01 reported a significant difference of more total serious AEs in DA4 compared with AC4. BCIRG 001 also reported significantly more allergy, infection and grade 3/4 severe non-haematological AEs in DAC6 compared with FAC6.

Paclitaxel
Few significance values were reported for AEs in the paclitaxel trials. HCOG reported significantly more peripheral neuropathy and hypersensitivity reaction in the paclitaxel group: E3-P3-CMF3 compared with E4-CMF4. HCOG also recorded that, regardless of treatment group, older patients (aged 65 years and over) had a significantly higher incidence of severe toxicities.

Health-related quality of life data
HRQoL data were reported for three docetaxel trials, BCIRG 001, TACT and GEICAM 9805, and one paclitaxel trial, HCOG.

Docetaxel
BCIRG 001 assessed HRQoL data with the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ) C30 version 2.0 and QLQ specific to breast cancer, BR23 version 1.0, which are validated scales.[79] The groups DAC6 and FAC6 were balanced at baseline. Both groups' scores worsened during treatment, with the DAC6 group having a significantly larger decline on the Global Health Status and Physical Functioning dimensions. There was no significant difference between groups, with both groups recovering, by 3–4 weeks after the last cycle of treatment. There continued to be no significant difference between groups at 6, 12 and 24 months after treatment.

TACT reported HRQoL before randomisation and after the last (eighth) cycle of chemotherapy, using EORTC QLQ-C30 and BR23, and also the Hospital Anxiety and Depression Scale (HADS) questionnaire, which has been validated.[80] Global quality of life (QoL) was statistically significantly worse for the docetaxel group (FEC4-D4) compared with the FEC8 control group ($p = 0.002$), although not compared with the E4-CMF4 group ($p = 0.18$). Physical functioning was statistically significantly worse for the docetaxel group compared with both control groups (FEC8 group, $p = 0.007$; E4-CMF4 group, $p = 0.003$). However, the differences in these domains were not considered clinically relevant (the differences were less than 10 points).

GEICAM 9805 administered EORTC QLQ-C30 at baseline, after each therapy cycle and 6, 12 and 24 months post-treatment. For those patients in the docetaxel group (DAC6) not receiving concomitant G-CSF, HRQoL was significantly worse than for those in the FAC6 group during chemotherapy (maximum difference of 8.0 points during cycle 4, $p = 0.008$). HRQol did not differ significantly between FAC6 group and patients in the DAC6 group receiving GCSF (maximum difference of 6.1 points during cycle 3). Post-treatment follow-up found no significant differences between groups.

Paclitaxel
HCOG reported HRQoL measured with EORTC QLQ-C30 in a subgroup of patients: 72 in the paclitaxel group (E3-P3-CMF3) and 67 in the control group (E4-CMF4). There was no significant difference between paclitaxel and control groups at baseline or at end of chemotherapy. Comparison of baseline and end of chemotherapy mean scores within each group found social functioning significantly worsened in the paclitaxel group only ($p = 0.003$), whereas only the control group showed significant improvement in the emotional functioning ($p = 0.031$) and pain ($p = 0.007$) domains.

Discussion

Quality of trials
None of the trials blinded patients or physicians to treatment allocation, which would have been impossible due to different numbers of treatment cycles, times of administration and the potential need for dose modifications due to treatment-related toxicity. None of the trials had blinding of outcome assessors. This may have been difficult in the context of large, multi-site trials; however, failure to blind outcome assessors could have introduced bias to the DFS measure (or TTR), for instance by altering the frequency of unscheduled check-ups. Method of randomisation and allocation concealment schedule were not made clear in many of the trial reports (Appendix 2). Trials showed a high rate of compliance with therapy (Appendix 3). Intention-to-treat (ITT) or analyses including 80% or more of the randomised population were available in all trials reporting effectiveness data (Appendix 2).

Generalisability
One docetaxel trial (BCIRG 001) and two paclitaxel trials (CALGB 9344, Elling Phase 2) used taxanes in accordance with current UK marketing authorisation, although two additional paclitaxel trials (NSABP B28 and GEICAM 9906) used paclitaxel in line with the licensed regimen but at different dose and/or frequency from those recommended in marketing authorisation. Paclitaxel is licensed sequentially;[25] one trial used paclitaxel concurrently with an anthracycline (ECTO). Docetaxel is licensed in combination with AC; five trials used docetaxel sequentially (PACS 01, one trial arm of BIG 2-98, Taxit 216, TACT and GOIM 9902).

Comparators used by most of the trials restrict the generalisability of results, as they do not conform to current standard care in the UK, either through having too few cycles of chemotherapy (ECOG 2197, USO 9735, RAPP 01, NSABP B28, CALGB 9344, Elling Phase 2) or using doxorubicin instead of the more widely employed epirubicin (BCIRG 001, BIG 2-98, GEICAM 9805, ECTO). Seven trials used comparators which may be considered current UK practice, of which three (TACT, PACS 04, MIG 5) have not yet reported effectiveness data. Four trials with adequate comparators had reported effectiveness data; two docetaxel trials (PACS 01, Taxit 216) and two paclitaxel trials (HCOG, GEICAM 9906). Thus, only one trial, GEICAM 9906, could be said to have an adequate comparator for UK practice and also be broadly in line with UK marketing authorisation, although the intervention did not comply with recommended dose or frequency of paclitaxel administration. At the time of publishing this review, only an interim analysis of GEICAM 9906 was available.

Effectiveness

Heterogeneity of interventions, comparators and populations precluded meta-analysis. Interventions differed in dose, frequency and place in schedule of taxane, and also constituent medications of chemotherapy. There were also differences in the use of prophylactic medication, endocrine therapy and radiotherapy.

Overall survival

Reported OS rates ranged from 77 to 92% in trials with a median follow-up of 55 months or more. Given an expected 5-year survival of 75% for Stage II patients and 90% for Stage I patients, the trial OS rates were fairly high, which may reflect a high proportion of patients with good prognosis in trials, or the fact that none of the trials included patients aged over 70 years.

Significant improvements in OS were reported for DAC6 over FAC6 (BCIRG 001), FEC3-D3 over FEC6 (PACS 01) and AC4-P4 over AC4 (CALGB 9344). HCOG reported a significant difference in OS between E3-P3-CMF3 and E4-CMF4; however, this trial did not find a difference in DFS/TTR between the two treatment arms, suggesting that any difference in OS was the result of chance, particularly given the small sample size. Other trials reported similar OS in treatment and comparator arms. The direction of effect did not favour the non-taxane comparator for any of the trials.

Disease-free survival or time to recurrence

Reported DFS rates ranged from 65 to 86% in trials with a median follow-up of 53 months or more. DFS or TTR, where reported, was reported to be significantly improved in the taxane group, compared with control group, for all trials except for ECOG 2197, the concurrent taxane comparison of BIG 2-98, Taxit 216 (although the HR just reached significance when adjusted on hormone receptor, nodal and menopausal status) and HCOG. None of the trials reported worsened DFS/TTR for the taxane group compared with the control group. ECOG 2197 reported similar DFS rates in the DA4 and AC4 groups and HCOG reported similar TTR and estimated DFS in the E3-P3-CMF3 and E4-CMF4 groups. The direction of effect did not favour the non-taxane comparator for any of the trials. ECOG 2197 had a relatively high rate of DFS in both arms, and included many N–ve patients, relatively small tumours and mostly HR+ patients. The AC4 group of ECOG 2197 had a slightly higher DFS rate than the AC4 group in the USO 9735 trial, although the DFS rate was high in both trials. HCOG had mostly N+ve, HR+ patients and a relatively low DFS rate in both treatment arms.

Higher survival rates than other docetaxel trials were found for ECOG 2197 and USO 9735, trials which had around 65 and 48% N–ve patients, respectively, whereas in BCIRG 001, PACS 01 and Taxit 216 all patients were N+ve and trials had lower survival rates. GEICAM 9906 had seemingly higher survival rates than other paclitaxel trials; however, this was an interim analysis and therefore had a shorter follow-up period (46 months) than other studies.

NSABP B28 and CALGB 9344 had seemingly similar comparisons, but NSABP B28 used a higher dose of paclitaxel (225 rather than 175 mg/m^2), with higher compliance in CALGB 9344 (see Appendix 3, table 'Paclitaxel – available data on treatment completion or relative dose intensities', p. 93), and in CALGB 9344 patients were randomised to one of three different doses of doxorubicin. There was also a difference in timing of tamoxifen therapy. A significant difference in OS was reported by CALGB 9344 but not by NSABP B28. NSABP B28 reported a higher survival rate, although it had a shorter follow-up period than CALGB 9344. The population of NSABP B28 had a relatively higher proportion of patients aged 60 years or above, with smaller tumour size, and with less nodal involvement than CALGB 9344 (see *Table 10*, p. 20).

Differences in comparator arms make it difficult to compare docetaxel and paclitaxel in terms of clinical effectiveness. It seems there was a slight advantage of docetaxel over paclitaxel in improving DFS. It is not clear whether this was due to docetaxel being administered concurrently and paclitaxel being administered sequentially to anthracyclines. A trial not included in this review (E1199) found that there was no significant difference in DFS for sequential docetaxel compared with sequential paclitaxel. However, BIG 2-98 reported no significant difference in DFS for docetaxel administered concurrently versus sequentially.

Subgroups

Subgroup analyses were based on small sample sizes, but suggested a significant improvement of docetaxel for patients with 1–3 positive nodes, but less of a treatment effect for patients with ⩾4 positive nodes. Only one study, USO 9735, reported on an N–ve subgroup, with a non-significant reduction in DFS for the docetaxel group; this was based on only 487 patients and the HR had a large CI. None of the paclitaxel trials reported nodal subgroup data.

HRs for taxane versus comparator for DFS were lower for HR– than for HR+ patients in BCIRG 001 and USO 9735; however, HR+ and HR– patients showed a significant improvement with DAC6 compared with FAC6 (BCIRG 001). ECOG 2197 considered oestrogen receptor and progesterone receptor status separately, and the only hormone receptor status with a significant treatment effect was ER– PR+, with a very small sample size, suggesting the play of chance.

NSABP B28 reported a significant treatment effect for HR+ but not for HR– patients. Conversely, CALGB 9344 found a significant treatment effect for HR– patients but only borderline significance for HR+ patients. However, neither trial reported a significant interaction between hormone receptor status and treatment effect, and in both trials point estimates suggest a treatment benefit for HR+ and HR– subgroups. The trials differed in treatment of HR+ patients – both trials prescribed tamoxifen, but NSABP B28 started tamoxifen administration at the start of chemotherapy, whereas CALGB 9344 patients did not receive tamoxifen until after completion of chemotherapy. Sequential tamoxifen following chemotherapy has been reported to lead to better DFS rates than concurrent tamoxifen.[81]

None of the trials reported data on combinations of subgroups, for example hormone receptor status and nodal status, possibly because this would have meant small sample sizes. Information on treatment effect according to prognostic status would have been useful. There are likely to be other potential influencing factors for the taxanes that future trials may need to take into account. Taxanes may have a synergistic action with trastuzumab, or their effect may be more marginal when added to trastuzumab. Mutant p53, expressed by a higher proportion of ER– than ER+ tumours,[18] may predict sensitivity to taxanes.[82]

Adverse events

The RAPP 01 trial was terminated due to deaths from toxicity; two patients who had received docetaxel died with febrile neutropenia. Docetaxel was also associated with severe gastrointestinal toxicity. The trialists recommended prophylactic G-CSF and/or antibiotics when DA is used in future. Docetaxel was associated with more febrile neutropenia/neutropenic fever than control groups. G-CSF use was found to reduce adverse effects of DAC6 in the trial GEICAM 9805.

Reporting and incidence of AEs were not consistent across trials. In addition to neutropenia, other AEs occurring more frequently in docetaxel than control groups were thrombocytopenia, anaemia, need for blood transfusions, stomatitis, mucositis, diarrhoea, neurosensory effects, nail disorders, skin toxicity, chemotherapy-related amenorrhea, arthralgia, myalgia, asthenia, oedema and infection. Docetaxel was associated with significantly less nausea and vomiting.

Significantly more mild to severe congestive heart failure (although not for grade 3 and above) was reported for DAC6 as compared with FAC6 (BCIRG 001); however, significantly less cardiotoxicity was reported for FEC3-D3 compared with FEC6 (PACS 01). For other trials reporting cardiac AEs, there were no differences between taxane and non-taxane arms.

Paclitaxel was associated with significantly more peripheral neuropathy and hypersensitivity reaction when E3-P3-CMF3 was compared with E4-CMF4 (HCOG). Fewer significant differences in AEs were reported in paclitaxel trials than in docetaxel trials. Because of the differences in study design, it is not possible to tell from these trials whether there is a difference in taxanes with regard to toxicity, or whether sequential taxanes have a better safety profile than concurrent taxanes. However, a trial not included in this

review (E1199) found docetaxel caused more AEs than paclitaxel when both taxanes were administered sequentially.

Quality of life

There were no differences in HRQoL between taxane and non-taxane groups following completion of chemotherapy.

HRQoL diminished for all groups during chemotherapy. During treatment, BCIRG 001 reported a larger decline in Global Health Status and Physical Functioning during DAC6 treatment than for FAC6. GEICAM 9805 also found a worse effect on HRQoL for DAC6 treatment than FAC6; however, this difference was not present when patients were receiving GCSF with DAC6. TACT did not find any differences considered clinically relevant between the FEC4-D4, FEC8 and E4-CMF4 groups. HCOG reported that at last chemotherapy E3-P3-CMF3 treatment was associated with worsened social functioning and lack of improvement in emotional functioning and pain, compared with E4-CMF4.

Chapter 4

Assessment of cost-effectiveness

This section of the assessment focuses on the health economics of taxanes in early breast cancer in comparison with standard therapies. It includes a review of existing economic evaluations of the relevant therapies and a detailed explanation of the methodologies and results of the independent assessment group economic model.

The next section presents the results of the systematic review of economic literature. The independent assessment group's modelling approach is discussed in the subsequent section, with the results of the analysis being presented in the section 'Independent assessment – results' (p. 48).

Systematic review of existing cost-effectiveness evidence

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

Methods

The literature was searched using the strategy described in the section 'Identification of studies' (p. 9) and filters to identify economic evaluations were utilised on MEDLINE and EMBASE. Published economic evaluations of taxane-containing chemotherapy compared with non-taxane-containing chemotherapy in the adjuvant treatment for early breast cancer were included in the review.

Results

No published economic evaluations of taxanes in early breast cancer were identified. The literature search yielded 510 citations when duplicates had been removed. Of these, 495 were rejected based on their title or abstract and 15 were rejected after the full paper had been considered. The majority of economic evaluations identified by the search related to non-taxane chemotherapy or taxanes in metastatic breast cancer. This literature search confirmed the need for new published economic evaluations in this area.

Independent economic assessment – methods

Objective

The aim of the model is to review the cost-effectiveness of docetaxel and paclitaxel compared with standard therapy in women with early-stage breast cancer eligible to receive anthracycline-based chemotherapy.

Treatment strategies

Taxanes are indicated for the adjuvant treatment of women with early breast cancer eligible to receive anthracycline-based chemotherapy; that is, they are administered following surgical resection in combination with or following anthracycline-based chemotherapy.

Docetaxel (Taxotere; Sanofi Aventis) has a UK marketing authorisation for the adjuvant treatment of patients with operable breast cancer and positive axillary lymph nodes, in combination with doxorubicin and cyclophosphamide. Docetaxel is currently also licensed in the UK for the treatment of other stages of breast cancer and for non-small cell lung cancer.

Paclitaxel has a UK marketing authorisation for the adjuvant treatment of patients with operable and N+ve breast cancer following anthracycline and cyclophosphamide therapy. Adjuvant treatment with paclitaxel should be regarded as an alternative to extended anthracycline and cyclophosphamide therapy. It is manufactured in the UK as Taxol (Bristol-Myers Squibb Pharmaceuticals). Generic paclitaxel is also manufactured by Mayne Pharma and by Teva. Paclitaxel is currently also licensed in the UK for the treatment of other forms of cancer, including other stages of breast cancer, and specific types of ovarian cancer, small-cell lung cancer and AIDS-related Kaposi's sarcoma.

The use of the two taxanes is proposed for the adjuvant treatment of early breast cancer. The current licensed indications are summarised in the

section 'Description of technology under assessment' (p. 4).

Structure of the model

A probabilistic state-transition model has been developed to explore the costs and health outcomes associated with treatment of women with early breast cancer eligible to receive anthracycline-based chemotherapy with or without taxanes.

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 quality-adjusted life year (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. Use of a shorter cycle length would therefore have had little impact on the results. The starting age of patients in the model is 50 years. The model is run for 35 years.

Disease pathway

Around 80% of women with breast cancer present with early disease. The mainstay of treatment for early-stage cancer is surgical removal of the tumour. Adjuvant therapy with chemotherapy agents may be indicated, based on their age and prognosis (typically Stage II, less than 70 years of age). Women are more likely to receive chemotherapy if the primary cancer in the breast is large or if the lymph nodes contain breast cancer cells. The aim of adjuvant therapy is to kill off any cancer cells that have broken away from the tumour in the breast and spread before it was removed. It therefore reduces the risk of the cancer coming back. Eligible patients (patients with HR+ tumours) should also receive 5 years of treatment with hormonal therapy. Patients may remain disease free until they die with no evidence of cancer, experience a relapse (locoregional 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. Those patients experiencing a locoregional relapse receive further treatment [surgical resection if the disease is operable, further chemotherapy plus radiotherapy (if radiotherapy-naive) and hormonal therapy (if eligible)]. They may 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 to 2 years, although there is wide variation between patients, depending on the distribution and extent of metastases at presentation. Patients experiencing a metastatic relapse receive active palliative treatment to control symptoms and improve QoL, 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. There are seven health states within the model:

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

The model pathways are shown in *Figure 2*. All patients start in the DFS state and remain in this state unless they experience relapse or contralateral disease or die from other causes.

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) locoregional relapse
   (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. Locoregional relapse
   Patients can move to
   (a) remission
   (b) metastatic relapse
   (c) death from other causes.

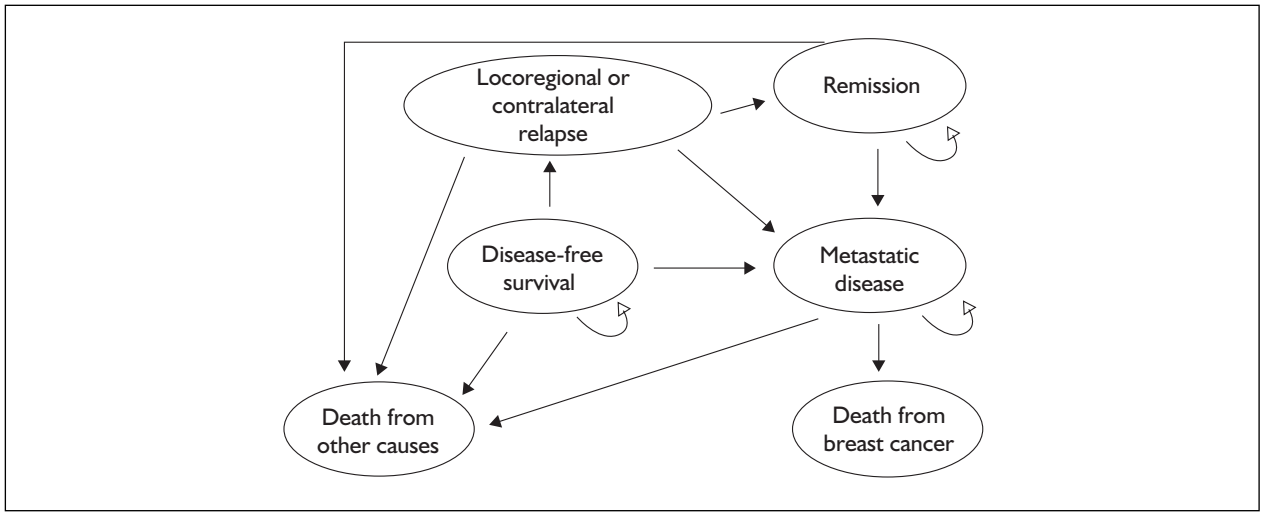

FIGURE 2 *Treatment pathways in the ScHARR model*

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 locoregional recurrence states for one cycle (1 year) only. They 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 locoregional recurrence 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 it 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 locoregional recurrence 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 taxanes may be slightly overestimated.

Trial evidence suggests that there is a high rate of compliance with therapy and few withdrawals were reported. Patients withdrawing from treatment due to AEs are assumed not to switch treatments.

Model assumptions

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

- A constant HR for recurrence during duration of trial period (which includes the period of treatment and the median duration of follow-up).
- In the base-case analysis, we assume that the risk of recurrence is equal in the taxane and comparator arms (in other words, HR = 1 for the treatment arm) after the trial period. This may underestimate the benefit in women with less aggressive tumours whose tumours recur after 5 years, although there is no evidence of benefit in these patients so far. Therefore, a sensitivity analysis is carried out assuming continued benefit up to 10 years.
- Long-term risk of recurrence is extrapolated from the available trial data using a parametric survival model. This is compared with 15-year survival rates from the EBCTG overview to assess whether this extrapolation is reasonable.
- Following contralateral disease or locoregional relapse, patients cannot experience further locoregional relapse, they can only experience metastatic relapse.
- 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 breast cancer but are in remission after 15 years are assumed to be cured. This is modelled by assuming that they remain in the disease-free state but are subject to the population level of mortality.
- Death from breast cancer can only occur following progression to metastatic relapse. However, patients may progress into the metastatic state and on to the death from breast cancer state within a single cycle length as this is possible during the 1-year cycle length.
- Death rates for non-breast cancer causes are based on UK mortality statistics and applied across all health states. These are not adjusted to exclude breast cancer mortality, and may overestimate the risk of dying due to non-breast cancer causes.

Clinical data

The ideal source of effectiveness data for populating the health economic model would be an RCT where the intervention has been used within its current UK marketing authorisation and the comparator is representative of current standard practice in the UK. Only one trial was identified which met both these criteria (GEICAM 9906), but it was not possible to populate the model based on this study as there was only an interim analysis available.

The next best available evidence came from those trials using taxanes within their licensed indication but with comparators that do not represent UK standard practice. One docetaxel trial (BCIRG 001) and two paclitaxel trials (CALGB 9344, Elling Phase 2) were identified which used taxanes in line with their current marketing authorisation and one further paclitaxel trial was identified which used paclitaxel within its licensed indication but at a different dose from that recommended in marketing authorisation ((NSABP B28). The model could not be populated using data from the Elling Phase 2 trial as it has not presented any effectiveness data. The model has therefore been populated using data from the BCIRG 001, NSABP-B28 and CALGB 9344 trials. All three trials were restricted to patients who were N+ve. These trials have been used independently as heterogeneity between these trials precluded meta-analysis.

The BCIRG 001 trial compared six 3-weekly cycles of DAC with six 3-weekly cycles of FAC. The NSABP B28 and CALGB 9344 trials both compare four 3-weekly cycles of AC followed by four 3-weekly cycles of P with four 3-weekly cycles of AC alone. The CALGB 9344 trial is slightly complicated by the use of three different doses of anthracycline in both the taxane and comparator arms, but as the anthracycline dose was not significantly related to either the hazard of recurrence or death we have combined the data to give one estimate of effectiveness regardless of dose.

Transition probabilities from disease-free survival

The rate of recurrence from the disease-free state is taken from the comparator arms in the relevant trials shown above. The HR from the relevant trial is applied to the recurrence rate in the comparator arm to derive the overall recurrence rate in the treatment arm.

Recurrences are modelled as either locoregional/contralateral or metastatic. The probability that a recurrence is a local recurrence, contralateral disease or a metastatic recurrence is taken directly from the distribution of recurrences in the relevant trial arm.

A table summarising the key clinical parameters from these trials used in the ScHARR analysis is included in Appendix 5.

Extrapolation of DFS curves

The maximum length of follow-up in the taxane trials to date is 69 months. The costs and benefits of treatment with taxanes will, however, extend over a patient's lifetime. It is therefore necessary to extrapolate the clinical data well beyond the trial period.

DFS curve for patients in the comparator arm

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; however, for patients with less aggressive disease, relapses may well come later.

Within the model, the recurrence curve for the comparator arm was extrapolated by fitting a parametric model to the DFS Kaplan–Meier graphs reported in the relevant trial. A more

detailed explanation of the methodology used to extrapolate the DFS is given in Appendix 6.

It is assumed that patients who have remained in the DFS state for up to 15 years are cured and have the same risk of death due to breast cancer as the general population.

DFS curve for patients on taxanes
HRs from the trials are applied to the event rates in the comparator arm to estimate event rates in the taxane arm. A key assumption within the model is what happens to the event rates in the two arms beyond the trial data.

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

- In the base-case analysis, it is assumed that the HR for recurrence between the taxane and the comparator arms is constant during the first 5 years, the current follow-up period for the majority of trials. After the first 5 years, the HR is assumed to be unity for all subsequent periods, giving parallel survival curves in the taxane and comparator arms. In this scenario, the benefits of taxanes achieved during the trial period are preserved, with no difference in the rates of recurrence between the two arms after the period of trial follow-up.
- In the sensitivity analysis of continued benefit, it is assumed that the HR for recurrence between the taxane and the comparator arms is constant for 10 years. In this scenario, the benefits of taxanes are continued allowing the DFS curves to continue to diverge for 10 years.

Transition probabilities from contralateral disease and locoregional relapse

Patients who experience a locoregional relapse 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 TTR. Kamby and Sengelov[83] 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 locoregional recurrence. Moran and Haffty[84] present survival and metastases-free survival data for patients diagnosed with locoregional recurrence. With a median follow-up of 14 years, the 10-year distant metastasis-free rate was 59%. A paper by Abner and colleagues[85] 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.

Progression to metastases in the ScHARR model was based on the study by Kamby and Sengelov,[83] which had the longest follow-up period.

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.[86] 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 may lead to differences in the survival and costs estimates between the treatment arms.

Resource use and costs

The model follows a health service perspective and only direct medical costs are included. All costs are adjusted to 2005–6. Costs are discounted at a rate of 3.5% in line with current guidance from HM Treasury.[87]

Chemotherapy costs

The drug costs for each chemotherapy regimen were calculated using the doses given in the trials, except for the CALGB 9344 trial, where several doses of doxorubicin were given but no dose effect was seen. For this trial we assumed that the lowest dose of doxorubicin would be given, as there is no evidence that a higher dose provides additional benefits.

In calculating the drug costs for each regimen, we assumed that unused drugs in open vials would be wasted and an average surface area of 1.8m^2. The drugs costs used in the model are summarised in *Table 26*. All drug costs are taken from the BNF.[88] Patients in the docetaxel arm of the BCIRG 001 trial received dexamethasone and ciprofloxacin to prevent hypersensitivity reactions and patients in the paclitaxel arm of NSABP-B28 received dexamethasone diphenhydramine and cimetidine or ranitidine before each paclitaxel cycle. These additional medication costs (£7.00 and £4.53 per cycle, respectively) were included in the model for each of these trials using the doses given in the trial and unit costs from the BNF.[88]

TABLE 26 *Drug costs for chemotherapy by trial arm*

Trial	Arm	Drug	Dose (mg/m^2)	Dose (mg/patient)	Vial size and strength	Price per vial (£)	Cost per cycle (£)	Total cost (£)
BCIRG 001	FAC6	F	500	900	1 × 20 ml of 50 mg/ml	12.80	12.80	1343.04
		A	50	90	2 × 25 ml of 2 mg/ml	103.00	206.00	
		C	500	900	1 × 1000 mg	5.04	5.04	
	DAC6	D	75	135	3 × 0.5 ml + 1 × 2 ml of 40 mg/ml	162.75 for 0.5 ml/534.75 for 2 ml	1023.00	7450.80
		A	50	90	2 × 25 ml of 2 mg/ml	103.00	206.00	
		C	500	900	1 × 1000 mg	5.04	5.04	
NSABP B28	AC4	A	60	108	3 × 25 ml of 2 mg/ml	103.00	309.00	1267.68
		C	600	1080	1 × 1000 mg and 1 × 500 mg	5.04 for 1 g/2.88 for 0.5 g	7.92	
	AC4+P4	A	60	108	3 × 25 ml of 2 mg/ml	103.00	309.00	7102.08
		C	600	1080	1 × 1000 mg and 1 × 500 mg	5.04 for 1 g/2.88 for 0.5 g	7.92	
		P	225	405	1 × 5 ml + 1 × 16.7 ml + 1 × 50 ml of 6 mg/ml	112.20 for 5 ml/336.60 for 16.7 ml/1009.80 for 50 ml	1458.60	
CALGB 9344	AC4	A	60	135	3 × 25 ml of 2 mg/ml	103.00	309.00	1267.68
		C	600	1080	1 × 1000 mg and 1 × 500 mg	5.04 for 1 g/2.88 for 0.5 g	7.92	
	AC4+P4	A	60	135	3 × 25 ml of 2 mg/ml	103.00	309.00	5755.68
		C	600	1080	1 × 1000 mg and 1 × 500 mg	5.04 for 1 g/2.88 for 0.5 g	7.92	
		P	175	315	1 × 5 ml + 1 × 50 ml of 6 mg/ml	112.20 for 5 ml/1009.80 for 50 ml	1122.00	

Administration costs, given in *Table 27*, were based on resource use estimates from Avon, Somerset and Wiltshire Cancer Services (ASWCS) Drug Policy Forum (Hodgetts and Raffle,[89] 2001, costs uplifted to 2005 prices) which gives the pharmacy, nursing time and consumable costs for various chemotherapy regimens. The cost of nursing time given by Hodgetts and Raffle did not seem to be sufficient to account for all the costs incurred by a patient attending to receive chemotherapy. Where time spent in the department has been estimated to be over 3 hours, which was only the case for paclitaxel, it has been assumed that patients incur the cost of chemotherapy as a day case (£285).[90] Otherwise, patients attending for chemotherapy are assumed to incur the costs of a medical oncology outpatient appointment (£129).[90] This publication did not consider DAC as a single regimen, so the administration cost for this regimen was estimated by combining the pharmacy and consumable costs of D alone and AC but assuming that the DAC regimen can by given in a single outpatient appointment. In addition, it was assumed that a full blood count (£3.13) and liver function test (£6.87) were required before each chemotherapy cycle.

Resource use and costs – health states

Disease-free survival

Patients are assumed to receive one clinic visit after their last chemotherapy cycle. Current clinical practice is for routine follow-up to continue for 5 years. NICE guidelines[1] suggest that routine follow-up should be stopped at 3 years. In the base-case analysis we assume six monthly visits for 2 years and annual visits in years 2–5. A sensitivity analysis is carried out to assess the impact of reducing follow-up duration to

TABLE 27 *Administration costs for chemotherapy by trial arm*

Regimen	Resource use[a] and cost per cycle (£)						Total costs per regimen (£)
	Pharmacy technician time (at £11.78 per hour + 12% employment costs)	**Pharmacist time (at £16.16 per hour + 12% employment costs)**	**Clinic time £285 if over 3 hours and £129 if under 3 hours**	**Consumables**	**Blood tests**	**Total costs per cycle**	
FAC6	30 minutes = 6.60	10 minutes = 3.02	129	3.21	10	151.83	910.98
DAC6	40 minutes for D + 20 minutes for AC = 13.20	10 minutes for D + 5 minutes for AC = 4.52	129	3.21 for AC + 10.58 for D	10	170.51	1023.06
AC4	20 minutes = 4.40	5 minutes = 1.51	129	3.21	10	148.12	592.48
P4	30 minutes = 6.60	10 minutes = 3.02	285	10.58	10	315.20	1260.80

[a] Resource use taken from Hodgetts and Raffle[89] and uplifted to 2006 prices.

TABLE 28 *Annual costs of hormonal therapy*

	Pack price (£)	No. of tablets	Cost per day (£)	Cost per annum (£)
Tamoxifen 20 mg	2.24 (generic) 8.71 (branded)	30 30	0.075 0.29	32.27
Anastrazole	68.56	28	2.45	893.73
Exemestane	88.80	30	2.96	1080.40
Letrozole	83.16	28	2.97	1084.05
Average for AI				1019.39
Average for hormonal therapy assuming 50% receive tamoxifen and 50% receive AI				525.83

AI, aromatase inhibitor.

3 years. It is assumed that all patients receive three mammograms in the first 5 years after treatment (annually for those patients treated with wide local excision and once every 2 years for those treated with mastectomy), at a cost per mammogram of £122 (NHS Reference Costs 2003 HRG code J32 op).[91] This cost was uplifted to 2006 prices.[92]

It is assumed that 81% of patients receive endocrine treatment. It is assumed that 50% of patients are on aromatase inhibitors and 50% on tamoxifen. It is expected that the proportion of patients on aromatase inhibitors will increase over time following the positive NICE recommendation in June 2006. The average cost of endocrine therapy, shown in *Table 28*, is used in both arms.

Locoregional recurrence and contralateral disease

Cost of diagnosis of recurrence/contralateral disease

The cost of diagnosis of locoregional recurrence or contralateral disease is shown in *Table 29*. Assumptions regarding the proportion of patients undergoing tests were based on expert clinical opinion.

Cost of treatment of recurrence/contralateral disease

After locoregional/contralateral recurrence, surgery, endocrine and radiotherapy treatment is assumed to be equivalent in the taxane and comparator arms whereas chemotherapy is assumed to vary depending on the regimen used to treat the primary tumour.

- *Surgery*

An average cost figure for surgery for local recurrence or contralateral recurrence is derived, based on the average cost of the major procedures, taken from NHS Reference Costs 2005,[90] identified in *Table 30*.

Based on expert clinical opinion, it is assumed that 90% of patients are treated with surgery, as some patients will be considered inoperable. Lymph dissection procedures are only appropriate for patients with recurrence in the axilla or patients presenting with contralateral disease.

- *Radiotherapy*

It is assumed that one-third of patients 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 £1880, based on NHS Reference Costs 2005 W15 (complex teletherapy with imaging >12 and <24 fractions).

- *Chemotherapy*

All patients are assumed to receive chemotherapy with one-fifth assumed to receive the same chemotherapy regimen as that given to treat their primary tumour and four-fifths assumed to receive a different regimen. For patients in the comparator arm who did not receive a taxane for their primary tumour, this different regimen is assumed to be a taxane-based regimen. For patients who received a taxane-based regimen for their primary tumour, this second chemotherapy regimen is assumed to be six cycles of either vinorelbine or capecitabine. The cost of a course of vinorelbine (£1282) is taken directly from Hodgetts and Raffle,[89] uplifted to 2006 prices, and the cost of a course of capecitabine (£1859) was calculated from the drug cost and dosing schedule given in the BNF[88] with no administration costs included as capecitabine is an oral drug which can be self-administered.

- *Endocrine therapy*

As in the first 5 years of DFS, it is assumed that 81% of patients receive endocrine treatment with

TABLE 29 *Cost of diagnosis of locoregional recurrence or contralateral disease*

	Proportion treated (%)	Frequency	Unit cost (£)	Total (£)	Sources
Physician visits					
Oncologist	100	2	95	190	NHS Reference Costs 2005 103[90]
Laboratory tests					
FBC, calcium, LFTs, ESR	100	1		12.20	Personal communication, Sheffield Teaching Hospital Trust, 2005–6
Radiological examinations					
Biopsy	90	1	130		NHS Reference Costs 2005 J28 op excision biopsy[90] (adjusted to 2006 prices)
Mammogram	90	1	130		NHS Reference Costs 2003 J25 op intermediate radiology[91] (adjusted to 2006 prices)
Bone scan	90	1	162		NHS Reference Costs 2003 op intermediate radiology[91] (adjusted to 2006 prices)
Liver scan	90	1	128		NHS Reference Costs 2003 J33 op ultrasound scan[91] (adjusted to 2006 prices)
Chest X-ray	100	1	87		NHS Reference Costs 2003 J35 op ultrasound scan[91] (adjusted to 2006 prices)
CT of chest	10	1	186		NHS Reference Costs 2003 J24 op ultrasound scan[91] (adjusted to 2006 prices)
CT of brain	10	1	186		NHS Reference Costs 2003 op ultrasound scan[91] (adjusted to 2006 prices)
CT of abdomen	5	1	186		NHS Reference Costs 2003 J24 op ultrasound scan[91] (adjusted to 2006 prices)
TOTAL				830.77	

CT, computed tomography; ESR, erythrocyte sedimentation rate; FBC, full blood count; LFT, liver function text.

TABLE 30 *Cost of surgery for locoregional recurrence or contralateral disease*

HRG code	HRG label	National average unit cost (£)
J01	Complex breast reconstruction using flaps	4383
J04 and J05	Intermediate breast surgery w/o cc	1407
J11	Lymph dissection procedures	2358
J46 and J47	Total mastectomy w/o cc	2642
Average		2811

w/o cc, without complications

an equal split between tamoxifen and aromatase inhibitors. The average cost of hormonal therapy is shown in *Table 28*.

Cost of remission (following contralateral disease and locoregional recurrence)

This is as for cost of follow-up for patients in the first 5 years of DFS, plus the cost of endocrine therapy, where appropriate.

The impact of an alternative assumption regarding the cost of recurrence/contralateral disease was tested in sensitivity analysis.

Distant recurrence

The choice of regimen depends on the extent and site of the disease, previous treatment experience and the patient's fitness and wishes. A course of chemotherapy should be no more than six cycles.

First-line systemic therapy for advanced or metastatic breast cancer in patients who have received anthracycline-containing chemotherapy for their primary tumour is likely to include taxanes, vinorelbine or capecitabine, although some patients may receive further anthracycline-

based therapy. Patients with ER+ tumours are also eligible for hormonal therapy. Trastuzumab monotherapy should be available as an option for people with metastatic cancer overexpressing HER2 at levels of 3+ who have received at least two chemotherapy regimens. 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 may be considered for people who have not previously had capecitabine in combination therapy or for 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.[93] 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). Remak and Brazil's 2004 paper[93] is based on resource usage in 2002 (costs used in the model have been uplifted to 2006 prices) and may underestimate the proportion of patients on trastuzumab. A sensitivity analysis is carried out to test the model sensitivity to higher costs in both arms due to recent increases in the use of trastuzumab.

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 £3218, based on costs taken from Coyle and colleagues' paper,[94] adjusted to present-day prices. The proportion of home care is assumed to be 20%.

Resource use and costs – adverse events

The most frequent AEs associated with taxanes include neutropenia, mucositis, nausea, muscle pain, alopecia, arthralgia, peripheral neuropathy and anaemia. Docetaxel can also cause skin toxicity and nail disorders.

Only severe or grade 3/4 AEs that are observed to differ significantly in frequency between the treatment groups are modelled. Some AEs were excluded as they overlapped with other AEs. For example, neutropenia and neutropenic infection were not modelled individually due to their overlap with febrile neutropenia (the rate for NCI CTC definition 2.0 rather than the protocol definition was used). Where available, the rate of blood transfusions due to anaemia was modelled rather than anaemia itself. Stomatitis and mucositis were assumed to be equivalent AEs. Grade 3/4 allergic reactions and hypersensitivity reactions were assumed to be equivalent to an anaphylactic reaction. The AEs from the BCIRG 001 trial which met the criteria to be included in the model are given in *Table 31*.

Few significance values were reported for AEs in the paclitaxel trials NSABP-B28 and CALGB 9344. As such, no additional AEs were identified as varying significantly between the taxane and comparator arms. The same AEs were therefore included in the model for the docetaxel and paclitaxel trials so that the results for these two interventions can be compared meaningfully. Many of the adverse event rates reported by the main study publications for these trials[63–69] are reported according to which treatment the patient was receiving when the AE occurred rather than by treatment randomisation to AC4+P4 or AC4 alone. Where these data are the only data available, it was assumed that patients in the AC4 alone arm had the same event rate as seen during treatment with AC4 and patients in the AC4+P4 arm had the event rate seen in patients during treatment with AC4 plus the event rate seen during treatment with P4. However, the manufacturer's submission for the NICE paclitaxel single technology appraisal[95] provided adverse event data for CALGB 9344, presented according to whether the patient was randomised to receive paclitaxel or not, so these data were used where possible. The AE rates used in the model for the NSABP B28 and CALGB 9344 analyses are given in *Table 32*. All AE rates have been sampled from a beta distribution in the probabilistic sensitivity analysis.

AEs were only included in the model if they are associated with significant resource use, QoL decrement or reduced survival. Minor AEs, such as myalgia and asthenia, or less severe AEs were considered to have relatively minor cost and utility implications and were therefore not modelled specifically but were assumed to be included in the utility decrement applied for time spent receiving chemotherapy.

TABLE 31 *Adverse event rates used in the model for docetaxel versus non-taxane comparators*

	FAC6 (%)	DAC6 (%)	Source/comment
Febrile neutropenia	4.4	28.8	BCIRG 001, NCI CTC definition 2.0
Diarrhoea (grade 3/4 or severe)	1.8	3.8	BCIRG 001
Vomiting (grade 3/4 or severe)	7.3	4.3	BCIRG 001
Mucositis (grade 3/4 or severe)	2.0	7.1	BCIRG 001, stomatitis (grade 3/4 or severe)
Need blood transfusion	1.5	4.6	BCIRG 001
Anaphylactic reaction	0.1	1.3	BCIRG 001, allergy (grade 3/4 or severe)

TABLE 32 *Adverse event rates used in the model for paclitaxel versus non-taxane comparators*

	AC4 (%)	AC4+P4 (%)	Source/comment
Febrile neutropenia	0.2	0.4	NSABP B28
Diarrhoea (grade 3/4 or severe)	1.0	1.6	CALGB[95]
Vomiting (grade 3/4 or severe)	7.9	8.8	CALGB[95]
Mucositis (grade 3/4 or severe)	6.2	4.9	CALGB,[95] stomatitis (grade 3/4)
Need blood transfusion	7.7	8.2	CALGB,[95] anaemia (grade 3/4)
Anaphylactic reaction	0.6	2.0	CALGB,[95] hypersensitivity reaction (grade 3/4/5)

It is assumed that a cohort of patients develops the AE during their period of chemotherapy based on the AE rate over the trial period. This approach was taken because all of the AEs considered are assumed to occur immediately as a result of chemotherapy and none are assumed to persist beyond the first year. It is assumed that AEs are mutually exclusive (i.e. a patient developing febrile neutropenia does not experience another AE).

No AEs are associated with a risk of mortality. Evidence from the trials, with the exception of the RAPP 01 trial, showed that treatment-related deaths rate is very low, ranging from 0 to 0.4%. Overall there were slightly more deaths from toxicity in the taxane-containing arms (17) than in the control arms (11). Cardiac and thromboembolic deaths occurred in the taxane and control arms. Neutropenia caused three deaths in patients taking docetaxel and hypersensitivity reaction to paclitaxel caused one death.

The following assumptions were made in the economic model:

- Diarrhoea/vomiting, which is grade 3/4 in severity, is likely to result in a hospital admission to ensure adequate hydration and exclude infection. Assume 3 days' hospital stay.
- Neutropenic sepsis (febrile neutropenia) is likely to require admission and administration of G-CSF for an average of 5 days. Neutropenia (grade 3/4) without infection is not associated with any additional resource use but may cause delays in therapy.
- Any patient experiencing febrile neutropenia is assumed to receive G-CSF (8 days; either 150 μ/m^2/day of lenograstim or 5 μ/kg/day of filgrastim) and oral ciprofloxacin (500 mg × 20 doses) for all subsequent cycles. G-CSF is assumed to be administered by a district nurse in the patient's home.
- Anaphylactic reactions during the administration of chemotherapy are not likely to cause admission but may require the patient to remain in hospital as an outpatient for intensive monitoring and treatment.
- Anaemia (grade 3/4) is treated by blood transfusion at a cost of £775 per transfusion (published estimate of cost of transfusion uplifted to 2005 prices) based on an average of 2.7 units of red blood cells and including hospital stay costs (average length of stay 1 day).
- Mucositis/stomatitis (grade 3/4) requires hospital admission (average 2 days) in order to administer intravenous fluids, pain relief and to treat any infection present.
- None of the AEs listed above are assumed to continue after chemotherapy has finished. Any cardiotoxicity is assumed to be equivalent in both arms in the base case.
- Less severe AEs (grade 1/2) are assumed not to be associated with any additional resource use as they do not require admission and treatment costs are likely to be small.

TABLE 33 *Cost of adverse events*

Adverse event	Unit cost (£)	Source
Neutropenia *Initial costs to manage event* 5 days admission = £364 × 5 = £1820	321	NHS Reference Costs 2005 for non-elective bed day[90]
5 days of G-CSF = 5 × 109.95 = £549.75	109.95	(150 μg/m^2/day of lenograstim at a cost of £67.95 for a 263-μg vial and £42.00 for a 105-μg vial)[88]
Total initial cost = £2155 *Costs of 8 days of prophylactic G-CSF and 10 days of ciprofloxacin on all subsequent cycles* (febrile neutropenia assumed to occur during first cycle) G-CSF = 8 × 109.95 = £879.60		
Ciprofloxacin (500 mg × 20 doses)= 2 × £2.05 = 4.10	2.05	Pack price for 10 doses[88]
District nurse visit to administer G-CSF = 8 × 23 = £184	23	Cost of district nurse home visit from Curtis and Netten 2005[92]
Total cost per subsequent cycle = £1067		
Diarrhoea/vomiting 3 days admission = 3 × 364 = £1092	365	NHS Reference Costs 2005 for non-elective bed day.[90]
Anaphylactic reaction Outpatient monitoring Cost £129	129	NHS Reference Costs 2005 for outpatient follow-up attendance – medical oncology (attendance without treatment)[90]
Anaemia Blood transfusion	774.57	£635 per transfusion (from Varney and Guest[96] based on an average of 2.7 units of red blood cells and including an average hospital stay of 1 day. Uplifted to 2006 prices
Mucositis 2 days admission = 3 × £364 = **£728**	321	NHS Reference Costs 2005 for non-elective bed day[90]

The costs of AEs included in the model are given in *Table 33*.

Long-term adverse events

The current model does not include long-term AEs. However, some AEs associated with polychemotherapy including a taxane and an anthracycline may have long-term implications.[31] The EMEA has highlighted particular concern over cardiotoxicity and severe gastrointestinal toxicity for docetaxel.

Utility data

Utilities associated with health states in the model are given in *Table 34*. 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,[97] which is a comprehensive database of preference weights for various health states sorted by disease areas, and from Tengs and Wallace,[98] which is a systematic review of HRQoL estimates from publicly available source documents.

In line with NICE recommendations, a choice-based technique was used (such as standard gamble and time trade-off) or a generic instrument for obtaining health state values (such as the 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 34* shows also who has elicited those values used to populate the economic model.

TABLE 33 *Cost of adverse events*

Adverse event	Unit cost (£)	Source
Neutropenia *Initial costs to manage event* 5 days admission = £364 × 5 = £1820	321	NHS Reference Costs 2005 for non-elective bed day[89]
5 days of G-CSF = 5 × 109.95 = £549.75	109.95	(150 μg/m^2/day of lenograstim at a cost of £67.95 for a 263-μg vial and £42.00 for a 105-μg vial)[88]
Total initial cost = £2155 *Costs of 8 days of prophylactic G-CSF and 10 days of ciprofloxacin on all subsequent cycles* (febrile neutropenia assumed to occur during first cycle) G-CSF = 8 × 109.95 = £879.60		
Ciprofloxacin (500mg × 20 doses)= 2 × £2.05 = 4.10	2.05	Pack price for 10 doses[88]
District nurse visit to administer G-CSF = 8 × 23 = £184	23	Cost of district nurse home visit from Curtis and Netten 2005[92]
Total cost per subsequent cycle = £1067		
Diarrhoea/vomiting 3 days admission = 3 × 364 = £1092	365	NHS Reference Costs 2005 for non-elective bed day.[90]
Anaphylactic reaction Outpatient monitoring £129	129	NHS Reference Costs 2005 for outpatient follow-up attendance – medical oncology (attendance without treatment)[90]
Anaemia Blood transfusion	774.57	£635 per transfusion (from Varney and Guest[96] based on an average of 2.7 units of red blood cells and including an average hospital stay of 1 day. Uplifted to 2006 prices
Mucositis 2 days admission = 3 × £364 = **£728**	321	NHS Reference Costs 2005 for non-elective bed day[90]

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

The QoL of patients with locoregional recurrence is assumed to be the same as that for patients with contralateral recurrence. A value of 0.74 is applied, which is based on patients with breast cancer who undergo chemotherapy. This value is slightly lower than the only value in Tengs and Wallace[98] corresponding precisely to local recurrence (a value of 0.8, based on standard gamble techniques).

The value of 0.85 for remission relates to a health state 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 our model.

For metastatic disease a value of 0.5 elicited from a clinician is used. Most of the values found in the literature span a range from 0.3 to 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.

All these values are elicited by either patient or clinical experts rather than the general public. Values from the general public are usually

TABLE 34 *Utilities for health states*

Health state	Mean	PSA values	How valued	Who valued	Source
Chemotherapy treatment period for primary tumour	0.74	Beta (α = 1.36, β = 0.48)	TTO	Patients	Tengs and Wallace[98]
Disease-free	0.94	Beta (α = 3.44, β = 0.21)	TTO	Patients	Tengs and Wallace[98]
Contralateral	0.74	Beta (α = 1.36, β = 0.48)	TTO	Patients	Tengs and Wallace[98]
Locoregional recurrence	0.74	As contralateral	As contralateral	As contralateral	As contralateral
Distant metastases	0.5	Beta (α = 2.75, β = 2.75)	TTO	Experts	Tengs and Wallace[98]
Remission (following contralateral recurrence and locoregional recurrence)	0.850	Beta (α = 1.97, β = 0.34)	Rating scale	Clinicians	CEA Analysis, Harvard School of Public Health[97]

PSA, probabilistic sensitivity analysis; TTO, time trade-off.

preferred as these preference weights are used to inform resource allocation, but none were identified in the literature.

Given that the HRQoL in the general population decreases with age, it is important to take this into account in the model. General population utility estimates from Kind and colleagues[99] were applied using a regression analysis of utility versus age. Patients are assumed to enter the model at age 50 years, which is the typical age of patient within the main taxane trials, and with an age-related utility of 0.85. Their utility is estimated to decline each year as their age increases, with a utility loss of 0.04 per 10 years' increase in age. The utilities for all health states are multiplied by this age-related utility value for each year of the model.

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

There is a utility decrement associated with time spent on chemotherapy. A weighted utility is applied to the first year in the model, assuming utility values of 0.74 during the period of chemotherapy and 0.94 for the remainder of the first year. This reflects the impact of AEs on patients' QoL for the period during which they are receiving chemotherapy.

Trial evidence suggests that HRQoL diminished for all groups during chemotherapy. However, there is some indication that the patients in the taxane arm may have a lower QoL than patients in the non-taxane arm in some of the trials. During treatment, BCIRG 001 reported a larger decline in Global Health Status and Physical Functioning during DAC6 treatment compared with FAC6. GEICAM 9805 also found a worse effect on HRQoL for DAC6 treatment compared with FAC6; however, this difference was not present when patients were receiving G-CSF with DAC6. TACT did not find any differences considered clinically relevant between groups FEC4-D4, FEC8 and E4-CMF4. HCOG reported that at last chemotherapy E3-P3-CMF3 treatment was associated with worsened social functioning and lack of improvement in emotional functioning and pain, compared with E4-CMF4. There is, however, no evidence to quantify this impact in terms of utility. It is therefore assumed that utility for patients on the taxane and the non-taxane arms is the same during chemotherapy. This assumption is tested in sensitivity analysis.

It is also assumed that utility for patients on the taxane and the non-taxane arms is the same after completion of chemotherapy. This is supported by the trial evidence, which suggests that there were no differences in HRQoL between taxane and non-taxane groups following completion of chemotherapy.

Discounting

The economic analysis assumes that both costs and QALYs are discounted at 3.5% per annum, in line with current recommendations from HM Treasury.[87]

Univariate sensitivity analysis

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

Long-term extrapolation

According to the EBCTCG overview,[16] the 15-year recurrence rate for patients receiving polychemotherapy is between 40 and 50% depending on age, although this recurrence rate was estimated in a population containing a mixture of N+ve and N–ve patients. The 15-year recurrence rate in the comparator arm of the model varies between 60 and 70%. This suggests that the model may be overestimating recurrence beyond the trial period. To assess the impact of this uncertainty on the model results, a sensitivity analysis was carried out in which the risk of recurrence in the comparator arm beyond the trial period was increased and decreased by 20 and 50%.

It was assumed that the HR for recurrence observed during the trial period is not maintained beyond the trial period as there is no evidence to show a continued benefit. To test whether any potential continued benefit would significantly affect the cost-effectiveness, a sensitivity analysis was carried out in which the HR for recurrence between the taxane and comparator arms taken from the trial was assumed to persist for 10 years.

Quality of life during DAC6 regimen

Patients in the DAC6 arm of the BCIRG 001 trial had a mean score of 62 (95% CI 61 to 64) on the global health status subscale of the Quality of Life Questionnaire at the end of chemotherapy, whereas those in the FAC6 arm had a mean score of 69 (95% CI 67 to 70). If this score is assumed to be proportionate to health utility and the maximum difference between the two arms is used, DAC6 would be associated with a utility of 0.87 relative to FAC6. This is likely to be an overestimate as this score relates to just one subscale of the QoL instrument. A sensitivity analysis was carried out to determine whether a 15% reduction in utility for patients receiving DAC6 compared with those receiving FAC6 has a large impact on the ICER of DAC6 versus FAC6.

Sensitivity on discounting

Until recently, NICE Health Technology Assessments used discount rates of 6% for costs and 1.5% for benefits, according to previous rates advised by the Treasury.[87] A sensitivity analysis was carried out using these rates so that the results of this analysis can be compared with other technology assessments using the old rates.

Alternative time frames

Two alternative time frames were considered, 5 and 10 years, to estimate the cost-effectiveness of taxanes when further costs and benefits are excluded after a specific time point. The 5-year estimate is essentially a within trial estimate.

Costs of recurrence

The costs of recurrence are strongly dependent on the chemotherapy regimen used to treat the recurrence. Assuming that the choice of chemotherapy regimen is dependent on the initial chemotherapy for the primary tumour, then the costs of recurrence can vary between the two arms of the model. In the base case it is assumed that recurrence costs are dependent on the initial chemotherapy regimen as four-fifths of patients receive a new regimen and one-fifth are re-challenged with the same regimen. This leads to higher costs in the comparator arm as some of these patients are switched to taxanes, which cost more than the second-line treatments employed in the taxane arm. A sensitivity analysis was then carried out assuming that all patients receive taxanes for treating their recurrent tumour regardless of the regimen they received to treat their primary tumour. This provides an estimate of cost-effectiveness when the costs of recurrence are higher but equal in both arms and shows whether this factor has a large or small impact on cost-effectiveness.

G-CSF following febrile neutropenia

In estimating the costs of managing febrile neutropenia, several simplifying assumptions were made that may have caused this cost to be overestimated in the model. It was assumed that febrile neutropenia always occurred during the first cycle of chemotherapy and that all patients received G-CSF on each subsequent cycle of chemotherapy, whereas in reality this AE may first occur in later cycles of chemotherapy and therefore have a lower overall cost. It was also assumed that prophylactic G-CSF would be administered by a district nurse during a home visit whereas it is possible for G-CSF to be self-administered in some cases. In order to test whether overestimating the costs of managing febrile neutropenia had a significant impact on the cost-effectiveness, a sensitivity analysis was carried out in which there were no costs associated with G-CSF.

TABLE 35 *Mid-point estimates of cost per QALY for docetaxel based on the BCIRG 001 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs			
Cost of adjuvant chemotherapy (£)	8,516	2,254	6,262
Cost of AEs (£)	2,396	465	1,932
Cost of recurrence and death from breast cancer (£)	12,778	14,011	–1,233
Total cost (£)	**23,690**	**16,730**	**6,961**
QALYs	8.36	7.80	0.56
Cost per QALY (£)			**12,418**

Follow-up period

A sensitivity analysis was carried out to assess whether the cost-effectiveness would be significantly different if the standard follow-up period was to fall from 5 to 3 years in response to NICE guidelines.[1]

Costs of metastatic disease

The cost used in the model for the treatment of metastatic cancer was based on resource use from 2002 and may underestimate the proportion of patients on newer interventions such as trastuzumab. A sensitivity analysis was carried out to see whether doubling the costs of treating metastatic cancer has any impact on the cost-effectiveness of taxanes.

Probabilistic sensitivity analysis

Probabilistic sensitivity analysis 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 OS 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 (for the two parameters of the parametric survival function) and V is the covariance matrix of these means. The HRs between treatments (for both DFS and OS) were sampled from the log-normal distribution.

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

The probabilistic sensitivity analysis was carried out by allowing all of the above parameters to vary according to the uncertainty specified in their probability distributions, with 10,000 sets of random numbers used to generate 10,000 sets of cost-effectiveness results. These results were then used to derive cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) for each direct treatment comparison.

Independent economic assessment – results

This section details the results of the health economic model. The cost-effectiveness results of the taxanes are presented as marginal estimates when compared against standard treatment. All results are presented in terms of marginal cost per life-year gained (LYG) and cost per QALY gained.

Base-case estimates of cost-effectiveness

The base-case estimates given below are mid-point estimates from the 10,000 runs of the probabilistic sensitivity analysis. All costs are discounted at 3.5% and benefits at 3.5% unless stated otherwise.

Docetaxel

The mid-point estimate of costs and benefits of docetaxel-containing chemotherapy versus non-taxane chemotherapy, based on BCIRG 001, are shown in *Table 35*.

The cost of adjuvant chemotherapy in the intervention arm is much higher than that in the comparator arm, due to the addition of docetaxel. There are also additional costs associated with AEs in the docetaxel arm. These costs are partly offset by lower rates of recurrence in the docetaxel arm, resulting in lower costs of treatment of recurrence and breast cancer death during the patient's lifetime. Despite these offsets, the total costs are substantially higher in the docetaxel arm.

The benefits in the docetaxel arm are estimated to be 0.56 QALYs, resulting in a cost per QALY of just over £12,000.

The cost-effectiveness plane for docetaxel-containing chemotherapy versus non-taxane

TABLE 36 *Mid-point estimates of cost per QALY for paclitaxel based on the CALGB 9344 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs			
Cost of adjuvant chemotherapy (£)	7,609	1,860	5,749
Cost of AEs (£)	257	215	42
Cost of recurrence and death from breast cancer (£)	13,472	14,820	–1,349
Total cost (£)	**21,337**	**16,896**	**4,442**
QALYs	8.35	8.24	0.11
Cost per QALY (£)			**39,332**

TABLE 37 *Midpoint estimates of cost per QALY for paclitaxel based on the NSABP B28 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs			
Cost of adjuvant chemotherapy (£)	8,973	1,860	7,113
Cost of AEs (£)	257	215	42
Cost of recurrence and death from breast cancer (£)	12,080	13,345	–1,265
Total costs (£)	**21,310**	**15,421**	**5,889**
QALYs	9.05	8.91	0.14
Cost per QALY (£)			**42,672**

chemotherapy is shown in *Figure 3* and the CEAC in *Figure 4*. The CEAC shows that by employing cost-effectiveness thresholds of £30,000 (£20,000) docetaxel has around 95% (86%) probability of being cost-effective when compared with non-taxane chemotherapy.

Paclitaxel

The costs and benefits of paclitaxel- versus non-taxane-containing treatment, based on two trials, CALGB 9344 and NSABP B28, are shown in *Tables 36* and *37*.

The cost of adjuvant chemotherapy in the intervention arm is much higher than that in the comparator arm in both *Tables 36* and *37*, due to the addition of paclitaxel. Treatment costs are different between the two trials due to the use of slightly different regimens in the two trials. There are additional costs associated with AEs in the paclitaxel arm, but these are lower than the AE costs estimated for the docetaxel arm and contribute only a small proportion to total costs.

These costs are partly offset by lower rates of recurrence in the paclitaxel arm, resulting in lower costs of treatment of recurrence and breast cancer death during the patient's lifetime. However, total costs remain higher in the paclitaxel arm in both analyses.

The benefits in the paclitaxel arm are estimated to be around 0.11 and 0.14 QALYs, resulting in a cost per QALY of just below £40,000 and £43,000 for the CALGB 9344 study and the NSAPB B28 study, respectively.

The results displayed in *Figures 5* and *6* show that in all 10,000 model runs the paclitaxel arm is more costly than the non-taxane arm, but is only more effective in around four-fifths of cases.

Figures 7 and *8* present the CEACs for paclitaxel, based on CALBG 9344 and NSABP B28, respectively, showing the likelihood that each treatment is cost-effective at various willingness to pay thresholds.

These plots show that by employing a cost-effectiveness threshold of £30,000 the paclitaxel-containing regimens have around 30–40% probability of being cost-effective when compared with the non-taxane chemotherapy regimens used in the comparator arms.

Univariate sensitivity analysis

Table 38 shows the results of univariate sensitivity analysis on the estimates of cost per QALY for docetaxel and paclitaxel.

Long-term extrapolation

Decreasing the risk of recurrence in the comparator arm increases the benefits of taxanes, as patients who have been prevented from recurring during the trial period are at a lower risk of recurrence following the trial period.

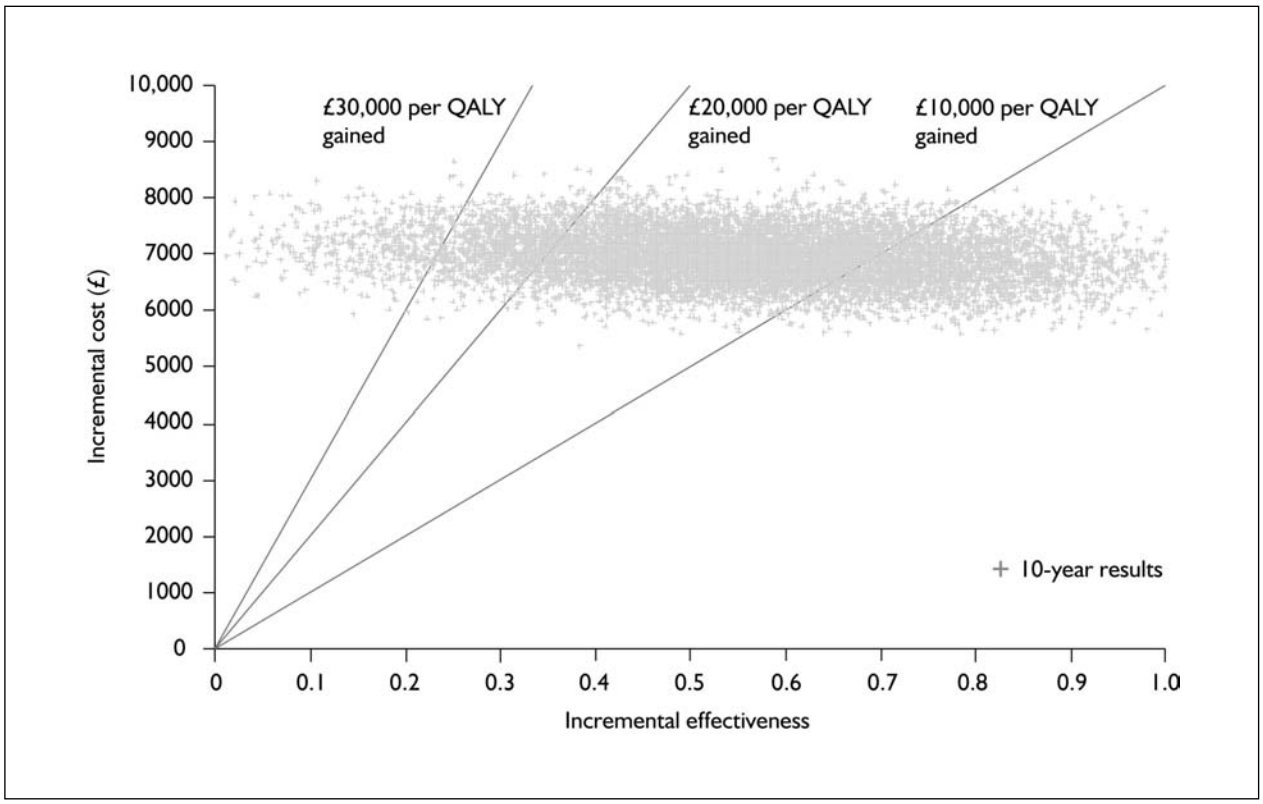

FIGURE 3 *Cost-effectiveness plane for docetaxel-containing chemotherapy versus non-taxane chemotherapy (based on BCIRG 001)*

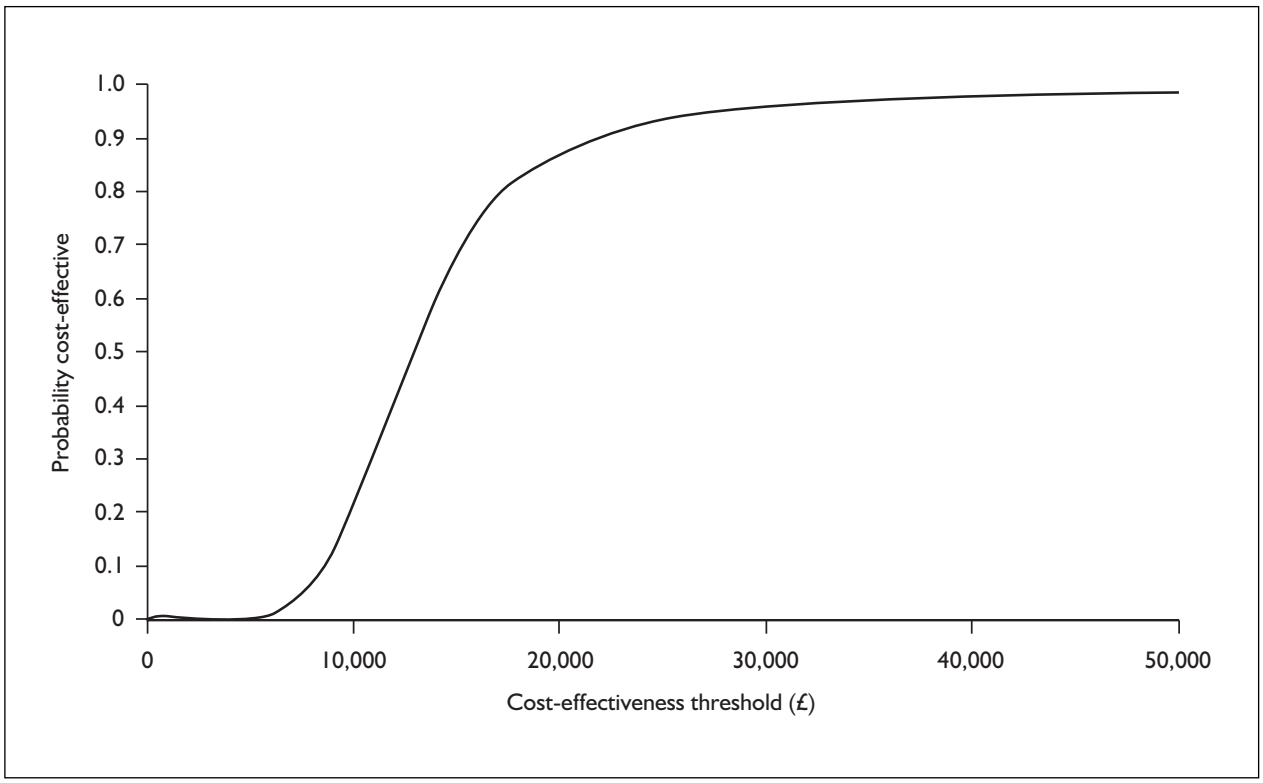

FIGURE 4 *CEAC for docetaxel-containing chemotherapy versus non-taxane chemotherapy (based on BCIRG 001)*

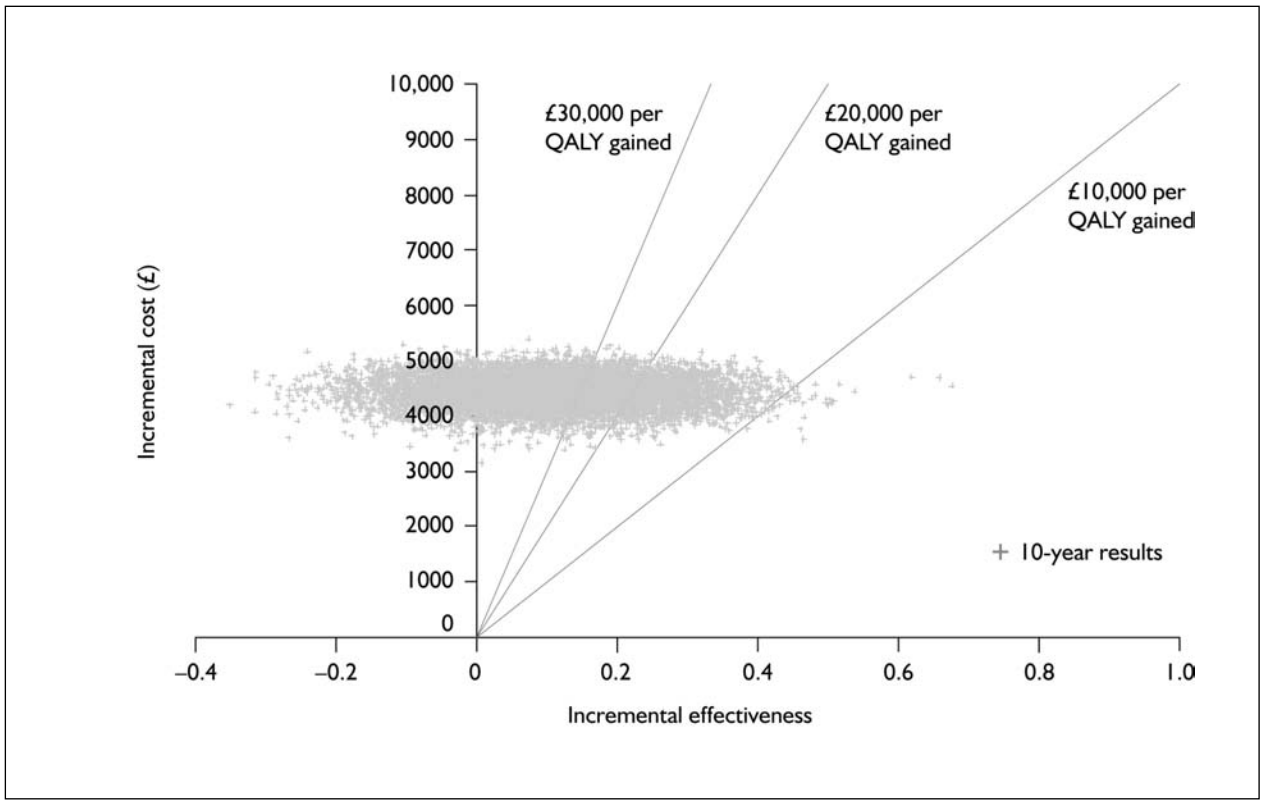

FIGURE 5 *Cost-effectiveness plane of paclitaxel-containing chemotherapy versus non-taxane containing chemotherapy (based on CALGB 9344)*

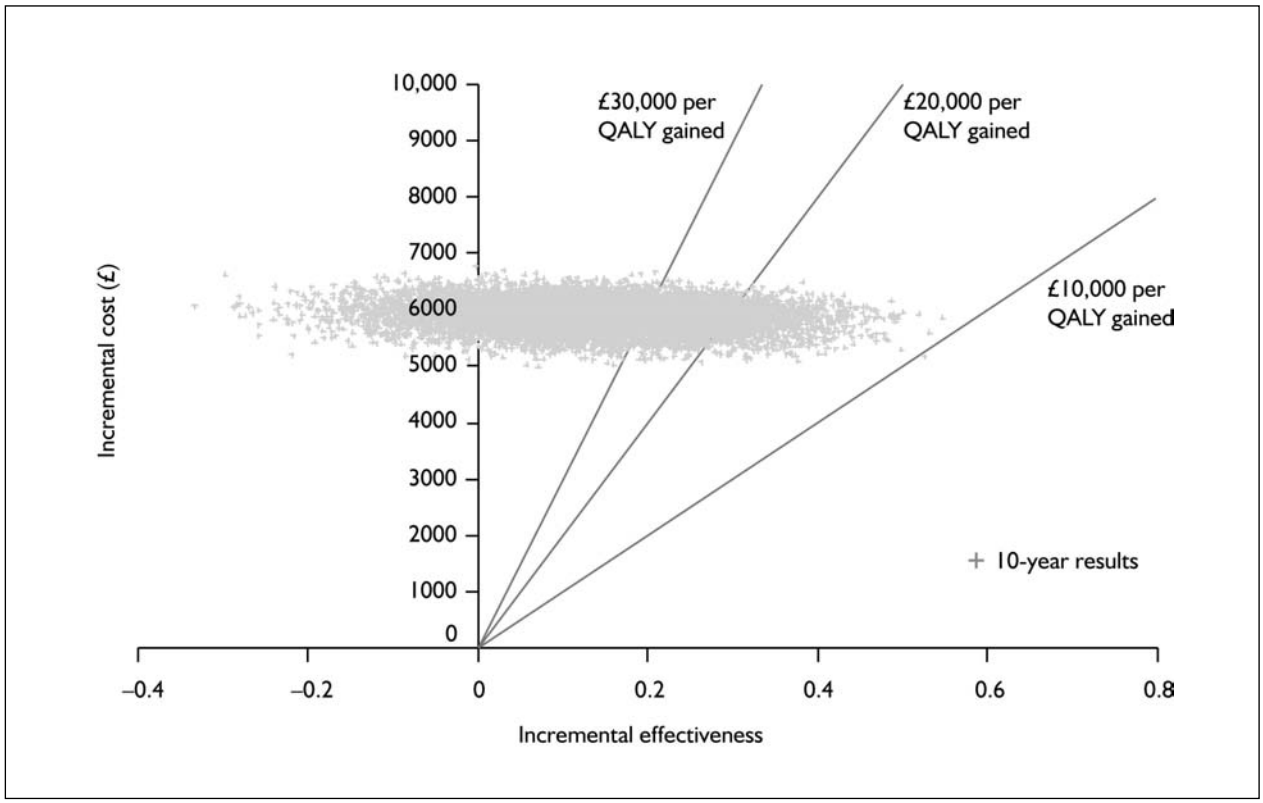

FIGURE 6 *Cost-effectiveness plane of paclitaxel-containing chemotherapy versus non-taxane chemotherapy (based on NSABP B28)*

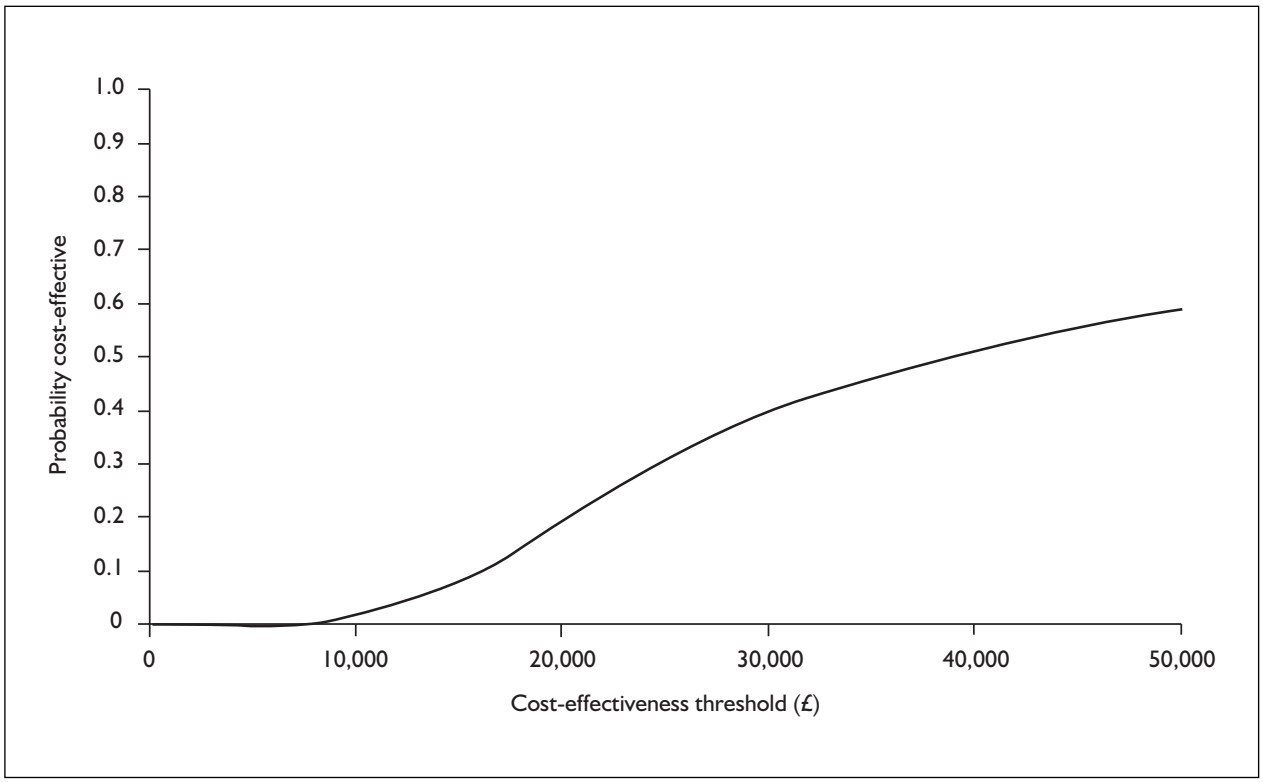

FIGURE 7 *CEAC for paclitaxel-containing chemotherapy versus non-taxane chemotherapy (based on the CALBG 9344 trial)*

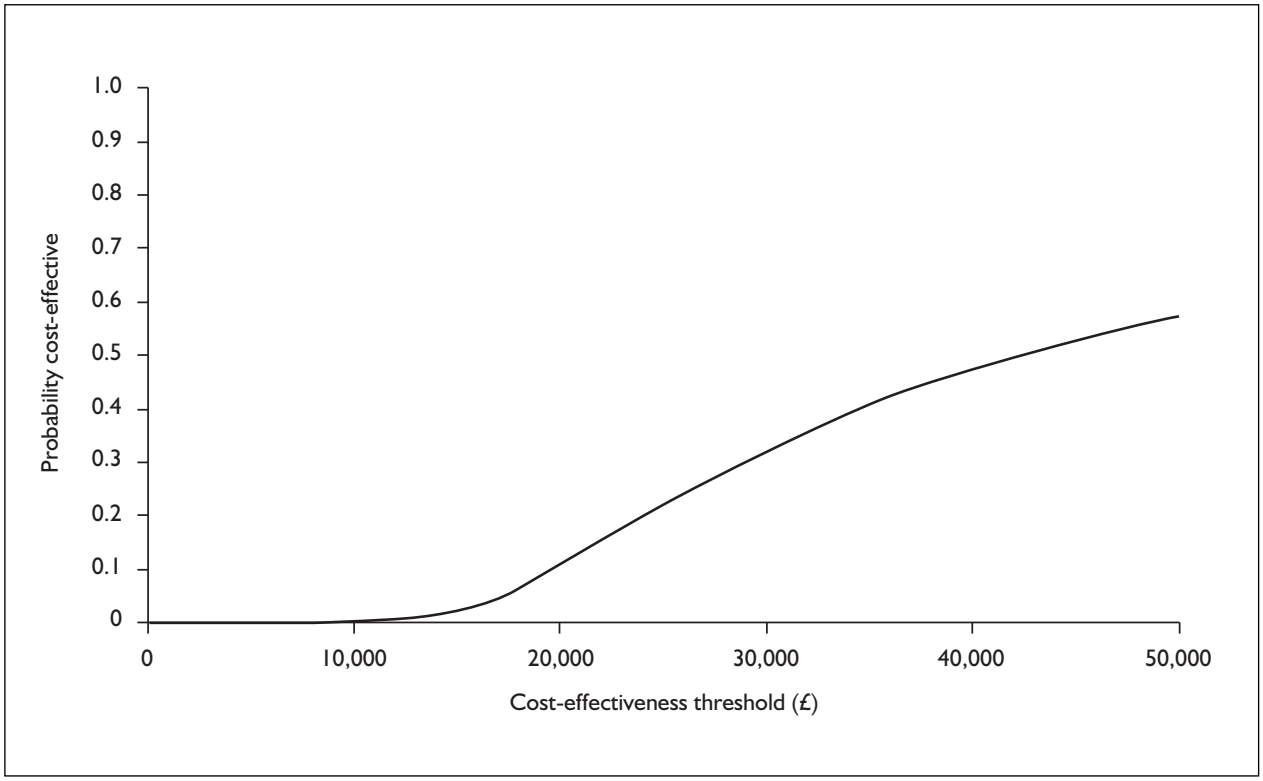

FIGURE 8 *CEAC for paclitaxel-containing chemotherapy versus non-taxane chemotherapy (based on the NSABP B28 trial)*

TABLE 38 *Univariate sensitivity analysis: cost per QALY estimates (£)*

Scenario	Comparison		
	DAC6 vs FAC6 (based on BCIRG 001)	**AC4 vs AC4+P4 (based on CALGB 9344)**	**AC4 vs AC4+P4 (based on NSABP-B28)**
Base-case cost per QALY	**12,418**	**39,332**	**42,672**
20% decrease in recurrence beyond trial period	11,373	30,817	35,728
20% increase in recurrence beyond trial period	13,494	51,916	51,782
50% decrease in recurrence beyond trial period	9,878	22,304	28,000
50% increase in recurrence beyond trial period	15,152	87,524	72,158
Trial-based HR for recurrence applied for 10 years	6,350	11,500	14,726
15% utility decrement for DAC6 compared to FAC6	13,181	N/A	N/A
6% discount for costs and 1.5% for QALYs	9,751	28,875	30,983
5-year (within trial) time frame	80,502	Dominated by comparator	Dominated by comparator
10-year time frame	25,642	131,888	159,628
All patients receive taxanes for recurrence	13,302	45,629	47,132
No cost for G-CSF following episode of febrile neutropenia	9,860	39,107	42,488
Routine follow-up for maximum of 3 years	12,470	39,338	42,676
Doubling the costs of treating metastatic disease	11,250	37,700	41,048

Decreasing the risk of recurrence by 50% lowered the ICER to under £10,000 for docetaxel and to between £20,000 and £30,000 for paclitaxel depending on the trial considered. This lower recurrence rate corresponds to a 15-year recurrence rate of 45–55% depending on the trial being modelled.

In a second sensitivity analysis, the HR for recurrence between the taxane and comparator arms taken from the trial was assumed to persist for 10 years, rather than the 5 years assumed in the base case. This lowers the ICERs to below £15,000 for all three analyses. To date there is limited evidence to support the assumption that benefits will continue for a further 5 years; however, other treatments for breast cancer, such as tamoxifen, have been shown to be effective for up to 10 years. Therefore, although this continued benefit scenario cannot be supported by the data at this time, it may be supported by longer term data from the taxane trials when they become available in the future.

Quality of life during DAC6 regimen

The impact of reducing the health-related utility for patients receiving DAC6 by 15% relative to the utility for patients receiving FAC6 was minimal.

Sensitivity on discounting

Using the discount rates of 6% for costs and 1.5% for benefits, used in earlier NICE technology assessments, reduced the estimates of cost per QALY by around 25%.

Alternative time frames

Two alternative time frames, 5 and 10 years, were considered to estimate the cost-effectiveness of taxanes. The 5-year estimate is essentially a within-trial estimate. In the 10-year analysis, the ICER for docetaxel increased to around £25,000 and for paclitaxel to between £130,000 and £160,000. In the 5-year analysis, the ICER for docetaxel increased to around £80,000; paclitaxel is dominated by the comparator arm in both analyses.

Costs of recurrence

Assuming that all recurrences are treated with taxanes regardless of whether the patient received taxanes for their primary tumour increased the cost per QALY to £13,000 for docetaxel and around £46,000 for paclitaxel.

Costs of managing febrile neutropenia

Assuming that there are no costs associated with G-CSF did not significantly alter the cost-effectiveness of taxanes. This suggests that although the costs used in the base case may have been overestimated, this did not significantly bias the cost-effectiveness estimate.

Duration of routine follow-up

Changing the duration of follow-up from 5 to 3 years had a minimal impact on cost-effectiveness, which suggests that if current practice changes in line with NICE guidelines, this will not affect whether taxanes are cost-effective.

Costs of treating metastatic disease
Doubling the costs of treating metastatic disease did not have a significant impact on the cost-effectiveness of taxanes.

Indirect comparisons

Rationale

Although these three trials provide evidence of the effectiveness of taxanes within their licensed indication, their comparators do not represent UK standard practice. Treatment in the UK varies widely, but commonly used regimens are FEC6 or E4-CMF4. It is unusual for only four cycles of chemotherapy to be used. Although AC4 may be chosen for patients aged over 50 years at very low risk, or for ER– patients aged 70 years or over, these patients are unlikely to be considered eligible for treatment with taxanes.

Evidence base

We carried out a systematic search of the literature to find RCTs comparing FAC6 or AC4 with FEC6 or E4-CMF4. The databases searched were MEDLINE, EMBASE and the Cochrane Library. Filters to identify systematic reviews, RCTs and economic evaluations were utilised on MEDLINE and EMBASE. Searches were also undertaken on conference abstracts on the ASCO and San Antonio Breast Cancer Symposium websites. All searches took place in May 2006. No studies were identified which compared these regimens directly in RCTs. However, several reviews were identified which reviewed the efficacy evidence for various adjuvant chemotherapy regimens.[100] It became clear from these reviews that although there is a scarcity of trials comparing between anthracycline-based regimens, many of these regimens have been compared against CMF. The review by Chilcott and colleagues[100] attempts to summarise the best evidence relating to the anthracycline-based regimens used in the UK and identifies six studies which compare these regimens with CMF. It also includes a study comparing the relative effectiveness of two different doses of anthracycline in the FEC6 regimen [FEC(50) and FEC(100)]. Chemotherapy regimens employed in these trials are shown in *Table 39*.

Using the studies identified by Chilcott and colleagues,[100] we constructed a network of evidence linking the effectiveness of the regimens used as comparators in the main taxane trials to the regimens in common use in UK practice (E4-CMF4 and FEC6), which is shown in *Figure 9*. Although some of the links made between regimens are not exact due to variations in the exact doses and timings of regimens, it provides a chain of evidence on which to base the relative effectiveness of taxanes compared with current standard practice.

Details of the treatment regimens and the patient characteristics from the studies identified in *Figure 9* are presented in *Tables 39* and *40*, respectively. Key outcomes are presented in *Table 41*.

Within-trial characteristics of baseline populations were well balanced (*Table 40*). However, trials differed in population eligibility criteria, most notably in nodal status, and there were also differences between trials in tumour size, hormone receptor status and age – all characteristics that affect prognosis.

DFS data, that is, outcome events including recurrence, second cancer or death, were available for most studies (*Table 41*). Where DFS data were not available, TTR data were reported. Not all studies reported HRs, so other statistical comparisons of treatment groups are presented.

Methodology

These trials were used to calculate indirectly the effectiveness of taxanes relative to the FEC6 and E4-CMF4 regimens that are used commonly in the UK. The dose of epirubicin used in the FEC6 regimen varies between 60 and 90 mg/m^2, so we shall consider comparisons with the FEC6 regimen using doses of 50 and 100 mg/m^2 [FEC6(50) and FEC6(100)] to give a range for the comparison with the FEC6 regimen as it is used in clinical practice. The effectiveness of the current standard regimens relative to the comparator regimen in the taxane trial was estimated by multiplying together the HRs for recurrence for each of the branches linking the regimens of interest in *Figure 9*. This HR was then applied to the hazard of recurrence in the comparator arm of the taxane trial to estimate what the recurrence rate would have been if the comparator had been one of the regimens in common use in the UK. Each HR was sampled independently from a log-normal distribution before being multiplied together to give the overall indirect effectiveness. For some of the linking trials the required HR was not presented in the published results and it was therefore necessary to estimate the HR from the results presented. Sometimes where the trials included both N+ve and N–ve patients, it was necessary to adjust the results to reflect the HR in N+ve patients only. The methodology used to

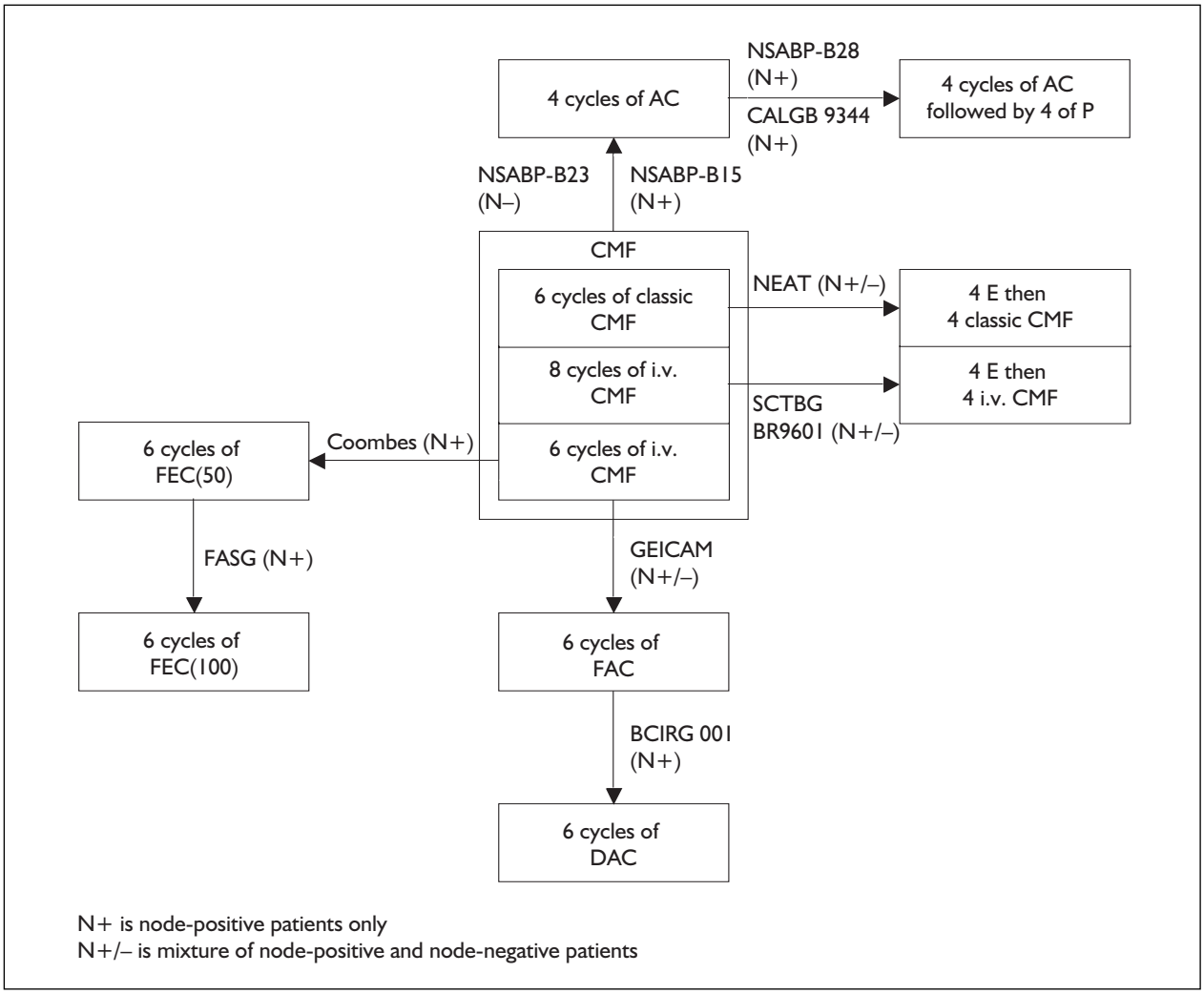

FIGURE 9 *Network of evidence linking effectiveness of taxanes with effectiveness of regimens in common use in the UK*

estimate each of the required HRs and their standard deviations (SDs) is described in Appendix 7.

This methodology is subject to significant uncertainty. It assumes that the populations involved are equivalent and that the regimens which link the various trials are equivalent even though there is some variation in the regimens used for each linking trial. For example, six cycles of classical CMF as used in the NSABP B15 trial was assumed to have equal efficacy to the six cycles of intravenous CMF as used in the GEICAM 8701 trial.

Each of the HRs employed in the calculation of the indirect effectiveness was sampled from a log-normal distribution to give an estimate of the uncertainty in the indirect comparison. This does not compensate for the uncertainty in assuming equivalence between different patient populations and similar regimens, but it does estimate the range of effectiveness difference possible in the indirect comparison due to the uncertainty in each of the trials used to estimate the difference in effectiveness.

The indirect comparison considers the following:

- DAC6 compared with FEC6(50)
- DAC6 compared with FEC6(100)
- DAC6 compared with E4-CMF4
- AC4+P4 compared with FEC6(50)
- AC4+P4 compared with FEC6(100)
- AC4+P4 compared with E4-CMF4.

The E4-CMF4 and FEC6 regimens were costed using the same evidence sources and methodology as employed for the main direct comparison (see the section 'Chemotherapy costs', p. 37) and the overall costs are summarised in Appendix 5. The AE rate in the comparator arm was assumed to be

TABLE 39 *Indirect comparisons – treatment regimens*

Trial	Interventions (abbreviated)	Interventions
BCIRG 001	DAC6	Doxorubicin 50 mg/m^2 i.v. infusion for 15 minutes, followed by cyclophosphamide 500 mg/m^2 i.v. for 1–5 minutes, after a 1-hour interval docetaxel 75 mg/m^2 i.v. infusion for 1 hour. Six 21-day cycles
	FAC 6	Doxorubicin 50 mg/m^2, followed by fluorouracil 500 mg/m^2, as IV infusion for 15 minutes, then cyclophosphamide 500 mg/m^2 i.v. infusion for 1–5 minutes. Six 21-day cycles
NSABP B28	AC4-P4	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles, followed by paclitaxel 225 mg/m^2 3-hour infusion. Four 3-week cycles
	AC4	Doxorubicin 60 mg/m^2, cyclophosphamide 600 mg/m^2. Four 3-week cycles
CALGB 9344	AC4-P4	Cyclophosphamide 600 mg/m^2, one of three doses of doxorubicin 60 or 75 or 90 mg/m^2. Four 3-week cycles, followed by paclitaxel 175 mg/m^2. Four 3-week cycles
	AC4	Cyclophosphamide 600 mg/m^2, one of three doses doxorubicin 60 or 75 or 90 mg/m^2. Four 3-week cycles
Coombes	CMF6	Cyclophosphamide 100 mg/m^2 p.o. days 1–14, methotrexate 40 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. days 1 and 8 of six 4-week cycles
	CMF6(IV)	Cyclophosphamide 600 mg/m^2 i.v., methotrexate 40 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. days 1 and 8 of six 4-week cycles
	FEC8(50)	Fluorouracil 600 mg/m^2 i.v., epirubicin 50 mg/m^2 i.v., cyclophosphamide 600 mg/m^2 i.v. Eight 3-week cycles
	FEC6(50)	Fluorouracil 600 mg/m^2 i.v. days 1 and 8, epirubicin 50 mg/m^2 i.v., cyclophosphamide 600 mg/m^2 i.v. days 1 and 8. Six 4-week cycles
NEAT	E4-CMF4	Epirubicin 100 mg/m^2 i.v. Four 3-week cycles. Then cyclophosphamide 100 mg/m^2 p.o. days 1–14, methotrexate 40 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. days 1 and 8. Four 3-week cycles
	CMF6	Cyclophosphamide 100 mg/m^2 p.o. days 1–14, methotrexate 40 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. days 1 and 8. Six 3-week cycles
SCTBG BR9601	CMF8(IV)	Cyclophosphamide 750 mg/m^2 i.v., methotrexate 50 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. Eight 3-week cycles
	E4-CMF4(IV)	Epirubicin 100 mg/m^2 i.v. Four 3-week cycles. Then cyclophosphamide 750 mg/m^2 i.v., methotrexate 50 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. Four 3-week cycles
FASG	FEC6(50)	Fluorouracil 500 mg/m^2 i.v., epirubicin 50 mg/m^2 i.v., cyclophosphamide 500 mg/m^2 i.v. Six 3-week cycles
	FEC6(100)	Fluorouracil 500 mg/m^2 i.v., epirubicin 100 mg/m^2 i.v., cyclophosphamide 500 mg/m^2 i.v. Six 3-week cycles
GEICAM 8701	CMF6(IV)	Cyclophosphamide 600 mg/m^2 i.v., methotrexate 60 mg/m^2 i.v. and fluorouracil 600 mg/m^2. Six 3-week cycles
	FAC6	Fluorouracil 500 mg/m^2 i.v., doxorubicin 50 mg/m^2 i.v., cyclophosphamide 500 mg/m^2 i.v. Six 3-week cycles
NSABP B15	AC4	Doxorubicin 60 mg/m^2 i.v., cyclophosphamide 600 mg/m^2 i.v. Four 3-week cycles
	AC4-CMF4(IV)	Doxorubicin 60 mg/m^2 i.v., cyclophosphamide 600 mg/m^2 i.v. Four 3-week cycles. Then 6-month break. Then cyclophosphamide 750 mg/m^2 i.v., methotrexate 40 mg/m^2 i.v. days 1 and 8 and fluorouracil 600 mg/m^2 days 1 and 8. Three 4-week cycles
	CMF6	Cyclophosphamide 100 mg/m^2 p.o. days 1–14, methotrexate 40 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. days 1 and 8. Six 4-week cycles
NSABP B23	AC4 (with placebo or tamoxifen)	Doxorubicin 60 mg/m^2 i.v., cyclophosphamide 600 mg/m^2 i.v. Four 3-week cycles
	CMF6 (with placebo or tamoxifen)	Cyclophosphamide 100 mg/m^2 p.o. days 1–14, methotrexate 40 mg/m^2 i.v. and fluorouracil 600 mg/m^2 i.v. days 1 and 8. Six 4-week cycles

TABLE 40 *Indirect comparisons – patient characteristics*

Trial	No. of patients	Treatment group	Tumour size/stage	Nodal status	Hormone receptor status	Age (years)	Other eligibility criteria
BCIRG 001	745	DAC6	T1 (up to 2 cm) 39.7%; T2 (2–5 cm) 52.6%; T3 (over 5 cm) 7.7%	N–ve 0%; 1–3 +ve nodes 62.7%; 4+ +ve nodes 37.3%	ER+ or PR+ 76.1%	Median 49	Aged 18–70 years; Karnofsky performance scale score 80% or more; primary surgery (mastectomy, tumourectomy or lumpectomy) with axillary node dissection (sentinel node biopsy was not routine practice) Randomisation within 60 days after surgery Excluded: history of cancer, motor or sensory neuropathy of grade 2 or more, pregnancy, lactation, any serious illness or medical condition other than breast cancer, prior therapy with anthracyclines or taxanes
	746	FAC6	T1 (up to 2 cm) 42.9%; T2 (2–5 cm) 51.3%; T3 (over 5 cm) 5.8%	N–ve 0%; 1–3 +ve nodes 61.5%; 4+ +ve nodes 38.5%	ER+ or PR+ 75.7%	Median 49	
NSABP B28	1531	AC4-P4	2 cm or less 58.4%; 2.1–4 cm 32.5%; over 4 cm 9%	N–ve 0%; 1–3+ve nodes 69.9%; 4–9 +ve nodes 25.9%; 10+ +ve nodes 4.2%	ER+ 65.7%; PR+ 60.5%	Under 40 15%; 40–49 36.6%; 50–59 29.8%; 60+ 18.7%	Excluded: history of breast cancer, prior radiation, chemotherapy, immunotherapy, hormonal therapy
	1528	AC4	2 cm or less 60%; 2.1–4 cm 32.2%; over 4 cm 7.6%	N–ve 0%; 1–3 +ve nodes 70%; 4–9 +ve nodes 26.2%; 10+ +ve nodes 3.9%	ER+ 66.3%; PR+ 62.1%	Under 40 13.5%; 40-49 36.3%; 50–59 31.7%; 60+ 18.5%	
CALGB 9344	1570	AC4-P4	2 cm or less 35%; over 5 cm 13%	N–ve 0%; 1–3 +ve nodes 46%; 4–9 +ve nodes 42%; 10+ +ve nodes 12%	ER+ 60%; ER+ or PR+ 67%	Under 40 20%; 40–49 41%; 50–59 26%; 60+ 13%	Systemic therapy to start within 84 days of patient's last surgery, initial surgical treatment either mastectomy or lumpectomy with axillary lymph node sampling Radiotherapy for all patients with less than mastectomy, begun after chemotherapy
	1551	AC4	2 cm or less 35%; over 5 cm 12%	N–ve 0%; 1–3 +ve nodes 47%; 4–9 +ve nodes 42%; 10+ +ve nodes 12%	ER+ 58%; ER+ or PR+ 66%	Under 40 21%; 40–49 39%; 50–59 28%; 60+ 12%	

continued

TABLE 40 *Indirect comparisons – patient characteristics (cont'd)*

Trial	No. of patients	Treatment group	Tumour size/stage	Nodal status	Hormone receptor status	Age (years)	Other eligibility criteria
Coombes	180	CMF6	T0–T2 87%; T3–T4 13%	N–ve 0%; 1–3 +ve nodes 60%; 4+ +ve nodes 40%	ER+ 67%; ER– 33%	Median 43 (range 24–57)	Premenopausal; primary surgery (mastectomy or wide local excision) recommended axillary dissection Excluded: prior malignancy, prior systemic therapy; non-malignant systemic disease (including cardiac) that would preclude treatment or long-term follow-up
	199	CMF6(IV)	T0–T2 80%; T3–T4 20%	N–ve 0%; 1–3 +ve nodes 69%; 4+ +ve nodes 31%	ER+ 65%; ER– 35%	Median 44 (range 23–55)	
	180	FEC8(50)	T0–T2 87%; T3–T4 13%	N–ve 0%; 1–3 +ve nodes 61%; 4+ +ve nodes 39%	ER+ 61%; ER– 39%	Median 44 (range 25–55)	
	200	FEC6(50)	T0–T2 82%; T3–T4 18%	N–ve 0%; 1–3 +ve nodes 76%; 4+ +ve nodes 24%	ER+ 65%; ER– 35%	Median 43 (range 26–55)	
NEAT SCTBG BR9601	1189	E4-CMF4 E4-CMF4(IV)	2 cm or less 43%	N–ve or unknown 28%; N+ve 72%	ER– 37%	50 or under 60%	Randomised within 6 weeks of surgery Excluded: prior chemotherapy or radiation therapy; prior malignancy
NEAT SCTBG BR9601	1202	CMF6 CMF8(IV)	2 cm or less 42%	N–ve or unknown 28%; N+ve 72%	ER– 41%	50 or under 58%	
FASG	289	FEC6(50)	2 cm or less 37%; over 2 cm 63%	N–ve 0%; 1–3 +ve nodes 18.5%; 4–10 +ve nodes 60.9%; over 10 +ve nodes 20.6%	HR+ 31.8%; HR– 68.2%	Median 50 (range 25–66)	Aged 18–64 years; normal haematological, hepatic and renal function; no cardiac dysfunction; more than 3 +ve nodes, or N+ve with SBR (Scarff Bloom Richardson) grade 2 or more and ER– or PR– Excluded: prior radiation, chemotherapy or hormone therapy; more than 42 days from surgery
	276	FEC6(100)	2 cm or less 39.7%; over 2 cm 60.3%	N–ve 0%; 1–3 +ve nodes 17%; 4–10 +ve nodes 60.1%; over 10 +ve nodes 22.9%	HR+ 33.5%; HR– 66.5%	Median 51 (range 23–67)	

continued

TABLE 40 *Indirect comparisons – patient characteristics (cont'd)*

Trial	No. of patients	Treatment group	Tumour size/stage	Nodal status	Hormone receptor status	Age (years)	Other eligibility criteria
GEICAM 8701	505	CMF6(IV)	T1 25.3%; T2 59.4%; T3 8.9%	N–ve 41.8%; 1–3 +ve nodes 32.9%; 4+ +ve nodes 25.3%	ER+/PR+ 33.7%; ER– and PR– 15%; unknown 51.3%	Under 50 36.4%; 50+ 63.6%	Aged 18–72 years; primary surgery mastectomy or tumourectomy with free margins plus axillary lymphadenectomy Excluded: history of cancer (except skin carcinoma or carcinoma *in situ* of the cervix); history of cardiac disease; major psychiatric disorder, serum creatine >1.5 mg/dl; serum bilirubin >1.5 mg/dl
	480	FAC6	T1 22.9%; T2 55.6%; T3 15%	N–ve 42.5%; 1–3 +ve nodes 27.3%; 4+ +ve nodes 30.2%	ER+/PR+ 27.5%; ER– and PR– 14.2%; unknown 59.4%	Under 50 37.9%; 50+ 62.1%	
NSABP B15	734	AC4	2 cm or less 28%; over 5 cm 8%	N–ve 0%; 1–3 +ve nodes 56%; 4–9 +ve nodes 30%; 10+ +ve nodes 14%	ER fmol under 10 46%	Under 50 79%; 50–59 21%	Therapy between 2 and 5 weeks post-operation; tamoxifen non-responsive
	728	AC4-CMF4(IV)	2 cm or less 28%; over 5 cm 7%	N–ve 0%; 1–3 +ve nodes 56%; 4–9 +ve nodes 30%; 10+ +ve nodes 15%	ER fmol under 10 44%	Under 50 77%; 50–59 23%	
	732	CMF6	2 cm or less 29%; over 5 cm 8%	N–ve 0%; 1–3 +ve nodes 56%; 4–9 +ve nodes 30%; 10+ +ve nodes 14%	ER fmol under 10 49%	Under 50 81%; 50–59 19%	
NSABP B23	1003	AC4 (with placebo or tamoxifen)	2 cm or less 53%; over 4 cm 5%	N–ve 100%	ER fmol under 10 98%	Under 50 55%; 50–59 27%; 60+ 18%	Life expectancy of at least 10 years
	1005	CMF6 (with placebo or tamoxifen)	2 cm or less 56%; over 4 cm 4%	N–ve 100%	ER fmol under 10 98%	Under 50 55%; 50–59 30%; 60+ 15%	

TABLE 41 *Indirect comparisons – outcomes (recurrence or DFS)*

Trial	Follow-up (median) (months)	Group	No. followed up	DFS (%)	HR (or other statistic) DFS (95%CI)	Free from recurrence (%)	HR (or other statistic) TTR (95% CI)
BCIRG 001	55	DAC6	745	77	HR 0.71 (0.58 to 0.87), $p < 0.001$		
	55	FAC6	746	70			
NSABP B28	64.4	AC4-P4	1531	74			
	64.8	AC4	1528	70			
CALGB 9344	69	AC4-P4	1570	70		69	HR 0.83 (0.73 to 0.94)
	69	AC4	1551	65		64	
Coombes[a]	58	CMF6	180			39	Log-rank 1.53 ($p = 0.22$)
		FEC8(50)	180			45	
Coombes[a]		CMF6(i.v.)	199			34	Log-rank 4.55 ($p = 0.03$)
		FEC6(50)	200			27	
NEAT	37	E4-CMF4	1009	84	Reduction in HR of 29% (SD 9)		
		CMF6	1012	79			
SCTBG		CMF8(i.v.)	190	71			
BR9601		E4-CMF4 (IV)	180	81	Reduction in HR of 40% (SD 17)		
FASG	110	FEC6(50)	271	45	Log-rank $p = 0.08$; RR of relapse 1.24 (1.11 to 1.36)		
		FEC6(100)	266	51	HR[b] 1.24 (0.97 to 1.59)		
GEICAM 8701[b]	60	CMF6(i.v.)	505			50	($p = 0.056$)
		FAC6	480			58	
NSABP B15	26.2	AC4	734	77			
		AC4-CMF4 (i.v.)	728	79	Ref. AC×4, $p = 0.5$; ref. CMF×6, $p = 0.2$		
		CMF6	732	77			
NSABP B23	65	AC4 (with placebo or tamoxifen)	988	82	$p = 0.6$		
		CMF6 (with placebo or tamoxifen)	994	83			

SD, standard deviation.
[a] Relapse-free survival did not include local recurrence following conservative surgery and no radiation therapy.
[b] Adjusted for surgery type and number of positive nodes.

similar for the regimens used as comparators in the main taxane trials (FAC6 and AC4) and the regimens used in current standard practice (FEC6 and E-CMF4). As AE costs do not have a large impact on cost-effectiveness, any bias introduced by this assumption is likely to be small.

Results

The cost-effectiveness planes for each indirect comparison are shown in *Figures 10–12*. These show that there is great uncertainty in the incremental benefits with QALY gains ranging from –1.5 to 2.0.

The probabilistic sensitivity analysis estimated that the docetaxel regimen used in the BCIRG 001 trial had a cost per QALY below £30,000 in 51% of samples when compared with E4-CMF4, 28% of samples when compared with FEC6(50) and 12% of samples when compared with FEC6(100). The paclitaxel regimen used in the NSABP B28 trial had a cost per QALY under £30,000 in 10, 4 and

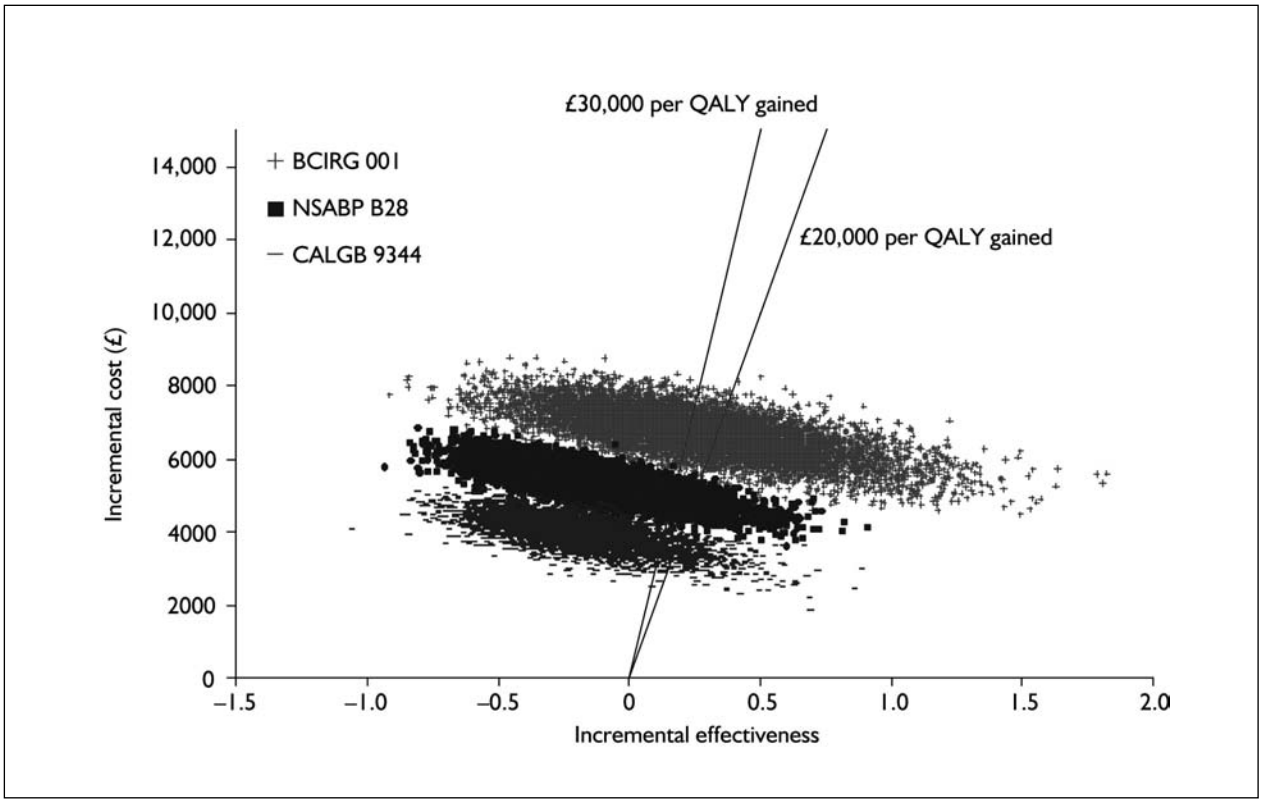

FIGURE 10 *Cost-effectiveness plane showing the incremental cost and effectiveness of the taxane regimens used in the BCIRG 001, NSABP B28 and CALGB 9344 trials compared with E4-CMF4*

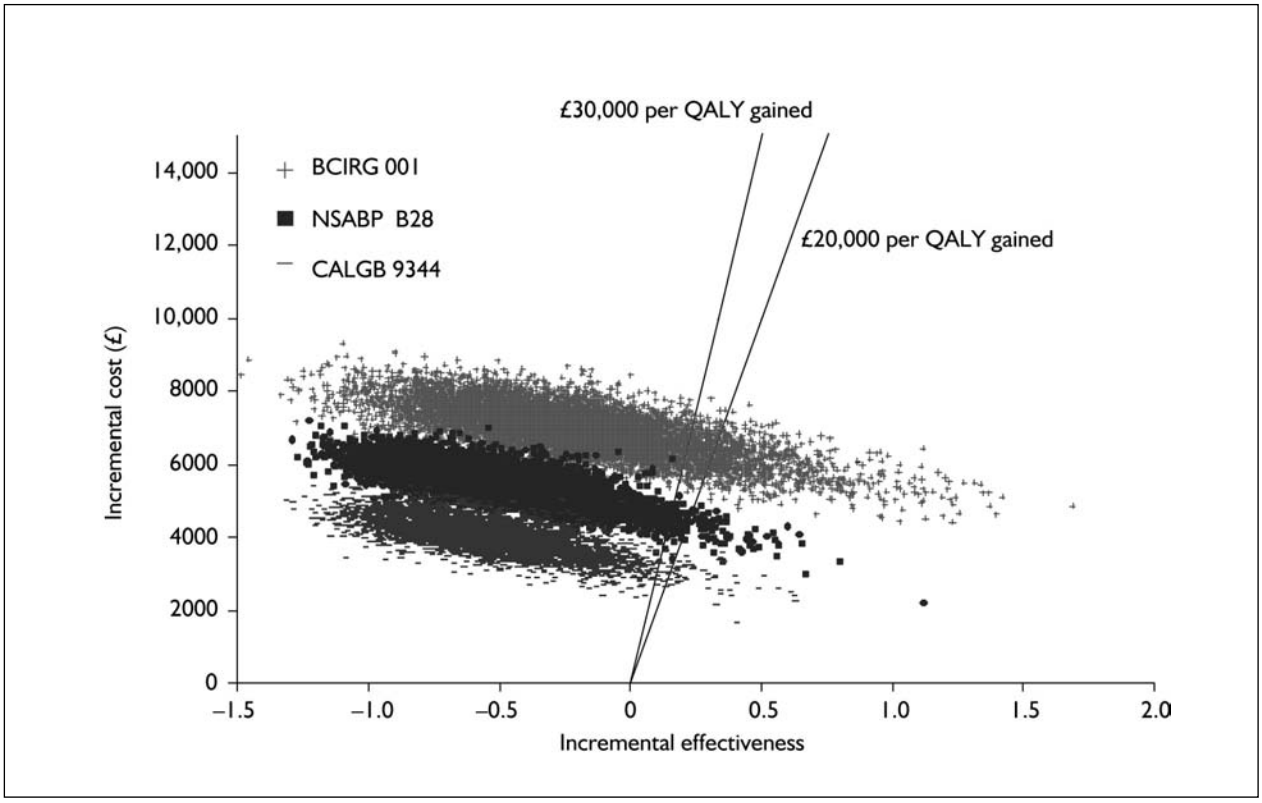

FIGURE 11 *Cost-effectiveness plane showing the incremental cost and effectiveness of the taxane regimens used in the BCIRG 001, NSABP B28 and CALGB 9344 trials compared with FEC6(100)*

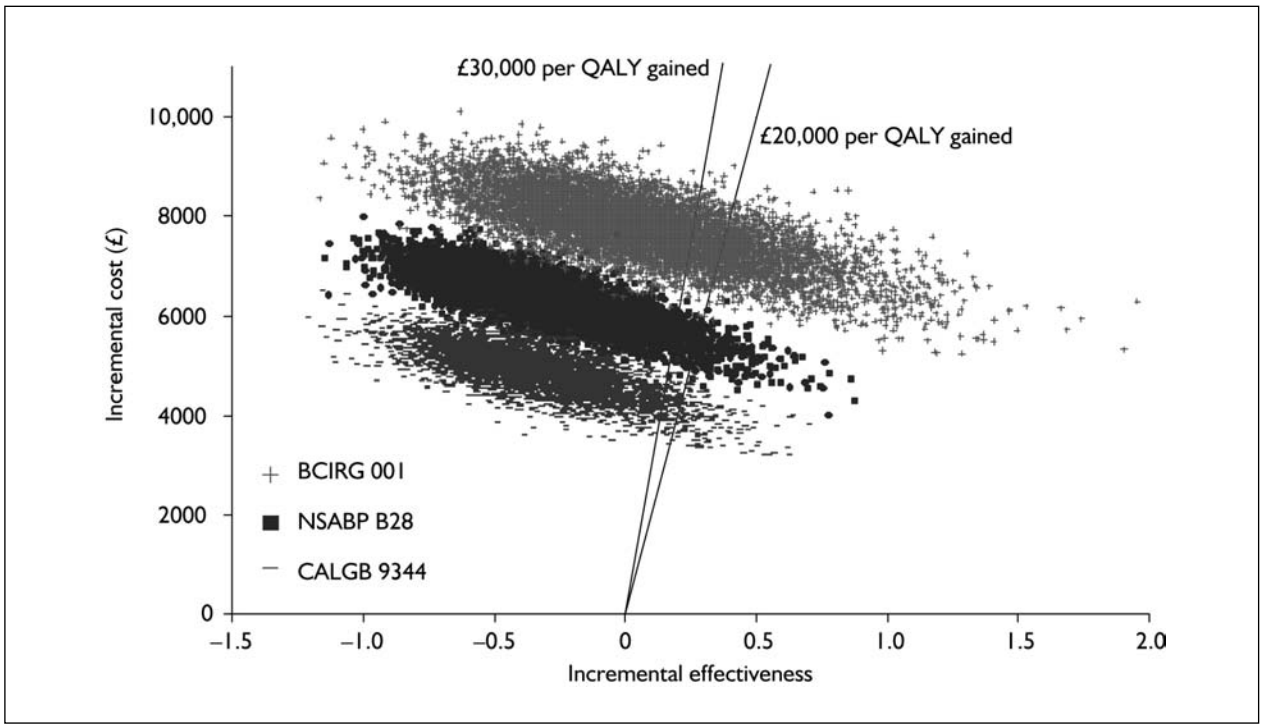

FIGURE 12 *Cost-effectiveness plane showing the incremental cost and effectiveness of the taxane regimens used in the BCIRG 001, NSABP B28 and CALGB 9344 trials compared with FEC6(50).*

TABLE 42 *Mid-point estimates of cost per QALY for docetaxel versus E4-CMF4 based on an indirect comparison with the BCIRG 001 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	23,694 (21,179–26,791)	16,987 (14,393–20,198)	6,716 (5,496–7,859)
QALYs	8.36 (5.72–9.34)	8.11 (5.61–9.30)	0.25 (–0.38 to 0.99)
Cost per QALY (£)			26,398 (5,836–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

1% of samples when compared with E4-CMF4, FEC6(50) and FEC6(100), respectively. The paclitaxel regimen used in the CALGB 9344 trial had similar results with a cost per QALY under £30,000 in 11, 5 and 1% of samples when compared with E4-CMF4, FEC6(50) and FEC6(100), respectively.

The mid-point estimates of cost per QALY for each indirect comparison are given in *Tables 42–50*. These mid-point estimates should be interpreted with caution as the uncertainty in these estimates is large, as shown in *Figures 10–12*. There was a gain in QALYs on average for docetaxel versus E4-CMF4 and docetaxel versus FEC6(50) over the 10,000 samples considered but a loss in QALYs on average for docetaxel versus FEC6(100). For each of the paclitaxel comparisons considered there was a loss in QALYs on average over the 10,000 samples.

When the FEC6 regimen is used in the UK it is most commonly used with doses of epirubicin ranging from 60 to 90 mg/m^2. The cost-effectiveness results for taxanes compared with the FEC6(50) and FEC6(100) regimens therefore provide a range for the cost-effectiveness of taxanes compared with FEC6 as it is used in the UK. When the docetaxel regimen used in the BCIRG 001 study is compared with the FEC6(50) regimen it has a cost per QALY of £158,517 (£7830 to dominated). When it is compared with FEC6(100), the cost per QALY has a range of £10,363 to dominated). This suggests that the

TABLE 43 *Mid-point estimates of cost per QALY for docetaxel versus FEC6(100) based on an indirect comparison with the BCIRG 001 study (10,000 runs)*

	Intervention	Comparator	Marginal
Cost (£)	23,694 (21,124–26,743)	16,714 (14,154–19,825)	6,980 (5,677–8,132)
QALYs	8.36 (5.67–9.44)	8.58 (5.78–9.80)	–0.22 (–0.88 to 0.58)
Cost per QALY (£)			Dominated[a] (10,363–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 44 *Mid-point estimates of cost per QALY for docetaxel versus FEC6(50) based on an indirect comparison with the BCIRG 001 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	23,708 (21,175–26,769)	15,940 (13,292–19,097)	7,768 (6,439–8,982)
QALYs	8.35 (5.67–9.42)	8.30 (5.58–9.56)	0.05 (–0.62 to 0.86)
Cost per QALY (£)			158,517 (7,830–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 45 *Mid-point estimates of cost per QALY for paclitaxel versus E4-CMF4 based on an indirect comparison with the NSABP B28 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	21,316 (19,165–23,870)	15,901 (13,667–18,508)	5,416 (4,537–6,206)
QALYs	9.05 (6.20–10.04)	9.19 (6.30–10.08)	–0.14 (–0.57 to 0.35)
Cost per QALY (£)			Dominated[a] (13,330–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 46 *Mid-point estimates of cost per QALY for paclitaxel versus FEC6(100) based on an indirect comparison with the NSABP B28 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	21,320 (19,161–23,964)	15,806 (13,642–18,450)	5,515 (4,536–6,358)
QALYs	9.04 (6.08–10.02)	9.54 (6.37–10.66)	–0.50 (–0.97 to 0.06)
Cost per QALY (£)			Dominated[a] (76,803–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 47 *Mid-point estimates of cost per QALY for paclitaxel versus FEC6(50) based on an indirect comparison with the NSABP B28 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	21,296 (19,155–23,844)	14,955 (12,745–17,615)	6,341 (5,374–7,166)
QALYs	9.05 (6.13–10.02)	9.35 (6.28–10.45)	–0.30 (–0.77 to 0.25)
Cost per QALY (£)			Dominated[a] (22,252–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 48 *Mid-point estimates of cost per QALY for paclitaxel versus E4-CMF4 based on an indirect comparison with the CALGB 9344 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	21,348 (18,904–24,256)	17,395 (14,896–20,345)	3,954 (3,093–4,731)
QALYs	8.35 (5.76–9.31)	8.52 (5.88–9.59)	–0.18 (–0.60 to 0.31)
Cost per QALY (£)			Dominated[a] (10,393–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 49 *Mid-point estimates of cost per QALY for paclitaxel versus FEC6(100) based on an indirect comparison with the CALGB 9344 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	21,325 (18,899–24,254)	17,296 (14,900–20,152)	4,029 (3,077–4,874)
QALYs	8.34 (7.83–8.82)	8.88 (5.95–9.96)	–0.53 (–1.01 to 0.02)
Cost per QALY (£)			Dominated[a] (192,904–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

TABLE 50 *Mid-point estimates of cost per QALY for paclitaxel versus FEC6(50) based on an indirect comparison with the CALGB 9344 study (10,000 runs)*

	Intervention	Comparator	Marginal
Costs (£)	21,361 (18,949–24,273)	16,483 (14,072–19,462)	4,869 (3,901–5,076)
QALYs	8.36 (5.76–9.31)	8.69 (5.97–9.77)	–0.33 (–0.81 to 0.22)
Cost per QALY (£)			Dominated[a] (18,441–dom[a])

[a] Dominated (dom) indicates that the intervention costs more and provides less benefit than the comparator.

uncertainty about where in the range of effectiveness the FEC6 regimen for doses of epirubicin commonly used in the UK lies between FEC6(50) and FEC6(100) is much less important than the overall uncertainty in the cost-effectiveness of docetaxel compared with FEC6 regimens in general.

The results of the indirect analysis should be interpreted with caution as the analysis was carried out by combining data from several trials, each of which differs slightly in terms of the trial populations enrolled and the exact doses and timings of the regimens. These factors introduce a higher potential for bias than seen in direct randomised comparisons.

Despite these limitations, the indirect comparison does show that the benefits of taxane-containing regimens compared with regimens in current use in the UK is subject to large uncertainty due to the lack of direct trial comparisons between these interventions. Consequently, the cost-effectiveness of taxanes relative to current standard care is unproven at this time.

Discussion of cost-effectiveness results

Summary of key results

The cost-effectiveness results suggest that the cost per QALY for taxane- compared with non-taxane-containing chemotherapy varies depending on the taxane under consideration and the specific trial used as the basis of the analysis. Docetaxel has a cost per QALY of £12,000 (range £7000–39,000) compared with non-taxane-containing

chemotherapy based on the regimens used in the BCRIG 001 study, whereas paclitaxel has a cost per QALY of £43,000 (range £16,000–dominated) compared with non-taxane-containing chemotherapy based on the regimens used in the NSABP B28 study and a cost per QALY of £39,000 (range £12,000–dominated) based on the regimens used in the CALGB 9344 study.

The estimated ICER for taxane- relative to non-taxane-containing chemotherapy is lower for docetaxel based on the BCIRG 001 study than it is for paclitaxel based on both the NSABP B28 and CALGB 9344 studies. This is partly due to the HR for recurrence, which is lower in BCIRG 0001 than the two paclitaxel trials which were modelled. In addition, the paclitaxel regimens have a larger number of cycles (four cycles of AC followed by four cycles of paclitaxel) than the comparator arm (four cycles of AC only) and therefore the period on treatment is 12 weeks longer in the intervention arm in the first year of the model. It is assumed that the QoL of patients is lower during the chemotherapy period and this QoL for patients receiving a longer period of therapy on paclitaxel reduces the QALY benefits for the paclitaxel arm. The impact of this QoL decrement due to time spent on chemotherapy is smaller when paclitaxel is compared with current standard UK regimens which employ more than four cycles of chemotherapy.

The assumption regarding the benefits in the taxane arm relative to the comparator arm, after the current follow-up period of 5 years, has a major influence on the ICER. The base case for the ScHARR model assumes that the benefits in terms of rates of recurrence are the same in both arms after the first 5 years. This is supported by the EBCTCG overview paper,[16] which provides an overview of randomised trials of chemotherapy and tamoxifen. This suggests that 6 months of anthracycline-based chemotherapy for patients with early breast cancer provides benefits in terms of a reduction in the risk of recurrence compared with non-anthracycline chemotherapy for around 5 years. There are other examples of treatments for early breast cancer which offer benefits, in terms of reduced risk of recurrence well beyond the treatment period. For instance, the benefits of 5 years of treatment with tamoxifen are shown to reduce the risk of recurrence for around 10 years, demonstrating a protective "carry-over" effect for 5 years beyond the treatment period. Assuming that the benefits are maintained for a further 5 years (10 years in total) reduces the ICERs by more than 50%.

Within the model, the recurrence curve for the comparator arm is extrapolated by fitting a parametric survival model to the published recurrence data from the relevant trial. This extrapolation may overestimate recurrence in the period between 5 and 15 years, as it is expected that the rate of recurrence will fall after the first few years and this may not be taken into account by the extrapolation. The EBCTCG overview[16] indicates that recurrence for all patients on polychemotherapy is between 40 and 50% at 15 years, compared with between 60 and 70% in our model. However, the patient group under consideration in the model is a higher risk group (N+ve women eligible for anthracycline-based chemotherapy) and therefore recurrence rates within this group are expected to be higher. Decreasing the annual recurrence rate by 50% in years 5–15 gave a 15-year recurrence rate of 45–55% and reduced the mean cost per QALY of paclitaxel to between £20,000 and £30,000 depending on the trial considered. This suggests that although the base-case cost-effectiveness results overestimate the long-term hazard of recurrence and therefore underestimate the cost-effectiveness of taxanes, the true recurrence is likely to be over 50% in the population eligible to receive taxanes and therefore the cost per QALY of paclitaxel is unlikely to be under £20,000.

The benefits of taxanes in terms of OS in the long term are not yet known due to the relatively short follow-up data available. The model assumes that benefits from reduced recurrence for patients in the taxane arm during the first 5 years will translate into OS benefits in the medium to long term. This is supported by the evidence available to date. Of trials reporting OS, two out of five docetaxel trials reported significant improvement for the taxane group, as did two out of five paclitaxel trials. Reported OS rates favoured taxane treatment in all cases, with absolute benefit of ranging from 1 to 5% for docetaxel and from 1 to 3% for paclitaxel.

The ScHARR model assumes the same rate of progression for patients with contralateral disease and locoregional recurrence. This may overestimate the benefits of taxanes as there is some evidence that patients with contralateral disease have a better prognosis than patients with locoregional recurrence. In the ScHARR model, these patients will have a worse prognosis than might be expected and will therefore benefit more from taxanes, in absolute terms, and this will produce a lower ICER. However, the proportion of patients who will develop contralateral disease is

very low and the impact on results is likely to be small.

A key influence on cost-effectiveness results is the length of analysis. The cost of taxanes occurs in the first few months. However, cost offsets for the taxane arm are accrued gradually over time, resulting from the lower rate of progression experienced. The model assumes that benefits from reduced recurrence will translate into OS benefits in the medium to long term. Restricting the analysis to a period of 10 years reduces the period over which benefits can be accrued and doubles the ICER for docetaxel and more than triples it for paclitaxel.

The cost of treating AEs is higher for taxane-containing regimens than for non-taxane-containing regimens. It is also higher for docetaxel-containing regimens than for paclitaxel-containing regimens, based on the trial evidence used in the economic model. This may result from a difference in taxanes with regard to toxicity profiles or possibly because sequential taxanes have a better safety profile than concurrent taxanes. Uncertainty exists in relation to serious AEs with potential long-term implications, namely cardiotoxicity and severe gastrointestinal toxicity. These are not currently included in the model, but could impact on future costs and QALYs, increasing the estimated ICER.

Generalisability of results

The trials selected as the basis for economic analysis were those which used the taxanes in accordance with current UK marketing authorisation and had also reported in full. However, the comparators used by these trials restrict the generalisability of the results, as they do not conform to current standard care in the UK. The comparators in these trials – FAC6 and AC4 – may be less effective than standard UK care. If this is the case, this would have the impact of lowering the benefits of taxanes compared with standard treatment in the UK, resulting in an increase in the estimates of the ICER. Equally, if the marginal cost of taxanes is smaller when compared with FEC6 and E4-CMF4, then this may counteract some of the potential increase, with the net effect being difficult to estimate.

For this reason, an indirect comparison was undertaken to allow a comparison of taxanes against FEC6 and E4-CMF4. We have presented results for taxane-containing regimens versus FEC6(50) and FEC6(100). These are not doses of epirubicin that are commonly used in the UK but these two estimates should be considered as providing a range for the cost-effectiveness of taxanes relative to doses in common use which vary between 60 and 90 mg/m^2. The indirect analysis shows that there is a high degree of uncertainty in the benefits of taxane-containing regimens when compared with standard regimens used in the UK. This high degree of uncertainty reflects the fact that we estimated the incremental effectiveness by combining multiple HRs, each with their own uncertainty. However, the probabilistic sensitivity analysis does not encompass all the uncertainty associated with making an indirect comparison. For example, in the indirect comparison of DAC6 versus FEC6(100) we had to assume that the FEC6(50) regimens used in the FASG and Coombes trials were equivalent when in fact the FEC6 regimen in the Coombe trial used 4-weekly FEC6 and 600 mg/m^2 of fluorouracil and cyclophosphamide whereas the GEICAM trial used 3-weekly FEC and 500 mg/m^2 of fluorouracil and cyclophosphamide. There were also differences in the patient populations enrolled in each trial. Although we were able to adjust the HRs for nodal status to obtain an estimate for the N+ve population, we were not able to adjust for all heterogeneity between the trial populations. All of these factors have the potential to introduce bias. Therefore, the indirect comparison should be considered as an indicative analysis showing the minimum uncertainty in the cost-effectiveness achievable with the current evidence base. As such, it does show that there is a high degree of uncertainty in the benefit of taxanes compared with current standard practice and therefore that the cost-effectiveness of taxanes relative to current standard care is unproven at this time. The cost-effectiveness of taxanes will need to be reconsidered when further data become available from ongoing trials comparing taxanes with standard UK regimens.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Sequential taxane administration would mean that patients require more chemotherapy sessions (concurrent taxane administration may mean longer chemotherapy sessions). This would increase the burden on chemotherapy administration units in terms of longer patient stay and staffing time.

More chemotherapy sessions will have an impact on patients, and almost certainly their carers/family, in terms of time spent in therapy and travel time, and transport requirements which will include financial cost. For employed patients, and in many cases their carers/family, therapy will involve time away from paid employment. Employers may be liable for statutory sick pay. Women incapable of paid employment for 28 weeks or more may be eligible for incapacity benefit.[101]

Serious AEs having implications for the NHS are those with long-term implications, namely cardiotoxicity and severe gastrointestinal toxicity. Long-term follow-up of patients will be required to assess for these conditions.

Family and friends may be affected by patients' serious AEs in terms of hospital visits. Side-effects during therapy may require carers to spend more time with patients, in addition to causing distress. Premenopausal patients may have concerns over implications for future fertility.

Patients require the provision of adequate information regarding possible side-effects and benefits in survival.[101] This is necessary as different patients will place different values on potential advantages and disadvantages of therapy, and want to be able to make an informed choice about chemotherapy. It is also important for patients commencing chemotherapy to know what they might expect before their first treatment session, as this can be a considerable cause of anxiety.[102]

However, given the expected benefits of taxanes in terms of improvements in DFS and the potential for improved OS, it is likely that women will make an informed choice to receive taxane therapy despite the short-term impact on their QoL. In addition, the reduction in the number of recurrences for patients on taxanes will result in a lower demand for NHS resources in the future.

Chapter 6
Discussion

Statement of principal findings

Eleven trials reporting effectiveness data were identified. These varied considerably in chemotherapy regimens of both taxane and comparator arms. Heterogeneity of interventions, comparators and populations precluded meta-analysis.

Eight of the 11 trials reported a significant improvement in DFS or TTR for taxanes over comparator regimens. For the four docetaxel trials reporting significant differences in DFS between groups, HRs varied from 0.67 to 0.83, with an absolute difference in DFS rates of 5–7% favouring the docetaxel groups. One docetaxel trial showed no difference in DFS rates between groups, and another found a non-significant difference favouring the docetaxel group. Two paclitaxel trials reported a significant improvement in DFS and two paclitaxel trials a significant improvement in TTR, for the paclitaxel over the comparator arms. HRs varied from 0.63 to 0.83, with absolute differences in DFS or TTR rates between trial arms of 4–6% favouring the paclitaxel group. For paclitaxel trials not finding a significant difference in DFS between groups, the direction of effect favoured paclitaxel.

Trials were powered to investigate DFS/TTR, but many trials also investigated OS. Of trials reporting OS, two out of five docetaxel trials reported significant improvement for the taxane group, as did two out of five paclitaxel trials, although one trial was based on a small sample size. Reported OS rates favoured taxane treatment in all cases, with absolute benefit ranging from 1 to 5% for docetaxel and from 1 to 3% for paclitaxel.

Docetaxel was associated with more AEs than paclitaxel, most notably febrile neutropenia. Taxanes produced cardiotoxicity, although this was not reported to be greater than for anthracycline comparator arms in all trials. Treatment-related deaths were uncommon, ranging from 0 to 0.64% across trials. Where reported, all chemotherapy regimens caused HRQoL to deteriorate during treatment. There was some indication that taxanes were associated with greater worsening of some aspects of HRQol, although in the case of docetaxel this may be ameliorated by receipt of G-CSF. Following treatment, there were no clinically significant differences in HRQoL between taxane and comparator treatment groups.

Differences in comparator arms make it difficult to compare docetaxel and paclitaxel in terms of clinical effectiveness. It seems there was a slight advantage of docetaxel over paclitaxel in improving DFS. However, docetaxel was associated with more AEs than paclitaxel. It is not clear whether this was due to docetaxel being administered concurrently and paclitaxel being administered sequentially to anthracyclines.

There were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK. One docetaxel trial and two paclitaxel trials used taxanes in strict accordance with current UK marketing authorisation. Four different trials used comparators which are frequently used in UK practice: two docetaxel and two paclitaxel trials.

The economic analysis shows that when employing a willingness to pay threshold of £30,000 per QALY, the DAC6 regimen has a high probability (95%) of being cost-effective compared with the FAC6 regimen, whereas AC4 followed by paclitaxel has a low probability (30–40%) of being cost-effective compared with AC4 alone.

However, these comparators do not reflect current standard practice in the UK. For this reason, an indirect comparison was carried out to assess the cost-effectiveness of taxanes relative to regimens in common use in the UK (FEC6 and E4-CMF4). The indirect comparison has many limitations and can therefore only be considered an indicative analysis showing the minimum uncertainty in the cost-effectiveness achievable with the current evidence base. As such, it does show that there is a high degree of uncertainty in the benefit of taxanes compared with regimens in common use in the UK and therefore that the cost-effectiveness of taxanes relative to current standard care is unproven at this time.

Strengths and limitations of the assessment

Strengths

- The model structure has been used in previous HTAs[103] and has been previously shown to be robust.
- The trial data were extrapolated beyond the current results to allow estimates of lifetime costs and benefits to be produced. Probabilistic sensitivity analysis was undertaken to take account of uncertainty in input parameters.

Limitations

- The effectiveness trials identified varied considerably in chemotherapy regimens of both taxane and comparator arms. Heterogeneity of interventions, comparators and populations precluded meta-analysis.
- The comparators used by taxane trials restrict the generalisability of the results from the direct comparisons. Only one docetaxel and two paclitaxel trials used taxanes in accordance with their current UK marketing authorisation, but the comparator arms in these trials do not conform to current standard care in the UK. An indirect comparison was undertaken, but the results of this must be interpreted with caution.
- Clinical data are lacking in some areas, which resulted in assumptions being made on the basis of expert opinion. In these cases, sensitivity analysis was used to test the impact of these assumptions on the results.
- The focus on taxanes used in line with their UK marketing authorisation restricted the evidence base on which we based our analysis, as many of the trials identified investigated taxane regimens which were not in line with the UK marketing authorisation.

Uncertainties

The major uncertainties in this assessment relate to the lack of trial evidence comparing taxanes used according to their current UK marketing authorisation with regimens commonly used in the UK. An indirect analysis was carried out but this is subject to a high degree of uncertainty as it combines data from several trials, each of which differs slightly in terms of the trial populations enrolled and the exact doses and timings of the regimens.

Other key areas of uncertainty include the length of benefits in the taxane arm relative to the comparator arm. This has a major influence on the ICER. The base case for the ScHARR model assumes that the rate of recurrence is the same in both arms after the first 5 years. Assuming that the benefits of taxanes continue for an additional 5 years reduces the ICERs by over 50%.

In addition, there is uncertainty regarding the benefits of taxanes in terms of OS. These benefits are not yet known with certainty due to the relatively short follow-up data available. The model assumes that benefits from reduced recurrence in the first 5 years will translate into OS benefits in the medium and long term. There is as yet no long-term evidence to support this as the maximum follow-up from the published trials is currently 69 months.

Chapter 7
Conclusions

There is a large degree of heterogeneity in the evidence base for the effectiveness of taxanes compared with non-taxanes containing regimens in terms of the interventions, comparators and populations. Eight of the 11 trials providing effectiveness data reported a significant improvement in DFS or TTR for taxanes over comparator regimens. The remaining three trials found no significant differences between the groups in DFS/TTR. There were few data available comparing licensed regimens of taxanes with chemotherapy regimens commonly used in the UK.

The cost-effectiveness results suggest that docetaxel-containing chemotherapy has a cost per QALY of £12,000 (range £7000–39,000) compared with non-taxane-containing chemotherapy based on the regimens used in the BCRIG 001 study, whereas paclitaxel-containing chemotherapy has a cost per QALY of £43,000 (range £16,000–dominated) compared with non-taxane-containing chemotherapy based on the regimens used in the NSABP B28 study and a cost per QALY of £39,000 (range £12,000–dominated) based on the regimens used in the CALGB 9344 study. However, the comparator regimens in these trials do not reflect the regimens currently used in the UK.

An indirect comparison was carried out but this is subject to a high degree of uncertainty. It does however demonstrate that there is a high degree of uncertainty in the effectiveness of taxane-containing regimens relative to regimens in common use in the UK and therefore the cost-effectiveness of taxanes compared with current standard practice is considered to be unproven at this time. The cost-effectiveness of taxanes will need to be reconsidered when further data become available from ongoing trials comparing taxanes with standard UK regimens.

Suggested research priorities

The greatest priority for future research is to compare taxanes in line with current UK marketing authorisation with anthracycline-containing regimens commonly used in the UK. Additional data on the effectiveness of taxanes for the over-70s is required. Further research is required into the long-term outcomes of taxane therapy, such as whether there are any long-term AEs which impact significantly on OS or QoL and whether the increases in DFS will translate into increases in OS.

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Contribution of authors

Sue Ward (Senior Research Fellow) was the review lead. Angie Rees (Information Officer) and Anna Wilkinson (Information Officer) developed the search strategy and undertook searches. Sue Ward, Emma Simpson (Research Fellow), Sarah Davis (Research Fellow) and Danny Hind (Research Fellow) undertook the clinical and cost-effectiveness reviews.

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Appendix 1

Literature search strategies

1 taxol.tw.
2 taxotere.tw.
3 anzatax.tw.
4 114977-28-5.rn.
5 33069-62-4.rn.
6 docetaxel.mp.
7 paclitaxel.mp. or exp PACLITAXEL/
8 Taxoids/
9 taxane$.tw.
10 or/1-9
11 [exp *Breast Neoplasms/]
12 ((breast$ or mamma$) adj5 (cancer$ or carcin$ or tumour$ or tumour$ or neoplasm$)).tw.
13 11 or 12
14 10 and 13
15 limit 14 to clinical trial
16 [from 15 keep 1-739]
17 randomized controlled trial.pt.
18 controlled clinical trial.pt.
19 Randomized Controlled Trials/
20 random allocation/
21 double blind method/
22 Single-Blind Method/
23 17 or 18 or 19 or 20 or 21 or 22
24 clinical trial.pt.
25 [exp clinical trials/]
26 PLACEBOS/
27 placebo$.ti,ab.
28 random$.ti,ab.
29 research design/
30 (clin$ adj25 trial$).ti,ab.
31 ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
32 or/24-31
33 (animals not human).sh.
34 23 not 33
35 32 not 33
36 35 or 34
37 Comparative Study/
38 [exp Evaluation Studies/]
39 Follow-Up Studies/
40 Prospective Studies/
41 (control$ or prospectiv$ or volunteer$).ti,ab.
42 or/37-41
43 42 not 33
44 43 not (34 or 36)
45 34 or 36 or 44
46 14 and 45

Appendix 2

Quality assessment

A critical appraisal form based on NHS CRD Report No. 4[35] is used.

Quality assessment: docetaxel trials

	BCIRG 001	ECOG 2197	PACS 01	USO 9735	BIG 298	Taxit 216	TACT	GEICAM 9805	RAPP 01	PACS 04	GOIM 9902
Was the method used to assign participants to the treatment groups really random?	Y	?	?	?	?	Y	?	?	Y	?	?
What method of assignment was used?	Stratified	?	?	?	Stratified	Computerised, stratified	?	?	Computerised random number generator, stratified	?	Stratified
Was the allocation of treatment concealed?	?	?	?	?	?	?	?	?	Y	?	?
What method was used to conceal treatment allocation?	?	?	?	?	?	?	?	?	Centralised randomisation	?	?
Was the number of participants who were randomised stated?	Y	?	Y	Y	Y	Y	Y – for QoL subgroup	Y	Y	Y	Y
Were details of baseline comparability presented?	Y	?	N	Y	N	N	N	N	Y	N	Y
Was baseline comparability achieved?	Y	?	Y	?	Y	?	?	?	Y	?	Y
Were the eligibility criteria for study entry specified?	Y	?	Y	Y	Y	Y	Y – for QoL subgroup	Y	Y	Y	Y
Were any co-interventions identified that may influence the the outcomes for each groups	N	N	N	N	N	N	N	G-CSF co-intervention, for intervention group during later part of study	N	N	N
Were the outcome assessors blinded to the treatment allocations?	N	N	N	N	N	N	N	N	N	N	N
Were the individuals who administered the intervention blinded to the treatment allocation?	N	N	N	N	N	N	N	N	N	N	N

continued

	BCIRG 001	ECOG 2197	PACS 01	USO 9735	BIG 298	Taxit 216	TACT	GEICAM 9805	RAPP 01	PACS 04	GOIM 9902
Were the participants who received the intervention blinded to the treatment allocation?	N	N	N	N	N	N	N	N	N	N	N
Was the success of the blinding procedure assessed?	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	Y	Y	?	?	NA	NA (safety analysis)	NA (trial ended, safety analysis)	NA (safety analysis)	NA (safety analysis)
Were the reasons for withdrawal stated?	Y	?	N	N	N	N	?	N	Y	N	N
Was an ITT analysis included?	Y	?	Y	?	?	?	NA	NA (safety analysis)	NA (trial ended, safety analysis)	NA (safety analysis)	NA (safety analysis)

NA, not applicable; N, no; ?, unclear; Y, yes.

Quality assessment: paclitaxel trials

	NSABP B28	CALGB 9344	HCOG	ECTO	GEICAM 9906	Elling Phase 2	MIG 5
Was the method used to assign participants to the treatment groups really random?	Y	?	Y	?	Y	?	?
What method of assignment was used?	Biased-coin minimisation method	?	Stratified; balanced by centre	?	Stratified	?	?
Was the allocation of treatment concealed?	Y	?	Y	?	?	?	?
What method was used to conceal treatment allocation?	Central randomisation	?	Centrally allocated	?	?	?	?
Was the number of participants who were randomised stated?	Y	Y	Y	Y	Y	Y	Y
Were details of baseline comparability presented?	N	Y	Y	Y	Y	Y	Y
Was baseline comparability achieved?	Y	Y	Y (except for nuclear grade)	Y	Y	Y	Y
Were the eligibility criteria for study entry specified?	Y	Y	Y	Y	Y	Y	Y
Were any co-interventions identified that may influence the outcomes for each group?	N	N	N	N	N	N	N
Were the outcome assessors blinded to the treatment allocations?	N	N	N	N	N	N	N
Were the individuals who administered the intervention blinded to the treatment allocation?	N	N	N	N	N	N	N
Were the participants who received the intervention blinded to the treatment allocation?	N	N	N	N	N	N	N
Was the success of the blinding procedure assessed?	NA	NA	NA	NA	NA	NA	NA

continued

	NSABP B28	CALGB 9344	HCOG	ECTO	GEICAM 9906	Elling Phase 2	MIG 5
Were at least 80% of the participants originally included in the randomised process followed up in the final analysis?	Y	Y	Y	Y	Y	NA	NA
Were the reasons for withdrawal stated?	Y	Y	Y	N	NA	N	N
Was an ITT analysis included?	Y (except for 1 patient with no data)	N (includes all patients who received any treatment, not all randomised)	N (includes all eligible, including drop-outs;. does not include 9 ineligible, randomised patients)	N	Y	NA	NA

NA, not applicable; N, no; ?, unclear; Y, yes.

Appendix 3

Data abstraction tables

Concomitant therapy

Docetaxel concomitant therapy

Trial	Concomitant therapy	Endocrine therapy
BCIRG 001	Docetaxel group – dexamethasone premedication (8 mg orally every 12 hours six times beginning the day before treatment started) and prophylactic antibiotic (500 mg of ciprofloxacin twice daily on days 5–14 of each cycle). Control group – prophylactic antibiotics only after an episode of febrile neutropenia or infection. Patients with one episode of febrile neutropenia or infection in subsequent cycles, administration of G-CSF was mandatory (150 μg/m^2/day of lenograstim or 5 μg/kg body wt/day of filgrastim on days 4–11). Adjuvant radiation therapy: docetaxel group 68.8%; control group 71.9%	Tamoxifen, 20 mg daily for 5 years, for patients with ER+ and/or PR+, after chemotherapy completed
ECOG 2197	Docetaxel group – prophylactic antibiotic (500 mg of ciprofloxacin twice daily on days 8–17 of each cycle). G-CSF "per ASCO guidelines"	Tamoxifen, 5 years, for patients with ER+ and/or PR+, after chemotherapy completed (60% across both groups on tamoxifen)
PACS 01	Docetaxel group – prophylactic corticosteroid therapy (methylprednisolone) for each cycle of docetaxel: 48 mg for 6 doses from day –1 to day +1, and antiemetic prophylaxis with 5-anti-HT3. G-CSF (filgrastim 5 μg/kg/day) prescribed in case of febrile neutropenia or delay in initiation at day 21, for all subsequent courses, not allowed for the 1st cycle of docetaxel. Radiation therapy within 4 weeks after last chemotherapy cycle. (Radiation therapy: docetaxel group 98.4%; control group 98.8%)	Tamoxifen, 20 mg daily for 5 years, HR+ patients, after chemotherapy completed (tamoxifen control 65.5%; docetaxel 68.4%)
USO 9735	Radiation therapy followed chemotherapy if indicated	Tamoxifen if indicated, after chemotherapy completed
BIG 2-98	Radiation therapy according to local guidelines	
GEICAM 9805	After enrolling 224 patients, study amended to require prophylactic G-CSF for docetaxel group but not control group	
RAPP 01	Use of G-CSF was recommended only for grade 3 or 4 febrile neutropenia with a temperature exceeding 38°C and requiring oral or intravenous antibiotics (National Cancer Institute Common Toxicity Criteria). Radiation therapy according to standard guidelines	Tamoxifen, 20 mg daily for 5 years, for patients with ER+ and/or PR+, after chemotherapy completed
PACS 04	Radiation therapy mandatory after conservative surgery	Tamoxifen for HR+ patients

Paclitaxel concomitant therapy

Trial	Concomitant therapy	Endocrine therapy
NSABP B28	Radiation therapy for lumpectomy patients, after completion of chemotherapy	Tamoxifen, 20 mg daily for 5 years, patients aged 50+ or under 50 years with ER+ or PR+ tumours received tamoxifen 20 mg daily for 5 years starting on day 1 of first AC cycle (tamoxifen 84.6%, control 84.5%)
CALGB 9344	GCSF and ciprofloxacin for all patients on high-dose doxorubicin, and for other patients following an episode of febrile neutropenia. Radiation therapy for all patients with breast-conserving surgery, and some postmastectomy (decided by clinician), after completion of chemotherapy (radiation to breast, for some patients also to regional lymph nodes)	Tamoxifen after completion of chemotherapy (tamoxifen 94% patients HR+, 21% patients HR–
HCOG	After completion of chemotherapy, prophylactic treatment with G-CSF (filgrastim 5 μg/kg) on days 3–10 of each cycle. Radiation therapy all patients with breast-conserving surgery or four or more positive lymph nodes and/or tumour size 5+ cm	Tamoxifen, 20 mg daily for 5 years, ER+ and/or PR+ or unknown receptor status, after completion of chemotherapy. Premenopausal patients – ovarian suppression with monthly intramuscular injections of 2.5 mg triptoreline for 1 year
ECTO	Radiation therapy for some patients	Tamoxifen for some patients
GEICAM 9906	Radiation therapy after conservative surgery, and recommended in patients with >4 axillary lymph nodes and tumours >5 cm	Tamoxifen, 5 years, HR+
MIG 5	Radiation therapy for some patients	Tamoxifen for some patients

Relative dose intensities

Docetaxel – available data on treatment completion or relative dose intensities (RDIs)

Trial	Group	Treatment completion or RDI
BCIRG 001	DAC6	Completed 6 cycles 91.3% patients. Modified by dose/delay 33.6% patients. Median RDI 99%
BCIRG 001	FAC6	Completed 6 cycles 96.6% patients. Modified by dose/delay 39.8% patients. Median RDI 98%
PACS 01	FEC3-D3	Treatment completed 93.4% patients. Mean RDI: epirubicin 99.6%; docetaxel 99.3%. <90% RDI epirubicin 15.1% patients; docetaxel 18.1% patients
PACS 01	FEC6	Treatment completed 95% patients. Mean RDI epirubicin 98.4%. <90% RDI epirubicin 15.2% patients
Taxit 216	E4-D4-CMF4	All cycles completed 73.3%. All patients ⩾90% planned dose intensity
Taxit 216	E4-CMF4	All cycles completed 89.8%. All patients ⩾90% planned dose intensity
RAPP 01	DA	Discontinued prematurely in 17 patients (5.5%) because of AEs (11 patients) or patient refusal to continue therapy (6 patients)
RAPP 01	AC	No discontinuation

Paclitaxel – available data on treatment completion or RDIs

Trial	Group	Treatment completion or RDI
NSABP B28	AC4-P4	8.8% patients did not start paclitaxel (88% of these due to patient withdrawal). 75.9% patients completed all 8 cycles of protocol therapy
NSABP B28	AC4	Both groups 98% patients completed 4 cycles AC
CALGB 9344	AC4-P4	3.6% patients did not start paclitaxel (70% of these due to patient withdrawal). 92% patients completed all 4 cycles paclitaxel
CALGB 9344	AC4	Both groups 98% patients completed 4 cycles AC[a]
HCOG	E3-P3-CMF3	Discontinued treatment 5% patients. Median cycles delivered 9 (range 1–11). Median RDI docetaxel 0.98; E 0.99; C 0.98; M 0.98; F 0.98. Delayed cycles 23%. Cycles with 90+% full dose: docetaxel 86%; E 92%; CMF 86%
HCOG	E4-CMF4	Discontinued treatment 3% patients. Median cycles delivered 8 (range 1–8). Median RDI E 0.97; C 0.97; M 0.96; F 0.97. Delayed cycles 26%. Cycles with 90+% full dose: E 90%; CMF 82%[b]
ECTO	PA4-CMF4	Withdrawal due to toxicity 2.1%; refusal to complete 3.2%
ECTO	A4-CMF4	Withdrawal due to toxicity 1.4%; refusal to complete 5.1%
GEICAM 9906	FEC4-P8	Median number of FEC cycles 4 (range 1–4). Median number of paclitaxel administrations 8 (range 1–8). RDI F 99.1%; E 98.8%; C 99.1% during the first 4 cycles. Median RDI paclitaxel 99.5%. Completed all cycles of FEC 99%. Completed paclitaxel 89%. RDI > 0.90 FEC 80% patients, paclitaxel 77% patients
GEICAM 9906	FEC6	Median number of FEC cycles 6 (range 1–6). RDI F 99.0%; E 98.8%; C 99.1% during the first 4 cycles. Patients completing all cycles of FEC 98%. RDI > 0.90 87% patients

[a] Dose reductions and delays significantly more frequent in patients receiving higher doxorubicin doses.
[b] Older patients (aged 65+ years) completed chemotherapy at a significantly lower rate in the paclitaxel group (95% <65 years versus 77% 65+ years; $p = 0.003$), but not in the control group (95% <65 years versus 98% 65+ years; $p = 0.48$).

Adverse events

Docetaxel – haematological adverse events (table 1 of 2)

Trial	Follow-up (median) (months)	Group	*N*	Neutropenia		Neutropenia grade 3/4		Febrile neutropenia		Neutropenic infection		Leukaemia		MDS/AML	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	71.4	<0.001	65.5	<0.001	(With grade 4 neutropenia) 28.8	<0.001	(With grade 4 neutropenia) 20.4	<0.001	0.27			
BCIRG 001	55	FAC6	746	82		49.3		(With grade 4 neutropenia) 4.4		(With grade 4 neutropenia) 10.8		0.13			
ECOG 2197	59	DA4	1444					53 months' follow-up 19. 59 months' neutropenia associated with fever or infection 28						0.48	
ECOG 2197	59	AC4	1445					53 months' follow-up 6. 59 months' neutropenia associated with fever or infection 10						0.48	
PACS 01	59.7	FEC3-D3	1001	Cycles 1–3 21.5; cycles 4–6 10.9	Cycles 1–3 0.79; cycles 4–6 <0.001			Cycle 4 4.6		0.001		0.34			
PACS 01	59.7	FEC6	995	Cycles 1–3 21.0; cycles 4–6 20.2				Cycle 4 1.0				0.5			
USO 9735	66	DC4	506	63	NS	59	NS	(Neutropenic fever) 6	(Neutropenic fever) 0.03						

continued

Trial	Follow-up (median) (months)	Group	*N*	Neutropenia		Neutropenia grade 3/4		Febrile neutropenia		Neutropenic infection		Leukaemia		MDS/AML	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
USO 9735	66	AC4	510	58		55		(Neutropenic fever) 3							
GEICAM 9805	24	DAC6	530					Without G-CSF 24.6; with G-CSF 5.8							
GEICAM 9805	24	FAC6	520					2.3							
RAPP 01	24	DA4	311					40.8	<0.001						
RAPP 01	24	AC4	316					7.1							
PACS 04	?	DE6	(Across both groups 2622)					31.4							
PACS 04	?	FEC6						10.3							
GOIM 9902	?	D4-EC4	254			Grade 3 21.3; grade 4 48.8		Grade 3/4 9.5							
GOIM 9902	?	EC4	241			Grade 3 29; grade 4 32.7		Grade 3/4 3.7							

NS, not significant; MDS/AML, myelodysplastic syndrome/acute myeloid leukaemia.

Docetaxel – haematological adverse events (table 2 of 2)

Trial	Follow-up (median) (months)	Group	*N*	Thrombocytopenia		Thrombocytopenia grade 3/4		Anaemia		Anaemia grade 3/4		Need for blood transfusions	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	39.4	<0.001	2	<0.001	91.5	<0.001	4.3	0.003	4.6	<0.001
BCIRG 001	55	FAC6	746	27.7		1.2		71.7		1.6		1.5	
ECOG 2197	59	DA4	1444										
ECOG 2197	59	AC4	1445										
PACS 01	59.7	FEC3-D3	1001			0.4	0.71			0.7	0.12		
PACS 01	59.7	FEC6	995			0.3				1.4			
USO 9735	66	DC4	506	<1	NS	<1	NS	6	NS	<1	NS		
USO 9735	66	AC4	510	<1		<1		9		1			
GEICAM 9805	24	DAC6	530										
GEICAM 9805	24	FAC6	520										
RAPP 01	24	DA4	311										
RAPP 01	24	AC4	316										
GOIM 9902	?	D4-EC4	254			1.6				Grade 3 2.4			
GOIM 9902	?	EC4	241			3.3				Grade 3 0			

Docetaxel – gastrointestinal adverse events (table 1 of 2)

Trial	Follow-up (median) (months)	Group	*N*	Nausea		Nausea grade 3/4		Vomiting		Vomiting grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	80.5	<0.001	5.1	0.001	44.5	<0.001	4.3	0.013
BCIRG 001	55	FAC6	746	88		9.5		59.2		7.3	
ECOG 2197	59	DA4	1444								
ECOG 2197	59	AC4	1445								
PACS 01	59.7	FEC3-D3	1001							(Nausea/vomiting) cycles 1–3 10.1; cycles 4–6 1.6	Cycles 1–3 0.031; cycles 4–6 <0.001
PACS 01	59.7	FEC6	995							(Nausea/vomiting) Cycles 1–3 13.2; cycles 4–6 11.0	
USO 9735	66	DC4	506	53	<0.01	2	<0.01	16	<0.01	<1	<0.01
USO 9735	66	AC4	510	81		7		43		5	
GEICAM 9805	24	DAC6	530								
GEICAM 9805	24	FAC6	520								
RAPP 01	24	DA4	311					Nausea/vomiting grade 0/2 94.5	Nausea/vomiting 0.05	Nausea/vomiting 5.5	Nausea/vomiting 0.05
RAPP 01	24	AC4	316					Nausea/vomiting grade 0/2 90.5		Nausea/vomiting 9.5	
PACS 04	"Preliminary data"	DE6	(Across both groups 2622)							Nausea/vomiting 7.5	
PACS 04	"Preliminary data"	FEC6								Nausea/vomiting 13.2	
GOIM 9902	?	D4-EC4	254							Nausea/vomiting 3.1	
GOIM 9902	?	EC4	241							Nausea/vomiting 6.2	

Docetaxel – gastrointestinal adverse events (table 2 of 2)

Trial	Follow-up (median) (months)	Group	*N*	Stomatitis		Stomatitis grade 3/4		Diarrhoea		Diarrhoea grade 3/4		Mucositis		Mucositis grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	69.4	<0.001	7.1	<0.001	35.2	0.002	3.8	0.02				
BCIRG 001	55	FAC6	746	52.9		2		27.9		1.8					
ECOG 2197	59	DA4	1444												
ECOG 2197	59	AC4	1445												
PACS 01	59.7	FEC3-D3	1001			5.9	0.05								
PACS 01	59.7	FEC6	995			4									
USO 9735	66	DC4	506												
USO 9735	66	AC4	510												
GEICAM 9805	24	DAC6	530							Without G-CSF 7.0. with G-CSF 2.6	0.0415	Grade 2/4 without G-CSF 35.1; with G-CSF 23.3	0.011		
GEICAM 9805	24	FAC6	520							0.8		Grade 2/4 24.4			
RAPP 01	24	DA4	311					Grade 0/2 97.1	Grade 0/2 0.03	2.9	0.03	Grade 0/2 95.2	Grade 0/2 0.04	4.8	0.04
RAPP 01	24	AC4	316					Grade 0/2 99.4		0.6		Grade 0/2 98		2	
GOIM 9902	?	D4-EC4	254							2.8				3.9	
GOIM 9902	?	EC4	241							0.4				3.7	

Docetaxel – neurological adverse events

Trial	Follow-up (median) (months)	Group	*N*	Neurosensory effects		Neurosensory effects grade 2		Paraesthesia		Paraesthesia grade 3/4		Peripheral neuropathy	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	25.5	<0.001	3.6							
BCIRG 001	55	FAC6	746	10.2		1.4							
ECOG 2197	59	DA4	1444										
ECOG 2197	59	AC4	1445										
PACS 01	59.7	FEC3-D3	1001										
PACS 01	59.7	FEC6	995										
USO 9735	66	DC4	506					6	NS	0	NS		
USO 9735	66	AC4	510					4		<1			
GEICAM 9805	24	DAC6	530										
GEICAM 9805	24	FAC6	520										
RAPP 01	24	DA4	311										
RAPP 01	24	AC4	316										
GOIM 9902	?	D4-EC4	254									9.9	
GOIM 9902	?	EC4	241									0	

Docetaxel – cardiac adverse events

Trial	Follow-up (median) (months)	Group	*N*	Cardiotoxicity grade 2/3			Congestive heart failure		Congestive heart failure grade 3/4/5		
				No.	%	*p*	%	*p*	No.	%	*p*
BCIRG 001	55	DAC6	745				(Mild to severe) 1.6	0.09		0.1	1.0
BCIRG 001	55	FAC6	746				(Mild to severe) 0.7			0.1	
ECOG 2197	59	DA4	1444						18	1.2	NS
ECOG 2197	59	AC4	1445						10	0.69	
PACS 01	59.7	FEC3-D3	1001		0.4	0.027	0				
PACS 01	59.7	FEC6	995		1.3		0.7				
USO 9735	66	DC4	506				0	NS		0	NS
USO 9735	66	AC4	510				0			0	
GEICAM 9805	24	DAC6	530								
GEICAM 9805	24	FAC6	520								
RAPP 01	24	DA4	311								
RAPP 01	24	AC4	316								
PACS 04	"Preliminary data"	DE6	(Across both groups 2622)	Grade 2 5							
PACS 04	"Preliminary data"	FEC6		Grade 2 4							
GOIM 9902	?	D4-EC4	254	Grade 3 0							
GOIM 9902	?	EC4	241	Grade 3 0.4							

Docetaxel – other adverse events (table 1 of 5)

Trial	Follow-up (median) (months)	Group	*N*	Nail disorder		Nail disorder grade 3/4		Skin toxicity		Skin toxicity grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	18.5	0.03	0.4	0.62	26.5	<0.001	0.8	0.51
BCIRG 001	55	FAC6	746	14.4		0.1		17.7		0.4	
ECOG 2197	59	DA4	1444								
ECOG 2197	59	AC4	1445								
PACS 01	59.7	FEC3-D3	1001	(Moderate to severe) cycles 4–6 10.3	<0.001						
PACS 01	59.7	FEC6	995	(Moderate to severe) cycles 4–6 1.0							
USO 9735	66	DC4	506								
USO 9735	66	AC4	510								
GEICAM 9805	24	DAC6	530								
GEICAM 9805	24	FAC6	520								
RAPP 01	24	DA4	311			0					
RAPP 01	24	AC4	316			0					

Docetaxel – other adverse events (table 2 of 5)

Trial	Follow-up (median) (months)	Group	*N*	Chemotherapy-related amenorrhoea		Alopecia		Arthralgia		Arthralgia grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	(3 months+) 61.7	0.007	97.8	0.39	19.4	<0.001	0.5	0.69
BCIRG 001	55	FAC6	746	(3 months+) 52.4		97.1		9		0.3	
ECOG 2197	59	DA4	1444								
ECOG 2197	59	AC4	1445								
PACS 01	59.7	FEC3-D3	1001	68.4	0.13						
PACS 01	59.7	FEC6	995	72.4							
USO 9735	66	DC4	506					24	<0.01	1	NS
USO 9735	66	AC4	510					15		1	
GEICAM 9805	24	DAC6	530								
GEICAM 9805	24	FAC6	520								
RAPP 01	24	DA4	311	77.4	<0.001						
RAPP 01	24	AC4	316	54.7							

Docetaxel – other adverse events (table 3 of 5)

Trial	Follow-up (median) (months)	Group	*N*	Myalgia		Myalgia grade 3/4		Asthenia		Asthenia grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	26.7	<0.001	0.8	0.03	80.8	<0.001	11.2	<0.001
BCIRG 001	55	FAC6	746	9.9		0		71.2		5.6	
ECOG 2197	59	DA4	1444								
ECOG 2197	59	AC4	1445								
PACS 01	59.7	FEC3-D3	1001								
PACS 01	59.7	FEC6	995								
USO 9735	66	DC4	506	33	<0.01	1	NS	79	NS	3	NS
USO 9735	66	AC4	510	17		<1		78		5	
GEICAM 9805	24	DAC6	530					Severe asthenia without G-CSF 20.2; with G-CSF 5.5	<0.0001		
GEICAM 9805	24	FAC6	520					Severe asthenia 1.8			
RAPP 01	24	DA4	311								
RAPP 01	24	AC4	316								

Docetaxel – other adverse events (table 4 of 5)

Trial	Follow-up (median) (months)	Group	*N*	Allergy		Allergy grade 3/4		Oedema		Oedema grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745	13.4	<0.001	1.3	0.007	33.7	<0.001	0.5	0.37
BCIRG 001	55	FAC6	746	3.7		0.1		12.6		0.1	
ECOG 2197	59	DA4	1444								
ECOG 2197	59	AC4	1445								
PACS 01	59.7	FEC3-D3	1001					(Moderate to severe) cycles 4–6 4.8	<0.001		
PACS 01	59.7	FEC6	995					(Moderate to severe) cycles 4–6 0.3			
USO 9735	66	DC4	506					35	<0.01	<1	NS
USO 9735	66	AC4	510					2		<1	
GEICAM 9805	24	DAC6	530								
GEICAM 9805	24	FAC6	520								
RAPP 01	24	DA4	311							0	
RAPP 01	24	AC4	316							0	
GOIM 9902	?	D4-EC4	254			Hypersensitivity reaction 4.3					
GOIM 9902	?	EC4	241			Hypersensitivity reaction 0					

Docetaxel – other adverse events (table 5 of 5)

Trial	Follow-up (median) (months)	Group	*N*	Grade 3/4 toxicity		Grade 3/4 severe non-haematologic AEs		Infection		Infection grade 3/4		Total serious AEs	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
BCIRG 001	55	DAC6	745			36.3	<0.001	39.4	0.22	3.9	0.05		
BCIRG 001	55	FAC6	746			26.6		36.3		2.2			
ECOG 2197	59	DA4	1444										
ECOG 2197	59	AC4	1445										
PACS 01	59.7	FEC3-D3	1001							1.6	0.98		
PACS 01	59.7	FEC6	995							1.6			
USO 9735	66	DC4	506					21	NS	11	NS		
USO 9735	66	AC4	510					23		12			
BIG 2-98	62.2	DA4-CMF3		28.6									
BIG 2-98	62.2	A3-D3-CMF3		35.3									
BIG 2-98	62.2	AC4-CMF3		24.7									
BIG 2-98	62.2	A4-CMF3		22.9									
GEICAM 9805	24	DAC6	530										
GEICAM 9805	24	FAC6	520										
RAPP 01	24	DA4	311									23.1	<0.001
RAPP 01	24	AC4	316									4.7	

Paclitaxel – haematological adverse events (table 1 of 3)

Trial	Follow-up (median) (months)	Group	*N*	Neutropenia		Neutropenia grade 3/4		Febrile neutropenia	
				%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531					During paclitaxel 3	
NSABP B28	64.8	AC4	1528					During AC (not just control group) 7	
CALGB 9344	69	AC4-P4	1570						
CALGB 9344	69	AC4	1551						
HCOG	61.7	E3-P3-CMF3	298	11.7	NS			2.35	
HCOG	62	E4-CMF4	297	11.2				2.69	
GEICAM 9906	46	FEC4-P8	610			21		9	
GEICAM 9906	46	FEC6	633			26		5	
Elling Phase 2	?	EC4-P4	15						
Elling Phase 2	?	EC4	13						
MIG 5	92% patients more than 12 months	PE4	268						
MIG 5	92% patients more than 12 months	FEC6	265						

Paclitaxel – haematological adverse events (table 2 of 3)

Trial	Follow-up (median) (months)	Group	*N*	Leukaemia		Myelodysplastic syndrome		MDS/AML		Thrombocytopenia		Thrombocytopenia grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531					0.39					
NSABP B28	64.8	AC4	1528					0.13					
CALGB 9344	69	AC4-P4	1570	0.25	NS	0.25	NS						
CALGB 9344	69	AC4	1551	0.45		0.13							
HCOG	61.7	E3-P3-CMF3	298									1	NS
HCOG	62	E4-CMF4	297									1	
GEICAM 9906	46	FEC4-P8	610										
GEICAM 9906	46	FEC6	633										
Elling Phase 2	?	EC4-P4	15							0			
Elling Phase 2	?	EC4	13							0			
MIG 5	92% patients more than 12 months	PE4	268										
MIG 5	92% patients more than 12 months	FEC6	265										

Paclitaxel – haematological adverse events (table 3 of 3)

Trial	Follow-up (median) (months)	Group	*N*	Leukopenia grade 3/4		Granulocytopenia		Thromboembolic events		Anaemia		Anaemia grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531			During paclitaxel (day 1) 3		During paclitaxel 1, following therapy additional 1%					
NSABP B28	64.8	AC4	1528			During AC (not just control group) (day 1) 8		During AC (not just control group) 2					
CALGB 9344	69	AC4-P4	1570			(60 mg/m^2 dose A) 16							
CALGB 9344	69	AC4	1551			During AC (not just control group) (60 mg/m^2 dose A) 62							
HCOG	61.7	E3-P3-CMF3	298	6.7	NS							1	NS
HCOG	62	E4-CMF4	297	6.4								1.7	
GEICAM 9906	46	FEC4-P8	610					0.66		1			
GEICAM 9906	46	FEC6	633					0.32		1			
Elling Phase 2	?	EC4-P4	15	10				(Phlebitis 0)				5	
Elling Phase 2	?	EC4	13	10				(Phlebitis 0)				3	
MIG 5	92% patients more than 12 months	PE4	268										
MIG 5	92% patients more than 12 months	FEC6	265										

Paclitaxel – gastrointestinal adverse events (table 1 of 2)

Trial	Follow-up (median) (months)	Group	*N*	Nausea		Nausea grade 3/4		Vomiting		Vomiting grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531								
NSABP B28	64.8	AC4	1528	During AC (not just control group) 6		During AC (not just control group) 5					
CALGB 9344	69	AC4-P4	1570	Grade 2/3/4 (60 mg/m^2 dose A) 3				Grade 2/3/4 (60 mg/m^2 dose A) 1			
CALGB 9344	69	AC4	1551	Grade 2/3/4 (60 mg/m^2 dose A) during AC (not just control group) 32				Grade 2/3/4 (60 mg/m^2 dose A) during AC (not just control group) 27			
HCOG	61.7	E3-P3-CMF3	298							Nausea/vomiting 3.7	
HCOG	62	E4-CMF4	297							Nausea/vomiting 4.5	
GEICAM 9906	46	FEC4-P8	610			5				7	
GEICAM 9906	46	FEC6	633			6				10	
Elling Phase 2	?	EC4-P4	15							7	
Elling Phase 2	?	EC4	13							6	
MIG 5	92% patients more than 12 months	PE4	268								
MIG 5	92% patients more than 12 months	FEC6	265								

Paclitaxel – gastro-intestinal adverse events (table 2 of 2)

Trial	Follow-up (median) (months)	Group	*N*	Stomatitis		Stomatitis grade 3/4		Mucositis		Obstipation grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531								
NSABP B28	64.8	AC4	1528	During AC (not just control group) 2							
CALGB 9344	69	AC4-P4	1570	Grade 2/3/4 (60 mg/m^2 dose A) 1							
CALGB 9344	69	AC4	1551	Grade 2/3/4 (60 mg/m^2 dose A) during AC (not just control group) 10							
HCOG	61.7	E3-P3-CMF3	298					2			
HCOG	62	E4-CMF4	297					2			
GEICAM 9906	46	FEC4-P8	610			4					
GEICAM 9906	46	FEC6	633			5					
Elling Phase 2	?	EC4-P4	15			0				1	
Elling Phase 2	?	EC4	13			0				1	
MIG 5	92% patients more than 12 months	PE4	268								
MIG 5	92% patients more than 12 months	FEC6	265								

Paclitaxel – neurological adverse events

Trial	Follow-up (median) (months)	Group	*N*	Peripheral neuropathy grade 3/4		Neurosensory effects		Neurosensory effects Grade 2		Paraesthesia	
				%	*p*	%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531			During paclitaxel 15		During paclitaxel grade 3+ neurosensory/ neuromotor 18			
NSABP B28	64.8	AC4	1528			(Interfered with normal functioning) 3		Developed permanent paralysis 0.07 (n = 1)			
CALGB 9344	69	AC4-P4	1570							15	
CALGB 9344	69	AC4	1551								
HCOG	61.7	E3-P3-CMF3	298	6.3	<0.001						
HCOG	62	E4-CMF4	297	0							
GEICAM 9906	46	FEC4-P8	610	4							
GEICAM 9906	46	FEC6	633	0							
Elling Phase 2	?	EC4-P4	15	0							
Elling Phase 2	?	EC4	13	0							
MIG 5	92% patients more than 12 months	PE4	268								
MIG 5	92% patients more than 12 months	FEC6	265								

Paclitaxel – cardiac adverse events

Trial	Follow-up (median) (months)	Group	*N*	Cardiotoxicity		Congestive heart failure		Congestive heart failure grade 3/4/5	
				%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531	Grade 3+ cardiac dysfunction 0.9					
NSABP B28	64.8	AC4	1528	Grade 3+ cardiac dysfunction 1.0					
CALGB 9344	69	AC4-P4	1570		NS	During therapy <1. post-therapy 2			
CALGB 9344	69	AC4	1551			During therapy <1. post-therapy 1			
HCOG	61.7	E3-P3-CMF3	298						
HCOG	62	E4-CMF4	297						
ECTO	43	PA4-CMF4		Grade 3+ 0					
ECTO	43	A4-CMF4		Grade 3+ 0.7					
GEICAM 9906	46	FEC4-P8	610	(Cardiac death/left ventricular function/arrhythmia) 0.98					
GEICAM 9906	46	FEC6	633	(Cardiac death/left ventricular function/arrhythmia) 0.47					
Elling Phase 2	?	EC4-P4	15						
Elling Phase 2	?	EC4	13						
MIG 5[a]	92% patients more than 12 months	PE4	268	Grade 2 1.5		0		0	
MIG 5	92% patients more than 12 months	FEC6	265	Grade 2 1.9		0		0	

[a] For MIG5, a subset of 28 patients in the paclitaxel arm and 35 in the control group, there was a non-significant difference in LVEF values "before chemotherapy and in the follow-up (68.4 vs 67.8 and 67.4 vs 66.5 in CEF and ET arm, respectively)".

Paclitaxel – other adverse events (table 1 of 3)

Trial	Follow-up (median) (months)	Group	*N*	Arthralgia		Arthralgia grade 3/4		Myalgia grade 3/4	
				%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531	During paclitaxel arthralgia/myalgia 12					
NSABP B28	64.8	AC4	1528						
CALGB 9344	69	AC4-P4	1570						
CALGB 9344	69	AC4	1551						
HCOG	61.7	E3-P3-CMF3	298			Arthralgia/myalgia 2			
HCOG	62	E4-CMF4	297			Arthralgia/myalgia 0.3			
GEICAM 9906	46	FEC4-P8	610					2	
GEICAM 9906	46	FEC6	633					0	
Elling Phase 2	?	EC4-P4	15						
Elling Phase 2	?	EC4	13						
MIG 5	92% patients more than 12 months	PE4	268						
MIG 5	92% patients more than 12 months	FEC6	265						

Paclitaxel – other adverse events (table 2 of 3)

Trial	Follow-up (median) (months)	Group	*N*	Fatigue grade 3/4		Asthenia grade 3/4		Allergy		Allergy grade 3/4	
				%	*p*	%	*p*	%	*p*	%	*p*
NSABP B28	64.4	AC4-P4	1531								
NSABP B28	64.8	AC4	1528								
CALGB 9344	69	AC4-P4	1570					Hypersensitivity reaction 6			
CALGB 9344	69	AC4	1551								
HCOG	61.7	E3-P3-CMF3	298	0.3						Hypersensitivity reaction 3.7	0.006
HCOG	62	E4-CMF4	297	0.7						Hypersensitivity reaction 0.3	
GEICAM 9906	46	FEC4-P8	610			6					
GEICAM 9906	46	FEC6	633			2					
Elling Phase 2	?	EC4-P4	15								
Elling Phase 2	?	EC4	13								
MIG 5	92% patients more than 12 months	PE4	268								
MIG 5	92% patients more than 12 months	FEC6	265								

Paclitaxel – other adverse events (table 3 of 3)

Trial	Follow-up (median) (months)	Group	*N*	Infection		Infection grade 3/4		Hepatotoxicity grade 3/4	
				%	*p*	%	*p*	%	*p*
NSABP B-28	64.4	AC4-P4	1531						
NSABP B-28	64.8	AC4	1528	During AC (not just control group) 3					
CALGB 9344	69	AC4-P4	1570	Infection requiring antibiotic (60 mg/m^2 dose A) 11					
CALGB 9344	69	AC4	1551	Infection requiring antibiotic during AC (not just control group) (60 mg/m^2 dose A) 17					
HCOG	61.7	E3-P3-CMF3	298					0.7	
HCOG	62	E4-CMF4	297					0	
GEICAM 9906	46	FEC4-P8	610						
GEICAM 9906	46	FEC6	633						
Elling Phase 2	?	EC4-P4	15			1			
Elling Phase 2	?	EC4	13			0			
MIG 5	92% patients more than 12 months	PE4	268						
MIG 5	92% patients more than 12 months	FEC6	265						

Appendix 4

Table of excluded studies with rationale

Ongoing trials

Trials that meet inclusion criteria of this review, but have not yet reported, are listed below.

Trial	Intervention and control groups
ADEBAR	ECx4-Dx4 vs FECx6
AGO AM02	ECx4-Dx4 vs FECx6 vs CMFx6
DEVA	Ex3-Dx3 vs Ex6 (concurrent or sequential tamoxifen)
MA-21	ECx6-Px4 vs ACx4-Px4 vs FECx6
NNBC3	FECx3-Dx3 vs FECx6

Excluded studies

Trial	Reason for exclusion
AngloCeltic 2	Neoadjuvant therapy
AGO (Mobus 2004)	Taxanes in both trial arms
CALGB9640/SWOG9623	Population Stage IIIa and above
CALGB9741	Taxanes in both trial arms
E1193	Population – advanced cancer
E1199	Taxanes in both trial arms
Elling/Kuemmel	Population Stage IIIa and above
EORTC 10994	Neoadjuvant therapy
FBCG 00-01	Vinorelbine comparator
ID01-580	Taxanes in both trial arms
MDACC (Buzdar)	Outcomes reported for neoadjuvant and adjuvant groups combined, no separate data for comparison of adjuvant groups
NeoTANGO	Neoadjuvant therapy
NSABP B27	Neoadjuvant therapy
NSABP B30	Taxanes in all trial arms
NSABP B31	Taxanes in both trial arms
Samuelkutty/Gluz	Insufficient information published (to date) to assess if population meets inclusion criteria
TANGO	Taxanes in both trial arms
TAX306	Population – advanced cancer

Appendix 5

Key clinical parameters from trials used in the ScHARR economic evaluation

Parameter	Value	Distribution	Comment
HRs			
BCIRG 001, DAC6 vs FAC6	0.71 (95% CI 0.58 to 0.87)	Log-normal	HR for DFS
NSABP B28, AC4+P4 vs AC4	0.82 (95% CI 0.72 to 0.94)	Log-normal	RR from Cox proportional hazards model
CALGB 9344, AC4+P4 vs AC4	0.83 (95% CI 0.73 to 0.94)	Log-normal	HR for recurrence
Type of recurrence in taxane arm			
BCIRG 001	Local, 19% Contralateral, 5% Distant, 76%	Dirichlet	
NSABP B28	Local, 29% Contralateral, 66% Distant, 5%	Dirichlet	
CALGB 9344	As for NSABP B28	Dirichlet	
Type of recurrence in comparator arm			
BCIRG 001	Local, 19% Contralateral, 4% Distant, 77%	Dirichlet	
NSABP B28	Local, 32% Contralateral, 7% Distant, 61%	Dirichlet	
CALGB 9344	As for NSABP B28	Dirichlet	
Annual probability of metastatic disease in patients with locoregional or contralateral recurrence			
Year 1	0.18 (95% CI 0.12 to 0.25)	Beta	
Year 2	0.19 (95% CI 0.13 to 0.27)	Beta	
Year 3	0.12 (95% CI 0.06 to 0.19)	Beta	
Year 4	0.09 (95% CI 0.04 to 0.16)	Beta	
Year 5 and beyond	0.12 (95% CI 0.05 to 0.20)	Beta	
Annual probability of death in patients with metastatic disease			
Each year	0.37 (95% CI 0.32 to 0.43)	Beta	
Age-related utility			
Utility = $M \times$ (Age) + C	M = –0.004, C = 1.060	Multivariate normal	
Costs of chemotherapy regimens			
Drug and administration costs for taxane regimens and their trial comparators	See *Tables 26* and *27*	Fixed during PSA	
Drug and administration cost of E4-CMF4 regimen	£2863	Fixed during PSA	
Drug and administration cost of FEC6(50) regimen	£2176	Fixed during PSA	
Drug and administration cost of FEC6(100) regimen	£3335	Fixed during PSA	

continued

Parameter	Value	Distribution	Comment
Costs per annum by health states			
Disease-free first 5 years	£637	Gamma	95% CI = mean ±25%
Disease-free subsequent years	£0	Gamma	
Locoregional recurrence, year of recurrence	£4590	Gamma	
Contralateral recurrence, year of recurrence	£4590	Gamma	
Remission from locoregional or contralateral recurrence (first 5 years only)	£622	Gamma	
Metastatic	£9880	Gamma	
Death due to breast cancer	£3218	Gamma	
Costs of AEs			
	See *Table 33*	Gamma	95% CI = mean ±25%
Utility of health states			
	See *Table 34*		
Extrapolation of recurrence			
	See *Table 51*		
HR of UK standard regimen relative to comparator in taxane trial			
	See Appendix 7		
Discount rates			
Costs	3.5%	Fixed in PSA	
QALYs	3.5%	Fixed in PSA	

Appendix 6

Methods of extrapolation of trial data

The long-term risk of recurrence was estimated in the model by extrapolating the DFS curves reported for the comparator arm of each trial. This was done by taking the proportion of patients surviving and the number of patients at risk for various time points (usually each year) from the Kaplan–Meier graphs reported in the trial publications. From this, the number of patients experiencing events or becoming censored was calculated for each time point. These data were then used to fit a range of parametric survival models in STATA (exponential, Weibull, log-normal, Gompertz) and the log-normal survival model was found to have the best fit for the majority of trials. The long-term survival in the comparator arm was estimated using a log-normal distribution with parameter values sampled from a multivariate normal distribution. Parameter values for each trial are summarised in *Table 51* and the log-normal survival functions for the mean parameter values are shown in *Figures 13–15*.

The survival function for the log-normal distribution is

$$S(x) = 1 - \phi\{[\ln(t) - \mu]/\sigma\},$$

where ϕ is the standard normal cumulative distribution and t is the time in months.

TABLE 51 *Survival function parameters*

Trial	μ	Ln(σ)	Variance of μ	Variance of ln(σ)	Covariance of μ and ln(σ)
BCIRG 001	4.603	0.106	0.005	0.003	0.003
NSABP B28	4.832	0.083	0.002	0.001	0.001
CALGB 9344	4.641	–0.039	0.001	0.001	0.001

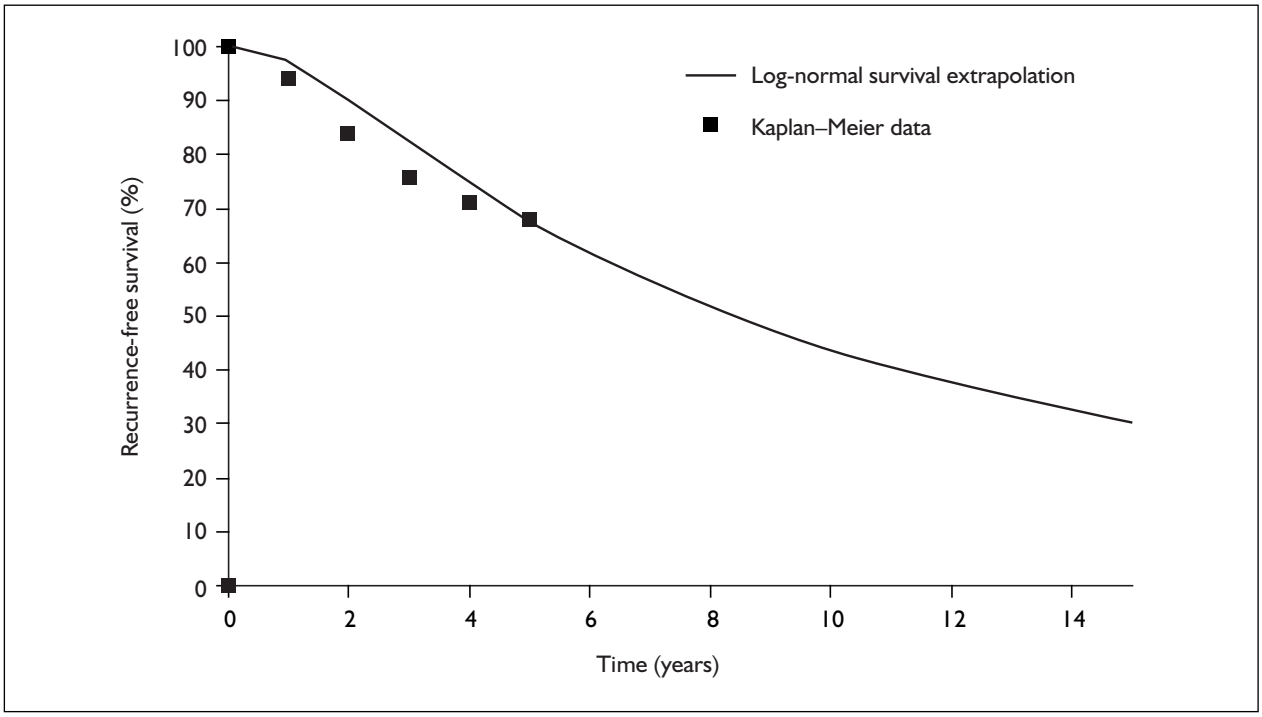

FIGURE 13 *Long-term extrapolation of recurrence-free survival based on Kaplan–Meier data from FAC6 arm of BCIRG 001*

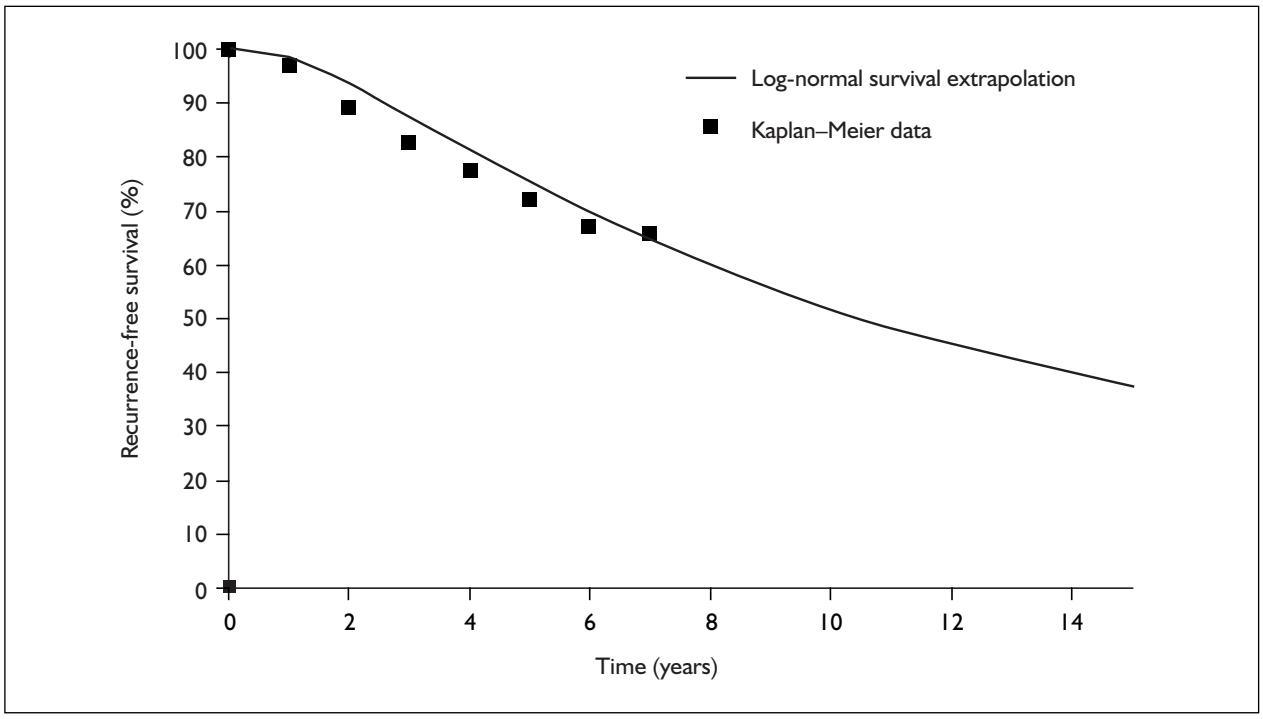

FIGURE 14 *Long-term extrapolation of recurrence-free survival based on Kaplan–Meier data from AC4 arm of NSABP B28*

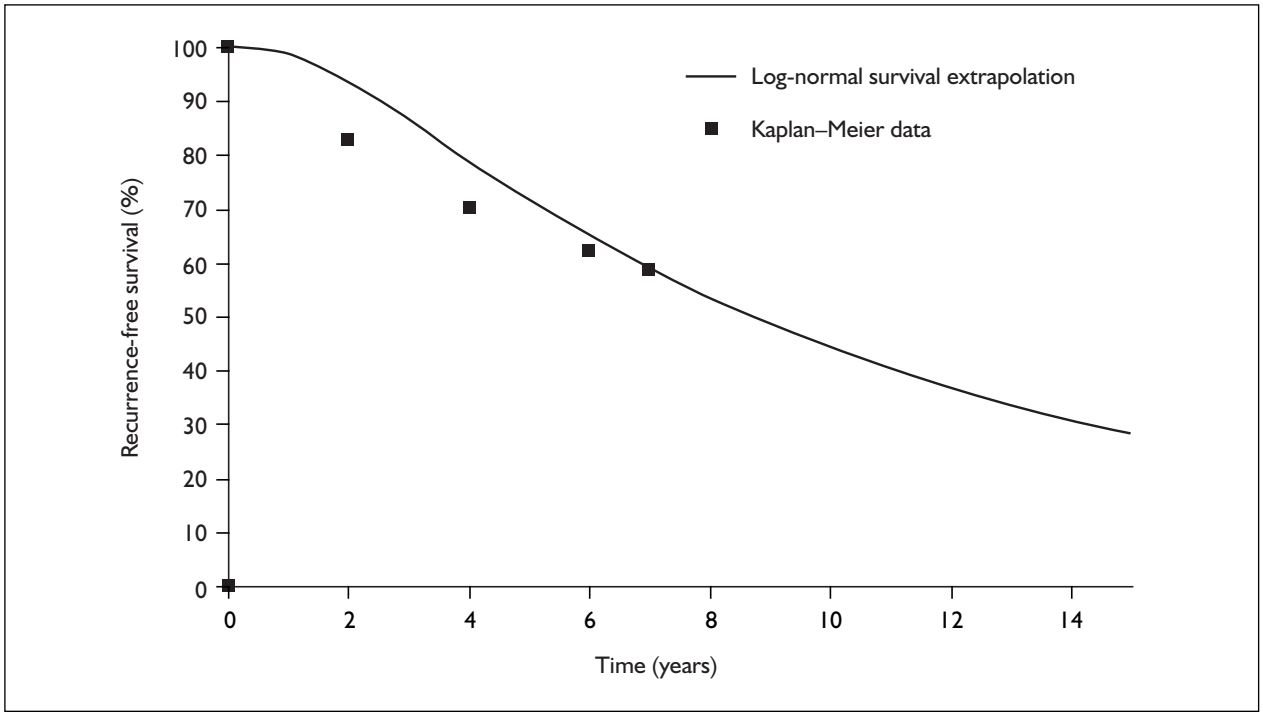

FIGURE 15 *Long-term extrapolation of recurrence-free survival based on Kaplan–Meier data from AC4 arm of CALGB 9344*

Appendix 7

Hazard ratios for the indirect comparison

GEICAM[58]

Martin and colleagues present RRs for DFS survival calculated using a Cox regression analysis for the whole subgroup (1.2, $p = 0.03$, adjusted for nodal status) and for the N–ve subgroup (1.4, $p = 0.047$). However, for the N+ve subgroup they simply state that the RR was non-significant. We assumed that the RRs are log-normally distributed. The mean log(RR) for the N+ve subgroup was calculated by assuming that the mean log(RR) for the whole population was equal to the weighted mean for the N+ve and N–ve subgroups. The mean log(RR) for the N+ve subgroup was then combined with the *p*-value for this subgroup, as calculated by the log-rank test ($p = 0.056$), to calculate the SD in log(RR). The mean and standard deviation of the RR for DFS were then calculated and assumed to be equivalent to the mean and SD of the HR for recurrence.

Coombes[104]

The HR for relapse-free survival in schedule 2 [six cycles of intravenous CMF versus six cycles of FEC(50)] was taken from the numbers presented in Figure 4 of Coombes and colleagues (32% reduction and SD = 15%).

FASG[105]

The HR of recurrence for FEC6(50) versus FEC6(100) was taken from the Cox proportional hazards model presented in Bonneterre and colleagues (HR= 1.24, 95% CI 0.97 to 1.59).

NSABP-B15[106]

Fisher and colleagues report that DFS at 3 years was 62% for patients who received AC4 and 63% for patients who received CMF6. Figure 1 of Fisher and colleagues, which shows the DFS for each patient group, gives a *p*-value of 0.5 (log-rank test) for treatment group assignment. Based on these results, we assumed that the HR for recurrence had a mid-point of 62%/63% = 0.98 and a *p*-value of 0.5.

NEAT/SCBTG BR9601[107]

The efficacy results of these two studies have not been published in a peer-reviewed publication but they were presented at the 2003 ASCO Annual Meeting and slides of the presentation have been published on the ASCO website. A 31% reduction (SD 8%) in hazard of recurrence was observed for both studies across all patients. The HR for recurrence was also presented by number of nodes involved (44% reduction, SD = 17% for N–ve; 23% reduction, SD = 13% for 1–3 nodes; 32% reduction, SD = 12% for 4+ nodes) but not for the N+ve subgroup as a whole. The majority (around two-thirds) of patients in the N+ve subgroup had 1–3 nodes involved. The HR of recurrence (*Table 52*) for the N+ve subgroup was assumed to be equal to that observed in the 1–3 node subgroup (0.77, SD = 0.13).

TABLE 52 *Calculated HRs for recurrence applied in the model to estimate efficacy for the indirect comparison (all HRs are assumed to be log-normally distributed in the model)*

Study	Comparison	HR for recurrence	Lower 95% CI	Upper 95%CI
GEICAM	CMF6 vs FAC6	1.07	0.92	1.25
Coombes	FEC6(50) vs CMF6	0.68	0.43	1.02
FASG	FEC6(50) vs FEC6(100)	1.24	0.97	1.59
NSABP-B15	AC4 vs CMF6	0.98	0.94	1.03
NEAT/SCBTG BR9601	E4-CMF4 vs CMF6	0.77	0.55	1.05

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