NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Fulvestrant 500 mg for the treatment of postmenopausal women with oestrogen receptor positive, locally advanced or metastatic breast cancer

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Contents

List of tables and figures

Definitions of terms

Terminology	Definition
Fulvestrant 250 mg (AD)	Fulvestrant 250 mg monthly
Fulvestrant 250 mg + loading dose (LD)	Fulvestrant 500 mg initially and then 250 mg on day 14, 28 and monthly
Fulvestrant 500 mg (HD)	Fulvestrant 500mg initially and then on day 14, 28 and monthly thereafter

List of Abbreviations

ABC	Advanced Breast Cancer
AEs	Adverse Events
AG	Aminoglutethimide
ALP	Alkaline Phosphatase
ALT	Alkaline Transaminase
AI	Aromatase Inhibitor
AO	Anti-Oestrogen
ASCO	American Society of Clinical Oncology
AST	Aspartate Transaminase
BOR	Best Objective Response
CB	Clinical Benefit
Cmax	Maximum concentration
CBR	Clinical Benefit Rate
CI	Confidence Interval
CNS	Central Nervous System
CONFIRM	Comparison of Faslodex™ in Recurrent Metastatic Breast Cancer
CRF	Case Report Form
CRR	Clinical Research Region
CSP	Clinical Study Protocol
DCO	Data Cut-Off
DIC	Disseminated Intravascular Coagulation
DoCB	Duration of Clinical Benefit
DoR	Duration of Response

EMA	European Medicines Agency
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
ER	Oestrogen receptor
ER+	Oestrogen receptor positive
EU	European Union
F250	Fulvestrant 250 mg
F500	Fulvestrant 500 mg
FACT-B	Functional Assessment of ChemoTherapy - Breast
FINDER	Faslodex Investigation of Dose evaluation in Oestrogen Receptor-positive advanced breast cancer
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HR	Hazard ratio
HRQL	Health-related quality of life
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
IM	Intra-Muscular
ITT	Intention-To-Treat
KOLs	Key Opinion Leaders
LA	Long-Acting
LHRH	Luteinising Hormone-Releasing Hormone
LYG	Life Year Gained
MA	Megesterol Acetate
MC	Marketing Company
ml	Mililitres
NCR	No Carbon Required
NE	Not Evaluable
OR	Objective Response
ORR	Objective Response Rate
OS	Overall survival
PD	Progressive Disease
PFS	Progression-Free Survival
PgR	Progesterone receptor
PgR+	Progesterone receptor positive
PgR-	Progesterone receptor negative
PPS	Per Protocol Set
PR	Partial Response
QALY	Quality-adjusted life year

qid	Four times daily
R&D	Research and Development
RCT	Randomised controlled trial
RECIST	Response Evaluation Criteria In Solid Tumours
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
TOI	Trial Outcome Index
TTD	Time To Detection
TTF	Time To Failure
TTP	Time To Progression
UICC	Union for International Cancer Control
UK	United Kingdom
ULRR	Upper Limit Reference Range
WHO	World Health Organisation

Executive summary

Disease background	Breast cancer is the most common malignancy affecting women in the UK accounting for 1 in 3 of all cancers in women. In 2006 over 40,000 women and 300 men were newly diagnosed with breast cancer in England and Wales. Over 12,000 deaths due to breast cancer occurred in the UK in 2007, an average rate of 38.6 deaths per 100,000 women and 0.3 deaths per 100,000 men. 5% of women with invasive breast cancer present with advanced breast cancer at primary diagnosis and it is estimated that around 35% of those presenting with early or localised breast cancer will eventually develop metastatic breast cancer[1]. In addition, there is a significant proportion of women that have previously been treated with curative intent who, during or after treatment, progress to an advanced form of the disease **(see section 2.1)**
Treatment pathway	In February 2009, NICE issued the guidelines 'Advanced Breast Cancer: diagnosis and treatment" (clinical guideline 81) which recommended[1]: "Offer an aromatase inhibitor (either non-steroidal or steroidal) to: - Postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy - Postmenopausal women with ER-positive breast cancer previously treated with tamoxifen." This NICE clinical guideline did not make any recommendations on fulvestrant 250 mg and the cost effectiveness of fulvestrant 500 mg was not reviewed during its development, as the 500mg dose had yet to receive its license at that time **(see section 2.3)**
Generic name **Brand name**	Fulvestrant Faslodex™ 250mg solution for injection
Indication and marketing status	Faslodex™ received its current marketing authorisation for the 500mg dose on the 9th of April 2010 from the European Medicines Agency (EMA). Faslodex™ received its first marketing authorisation, for the now superseded 250 mg dose, on the 10th March 2004.
Formulation, strength and pack size	Faslodex™ 250mg solution for injection is available in packs of 2 x 250 mg injections
Mechanism of action	Fulvestrant is a competitive oestrogen receptor (ER) antagonist with an affinity comparable to oestradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with down-regulation of oestrogen receptor protein levels
Proposed course of treatment	The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose. Average length of course of treatment is 14 months discounted base case derived from the network meta-analysis. Duration of treatment is based on time-to-progression clinical endpoint **(see section 5.7)**
Clinical results of Faslodex™ 500mg in treatment of oestrogen	The Comparison of Faslodex™ in Recurrent Metastatic Breast Cancer (CONFIRM) study demonstrated that fulvestrant 500 mg offers a significantly longer time to

receptor positive, postmenopausal women with Advanced Breast Cancer	progression (TTP) compared with fulvestrant 250 mg (HR=0.80 [95% CI 0.68 to 0.94]; 2-sided p=0.006). The treatment effect (TTP) favouring fulvestrant 500 mg was consistent across all of the subgroups analysed. Overall survival (OS) was not formally analysed at the primary data cut-off (DCO) for TTP. At DCO, 378/736 (51.4%) of the patients had died (175 [48.3%] in the fulvestrant 500 mg group and 203 [54.3%] in the fulvestrant 250 mg group). Median OS was 25.1 months in the fulvestrant 500 mg group and 22.8 months in the fulvestrant 250 mg group. The log rank analysis indicates that there is a trend for improved OS for patients in the fulvestrant 500 mg group compared with those in the fulvestrant 250 mg group, however, this does not reach statistical significance (hazard ratio=0.84 [95% CI 0.69 to 1.03]; p=0.091). Fulvestrant 500 mg offered a 16% reduction in risk of death compared to fulvestrant 500 mg. This trend for improved survival suggests that the benefit provided by treatment with fulvestrant 500 mg until progression, is maintained past progression. An exploratory analysis of OS, adjusted for the 6 predefined baseline covariates, is consistent with the unadjusted analysis (hazard ratio=0.81 [95% CI=0.66 to 0.99]; p=0.037. Faslodex™ Investigation of Dose evaluation in Oestrogen Receptor-positive advanced breast cancer (FINDER) I and FINDER II studies demonstrated that fulvestrant 250 mg and fulvestrant 500 mg were similar with respect to the primary endpoint of objective response rate (ORR) **(see section 5.5.3)**.
Safety	A pooled analysis of safety included data from 560 patients treated with fulvestrant 500 mg (mean exposure: 261.89 days) and 567 patients treated with fulvestrant 250 mg (mean exposure: 218.43 days). In addition to this, 101 patients were treated with fulvestrant 500 mg in the FIRST study (mean exposure: 283.86 days). In the pooled database, the most frequently reported adverse event (AE) was injection site pain with 13.9% vs. 10.2% of patients in the fulvestrant 500 mg and 250 mg groups, respectively. This was followed by nausea, fatigue, hot flush and headache with 10.2% vs. 13.9%, 9.6% vs. 7.1%, 8.8% vs. 8.6% and 8.0% vs. 7.2%, respectively, in the 500 mg and 250 mg groups, respectively. There were no important differences between the treatment groups in the reporting of these AEs **(see section 5.9)**
Source of clinical evidence for economic evaluation	Aromatase inhibitors were considered to be the primary comparators in the economic evaluation, since these are the most frequently used second line treatments for advanced breast cancer (ABC) which have progressed after prior anti-oestrogen use in England and Wales. There are no head-to-head randomised clinical trials evaluating the clinical benefits of fulvestrant 500 mg versus aromatase inhibitors (anastrozole, letrozole and exemestane) in an oestrogen receptor positive, postmenopausal advanced breast population. The clinical evidence for the primary comparison was sourced from a network meta-analysis (**see section 5.7**).

Table 1 Base-case cost-effectiveness results

	Fulvestrant 500 mg	Letrozole	Anastrozole	Fulvestrant 250 mg
Technology acquisition cost	£7,956	£892	£687	£3,623
Other costs	£23,119	£17,944	£21,780	£21,980
Total costs	£31,075	£18,836	£22,467	£25,603
Total costs difference vs. fulvestrant 500mg	n/a	£12,239	£8,608	£5,472
LYG	2.624	1.996	2.264	2.299
LYG difference vs. fulvestrant 500mg	n/a	0.628	0.359	0.325
QALYs (discounted)	1.487	1.105	1.214	1.256
QALY difference vs. fulvestrant 500mg	n/a	0.383	0.274	0.232
ICER (fulvestrant 500mg vs. comparator)	n/a	£31,982	£31,461	£23,636
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio; ED, Extended dominance				

Table 2 Incremental cost-effectiveness results (base-case)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Letrozole	**£18,836**	**1.996**	**1.105**	**-**	**-**	**-**	**-**	**-**
Anastrozole	**£22,467**	**2.264**	**1.214**	**£3,631**	**0.269**	**0.109**	**£33,286**	**ED**
Fulvestrant 250 mg	**£25,603**	**2.299**	**1.256**	**£3,136**	**0.035**	**0.042**	**£44,763**	**ED**
Fulvestrant 500 mg	**£31,075**	**2.624**	**1.487**	**£5,472**	**0.325**	**0.232**	**£31,982**	**£31,982**
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; ED, extended dominance								

Results of the economic evaluation	In the base-case analysis, based on an incremental ranking of technologies, the base-case results demonstrate that there is extended dominance for anastrozole and fulvestrant 250 mg. The ICER of fulvestrant 500 mg versus letrozole in the base case is £31,982 per QALY, with incremental costs of £12,239 and incremental QALYs of 0.383 associated with fulvestrant 500 mg in comparison with letrozole **(see Table 1 and 2).**
Place of fulvestrant 500mg in the treatment of second line ABC	Fulvestrant should be considered a treatment option for the postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy **(see section 2.4)**.
Estimated budget impact	The estimated annual budget impact for the NHS in England and Wales, in the first five years following the introduction of fulvestrant 500 mg as a

	second-line hormonal therapy option for advanced breast cancer patients has been analysed in section 7. Based on analysing the costs associated with the drug, administration, serious adverse events and treatment-independent costs, the net estimated annual budget impact for the NHS in England & Wales in 2011 is £116,895, rising to £1,619,909 in 2015 **(see section C).**
Conclusion	Fulvestrant 500 mg offers improved efficacy, and similar safety and tolerability compared to fulvestrant 250 mg and clearly supports the improved benefit-risk profile for fulvestrant 500 mg treatment after an anti-oestrogen for postmenopausal women with advanced breast cancer. Taken together, these findings support the use of fulvestrant 500 mg in this patient group and make it a valuable treatment option for the advanced breast cancer treatment algorithm in England and Wales.

Section A – Decision problem

1 Description of technology under assessment

1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Faslodex ™ 250 mg solution for injection (fulvestrant)

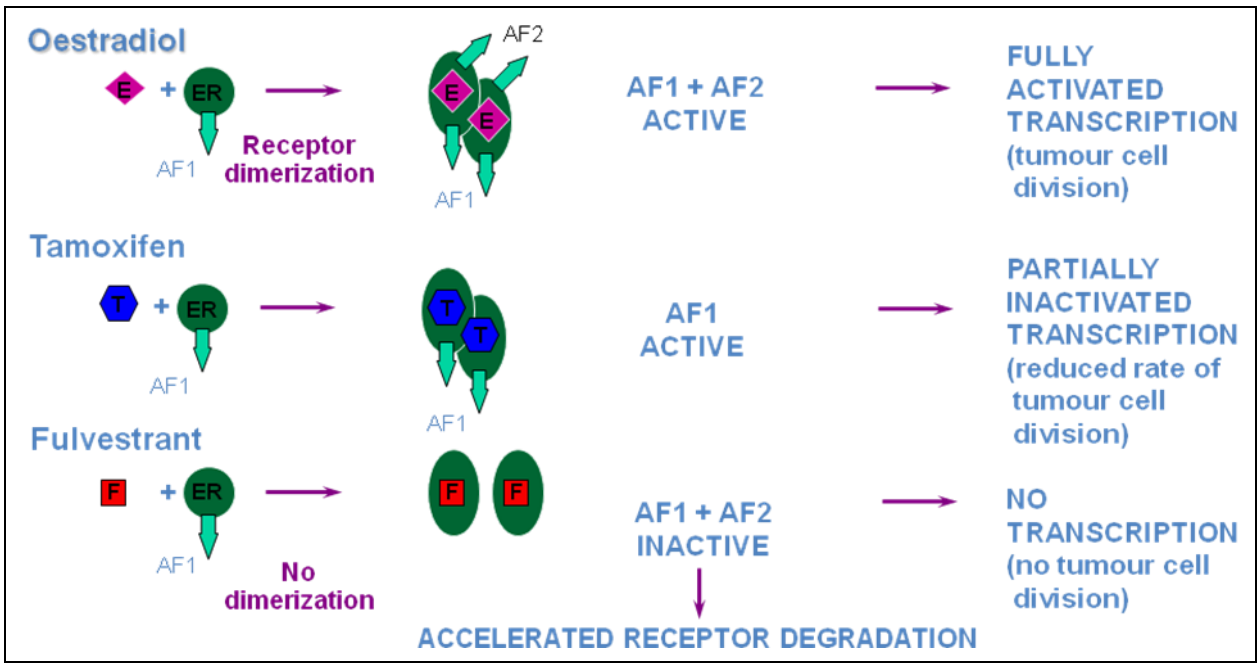
Pharmacotherapeutic group: Selective oestrogen receptor (ER) down regulator.

1.2 What is the principal mechanism of action of the technology?

Fulvestrant is a competitive ER antagonist with an affinity comparable to oestradiol. Fulvestrant blocks the trophic actions of oestrogens without any partial agonist (oestrogen-like) activity. The mechanism of action is associated with down-regulation of oestrogen receptor protein levels

The main features of the mechanism of action are ER down-regulation, antiproliferative activity, induction of apoptosis, lack of cross-resistance with tamoxifen, and the absence of ER-agonist activity (Robertson et al, 2001)[2].

Figure 1: Fulvestrant's mechanism of action



Fulvestrant's mode of action differs significantly from aromatase inhibitors which are potent and highly selective non-steroidal aromatase inhibitors. In postmenopausal women, oestradiol is produced primarily from the conversion of androstenedione to estrone through the aromatase enzyme complex in peripheral tissues. Estrone is subsequently converted to oestradiol. Reducing circulating oestradiol levels has been shown to produce a beneficial effect in women with breast cancer[3].

1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Faslodex™ received its current marketing authorisation for the 500 mg dose on 9 April 2010 from the European Medicines Agency (EMA). Faslodex™ received its first marketing authorisation, for the now superseded 250 mg dose, on 10 March 2004.

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the licence).

EPAR II/0017 (accessed at http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000540/human_med_000786.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d124):

'No clinically relevant differences with respect to tolerability and toxicity has been demonstrated comparing the 500 mg and the 250 mg doses, but the higher dose was associated with prolonged time to tumour progression or death (HR: 0.8, P = 0.006) and a trend for better overall survival.'

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The licensed indication for Faslodex™ is as follows:

Faslodex™ is indicated for the treatment of postmenopausal women with oestrogen receptor positive (ER+), locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with an anti-oestrogen.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

The CONFIRM study is likely to present a mature overall survival analysis within the next 18 months. No other study data for the licensed Faslodex™ dose is expected in this time period.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

Not Applicable.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

The licence update is granted through the European Union (EU) (and Norway and Iceland).

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Currently, there are no other HTA assessments planned for fulvestrant.

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table A1 Unit costs of technology being appraised

Pharmaceutical formulation	Solution for injection. Available with with safety needle (BD SafetyGlide™).
Acquisition cost (excluding VAT)	£522.41
Method of administration	Faslodex™ should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock.
Doses	The recommended dose is 500 mg
Dosing frequency	The recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose.
Average length of a course of treatment	14 months discounted base case derived from the network meta-analysis **(see section 5.7)**
Average cost of a course of treatment	£7,313,74
Anticipated average interval between courses of treatments	None
Anticipated number of repeat courses of treatments	None
Dose adjustments	None

1.11 **For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs**.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

Fulvestrant 500 mg should be administered as two consecutive 5 ml injections by slow intramuscular injection (1-2 minutes/injection), one in each buttock.

There are no additional tests or investigations needed for the use of fulvestrant.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

None.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

None.

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Incidence and prevalence of advanced breast cancer

Breast cancer is the most common malignancy affecting women in the UK accounting for 1 in 3 of all cancers in women. There were over 40,000 women and 300 men newly diagnosed with breast cancer in England and Wales during 2006. Furthermore, over 12,000 deaths due to breast cancer occurred in the UK in 2007, an average rate of 38.6 deaths per 100,000 women and 0.3 deaths per 100 000 men. 5% of women presenting with breast cancer have advanced disease with distant metastases (where cancer cells have spread to other parts of the body), and it is estimated that around 35% of those presenting with early or localised breast cancer will eventually develop metastatic breast cancer(Advanced Breast Cancer NICE Clinical Guideline, 2009)[1]. Also, there is a significant population of women that have been previously treated with curative intent who during or after treatment progress to an advanced form of the disease.

Treatment options for advanced breast cancer

The treatment of breast cancer is determined by the extent of the disease and a variety of other prognostic factors, including age and hormone receptor status (Guarneri et al, 2004)[4]. It has long been acknowledged that many breast cancers are hormone dependent and that hormonal manipulation can affect the progress of the disease. The most important factor determining response to hormonal manipulation is the presence of the oestrogen receptor (ER) in the target tissue (Fisher et al, 2001) [5].

In postmenopausal women with hormone receptor positive disease, early breast cancer is often treated by a combination of surgery and radiotherapy, with adjuvant endocrine therapy following surgery. Postmenopausal women with hormone receptor positive disease who present with advanced disease are generally treated with a sequence of endocrine therapies before receiving cytotoxic chemotherapy.

NICE clinical guidelines for advanced breast cancer

NICE clinical guideline 81 recommends that an aromatase inhibitor should be used for postmenopausal women with ER+ breast cancer, either as a first-line treatment or if they have previously been treated with adjuvant endocrine therapy (such as tamoxifen)[1]. In clinical practice, individuals may be treated with several endocrine therapies, such as aromatase inhibitors, ER

antagonists and progestogens, either as monotherapy or as combinations. Appropriate endocrine treatment options are determined by prior endocrine treatment, the extent and duration of any previous response to treatment, and menopausal status. The key research recommendations from the NICE guidelines for Advanced Breast Cancer highlighted that while there is good evidence to support the use of non-steroidal aromatase inhibitors for postmenopausal women with ER-positive tumours, there is little evidence to determine what the best sequence of alternative hormone treatment is when they progress.

Tamoxifen

The anti-oestrogen tamoxifen has been the most widely used endocrine therapy for breast cancer in postmenopausal women. However, despite its demonstrated efficacy, de novo or acquired resistance may occur during treatment. In some patients, the disease progresses during therapy because tumour growth may be stimulated by tamoxifen, due to its partial agonist activity on the ER (Wiebe et al, 1993)[6].

Non-steroidal aromatase inhibitors (NSAI)

NSAIs are a common treatment option for patients who have progressed on an anti-oestrogen (Bevers et al, 2009)[7]. Other therapies, such as fulvestrant 250 mg dose and exemestane, are also used to treat patients who progress on an anti-oestrogen.

Fulvestrant 250 mg and exemestane

Fulvestrant 250 mg is well tolerated and has demonstrated efficacy in women whose breast cancer had progressed following anti-oestrogen therapy, having been shown to be as effective as the aromatase inhibitor anastrozole in this setting (Howell et al, 2002, Osborne et al, 2002) [8,9]. Similarly, the steroidal aromatase inhibitor exemestane has demonstrated efficacy in this patient population in the phase III setting (Kaufmann et al, 2000)[10].

2.2 How many patients are assumed to be eligible? How is this figure derived?

The number of advanced breast cancer (ABC) patients that are eligible for second-line hormonal therapy figure has been estimated for England and Wales. The total number of women with ABC in England only was estimated to be 10,786 in 2009 (Advanced Breast Cancer NICE Clinical Guideline, 2009)[11]. The same methodology used in the NICE costing template has been used to estimate the total number of women with ABC in England and Wales in 2011.

According to the latest available National Statistic data, there were 23,147,700 women in England and Wales 15 years or older in mid-2009. To estimate the population estimate for women 15 years or older in England and Wales in 2011 until 2015, a constant annual growth rate of 0.7%, which is based on the annual population growth rate between 2008 to 2009, (National Statistics,

2009) [12] has been applied to the mid-2009 estimate. Applying the 0.7% year-on-year growth and following the same methodology as the NICE advanced breast cancer guideline costing template, the estimated that the total number of women with ABC in England and Wales will be 11,603 in 2011. For further information about how this figure was derived, see **section 7**.

The number of the patients that are considered eligible for second-line hormonal treatment in-line with the license for fulvestrant 500 mg dose was then estimated from the total population of women with ABC in England and Wales estimated above, by applying the following assumptions:

- the proportion of women with oestrogen hormone receptor-positive breast cancer (85%) (West Midlands Cancer Intelligence Unit, 2009)[13];
- the proportion of women with hormone receptor-positive ABC for whom endocrine (hormonal) therapy is appropriate (70%) (Advanced Breast Cancer NICE Clinical Guideline, 2009) [14];
- the proportion of women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy (32%) (AstraZeneca Data on file, 2010) [15].

It has been assumed these same assumptions are applicable to Wales. Based on these assumptions, it is estimated that up to 2,209 patients in England and Wales are considered eligible for fulvestrant 500 mg treatment in 2011 in 2015 based on population in the marketing authorisation, growing to 2,272 in 2015. For further information regarding this estimation, see **section 7**.

2.3 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

In February 2009 NICE issued the guidelines 'Advanced Breast Cancer: diagnosis and treatment" (clinical guideline 81) which recommended[1]:
"Offer an aromatase inhibitor (either non-steroidal or steroidal) to:

- Postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy;
- Postmenopausal women with ER-positive breast cancer previously treated with tamoxifen."

These NICE guidelines did not make any recommendations on fulvestrant but did review the fulvestrant 250 mg dose data – fulvestrant 500 mg dose was not licensed at time of publication:

"Fulvestrant and exemestane showed equal clinical benefit for women that had previously received non-steroidal AIs for the treatment of ABC. Limited evidence also suggested that fulvestrant conferred short term benefit to heavily pre-treated women with metastatic disease by postponing the requirement for chemotherapy. An equivalence analysis of pooled data from two trials showed that fulvestrant and anastrozole were not significantly

different from one another in their effects on overall survival (Howell et al, 2005)[16]. Study participants given fulvestrant reported fewer incidences of joint pain."

These NICE Guidelines also identified key research recommendations, one of these was: "for advanced breast cancer highlighted that while there is good evidence to support the use of non-steroidal aromatase inhibitors for postmenopausal women with ER-positive tumours, there is little evidence to determine what the best sequence of alternative hormone treatment is when they progress."

2.4 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

The current Advanced Breast Cancer NICE clinical guidelines present the following treatment algorithm[1]:

Figure 2: Advanced breast cancer treatment algorithm

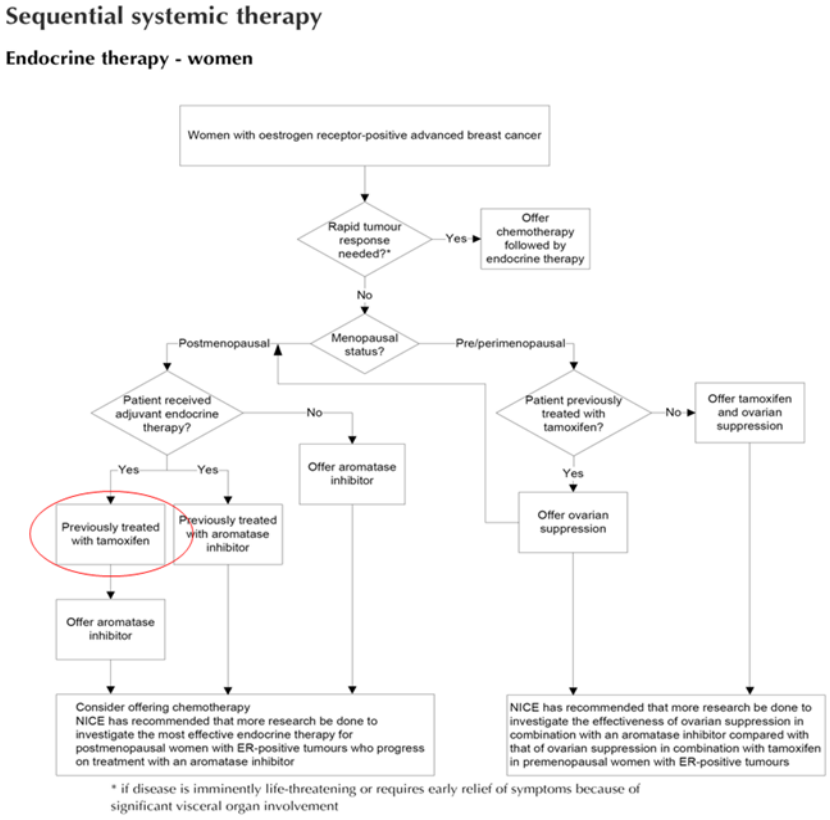
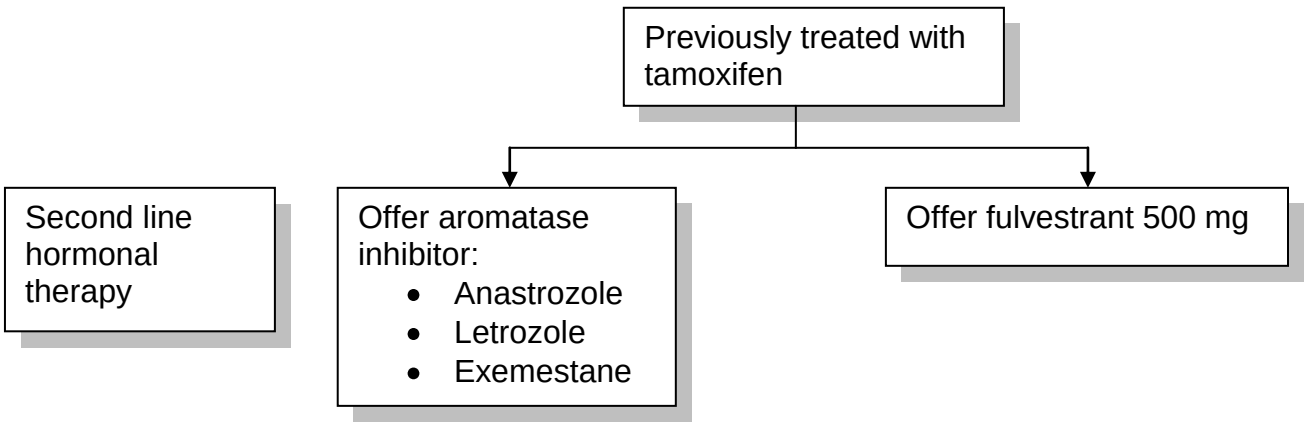


Figure 3: Proposed modification to the treatment algorithm for sequential systemic therapy for women with oestrogen receptor positive advanced breast cancer



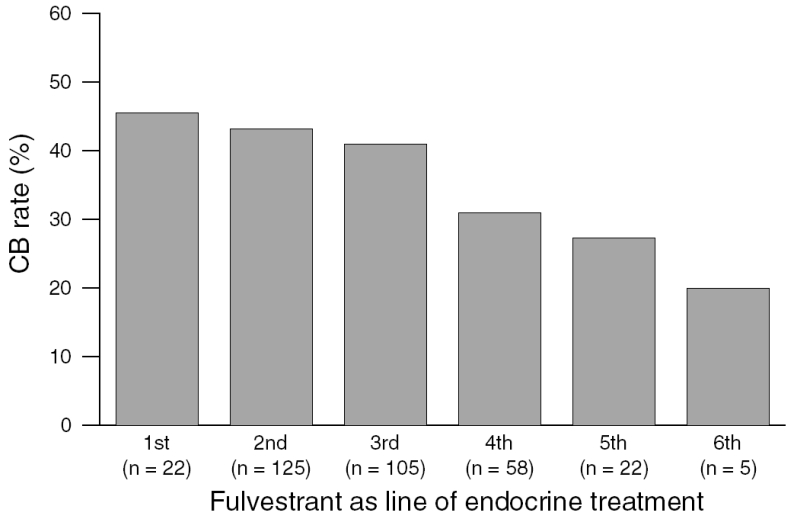
Fulvestrant offers an alternative to aromatase inhibitors for patients previously treated with tamoxifen.

It has been assumed for the purpose of this submission that there has been no adjuvant switch strategies initiated.

2.5 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

In the UK, current clinical practice in ABC sees the use of fulvestrant being used third or fourth line after aromatase inhibitors and tamoxifen. Guenther Steger and his colleagues in their paper regarding their clinical experience of the Faslodex Compassionate Programme were able to show that earlier use of fulvestrant resulted in better clinical benefit rates (Steger et al, 2005)[17]. Clinical benefit rate is defined as the number of patients who have had a complete or a partial response or a stable disease greater than 24 weeks.

Figure 4: Clinical benefit rate (CBR) achieved with fulvestrant by number of endocrine treatments for advanced breast cancer.



Please note that no statistical analysis undertaken as data from pool analysis of experiential data

The key research recommendations from the NICE guidelines for Advanced Breast Cancer highlighted that while there is good evidence to support the use of non-steroidal aromatase inhibitors for postmenopausal women with ER-positive tumours, there is little evidence to determine what the best sequence of alternative hormone treatment is when they progress.

The growing mixture of treatment sequences in the adjuvant treatment of early breast cancer (e.g. Switch and extended adjuvant strategies) that use multiple agents confuses what the best sequence of alternative hormone treatment is when patients progress.

2.6 Please identify the main comparator(s) and justify their selection.

The main comparators, as defined by the scope, are anastrozole, exemestane, letrozole and fulvestrant 250 mg dose.

For postmenopausal women with ER+ ABC who have failed on or after adjuvant tamoxifen treatment or had disease progression on tamoxifen treatment, NICE guidelines for Advanced Breast Cancer recommend the use aromatase inhibitors (letrozole / anastrozole / exemestane).

Fulvestrant 250 mg dose has been selected on the basis of it being the comparator for the 500 mg dose in the CONFIRM study and because it was the previously approved dose for fulvestrant, as a result of showing non-inferiority to anastrozole in two Phase III trials (Osborne et al, 2002, Howell et al, 2002, Robertson et al, 2001)[2,8,9].

2.7 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

Table A2: Therapies that may be prescribed to manage adverse reactions associated with fulvestrant 500 mg (Fulvestrant SmPC) [18]

Incidence	Adverse reactions	Therapy
Very common (1/10)	nausea	Standard anti-nausea. For example: domperidone and cyclizine
	injection site reactions	Simple analgesia
Common (≥1/100 to <1/10)	hypersensitivity reactions	Antihistamines
	Headache	Standard analgesia
	venous thromboembolism	Anticoagulants
	Vomiting	Anti-emetics
	Diarrhoea	Standard anti-diarrhoeals
	Rash	Topical steroids/Aqueous Cream)
	hot flushes	Suggested treatment: venlafaxine 37.5mg three times daily for 3 days
Uncommon (1/1,000 to <1/100)	Leukorrhea	Not usually actively treated
	vaginal haemorrhage	Depends on degree, might require hysterectomy depending on source (i.e. Not true vaginal haemorrhage) otherwise regular blood tests and possibly regular blood transfusions

2.8 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

One oncologist visit is required to initiate a fulvestrant 500 mg therapy in the outpatient setting. Subsequent doses of fulvestrant 500 mg are either administered by nurses as a 15 minute appointment in the outpatient setting or in the primary care setting. See **section 6.5.5** for further details for costings.

No additional monitoring or tests are required for patients prescribed fulvestrant 500 mg.

2.9 Does the technology require additional infrastructure to be put in place?

No.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

None identified.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

None identified.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable.

4 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy.	***Base case analysis***: postmenopausal women with oestrogen receptor positive locally advanced or metastatic breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy*. ***Secondary analysis (results presented in section 6.7.9 & appendix 9.17)***: postmenopausal women with oestrogen receptor positive metastatic or locally advanced breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) or aromatase inhibitor therapy*. * The inclusion of the post AI group did not alter the result in favour of fulvestrant 500 mg and considering that CONFIRM was the licensing trial and powered for the total population it was considered most appropriate to include the total population.	In the base-case analysis, based on the licensed population for fulvestrant 500 mg, no published clinical data is available for the comparator, exemestane. As a result, a secondary analysis is presented in section 6.7.9, where clinical data is available for exemestane.
Intervention	Fulvestrant at its licensed dose of 500 mg	Fulvestrant at its licensed dose of 500 mg	-
Comparator(s)	Monotherapy or combination regimens of the following anti-oestrogen (endocrine) treatments: • Low-dose (250 mg) fulvestrant every four weeks plus loading dose • aromatase inhibitors (anastrozole, exemestane, letrozole)	***Base case analysis***: fulvestrant 250 mg (one monthly), anastrozole and letrozole ***Secondary analysis:*** fulvestrant 250 mg, anastrozole, exemestane and letrozole	The dosing schedule of fulvestrant 250 mg is based on the previous SPC (once monthly). In the base-case analysis, based on the licensed population for fulvestrant 500 mg, no clinical data is available for the comparator, exemestane. As a result, a secondary analysis is

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			presented in section 6.7.9, where clinical data is available for exemestane.
Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • adverse effects of treatment • health-related quality of life	The outcome measures to be considered include: • overall survival • progression-free survival • adverse effects • health-related quality of life	Progression-free survival in the model is based on TTP from the CONFIRM trial which included death. This definition of progression is commonly referred to as progression-free survival (Saad et al, 2010) [19] Objective response is not routinely assessed in England and therefore was not considered clinically relevant to include in the model
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	• Cost-effectiveness presented as incremental cost per quality-adjusted life year (QALY) • Time horizon: lifetime (13 years) • Perspective: NHS and Personal Social Services	
Subgroups to be considered	-	None	No appropriate sub-group was

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
			identified. The analysis of TTP in CONFIRM included 12 pre-specified subgroups, chosen to investigate the consistency of any treatment effect across 6 covariates, which are potential prognostic factors for TTP. The treatment effect was consistent across all subgroups analysed (see section 5.5.3 for further detail)
Special considerations, including issues related to equity or equality	n/a	n/a	n/a

Section B – Clinical and cost effectiveness

5 Clinical evidence

5.1 Identification of studies

5.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 9.2, appendix 2.

A full online search of Medline, Embase, Medline (R) In-Process and the Cochrane Library was conducted in January 2010. All clinical abstracts for the past two years from ASCO, the National Cancer Institute, and the San Antonio Breast Cancer Symposium were reviewed. Articles from these searches were combined with the abstracts retrieved from the literature database search.

5.2 Study selection

5.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

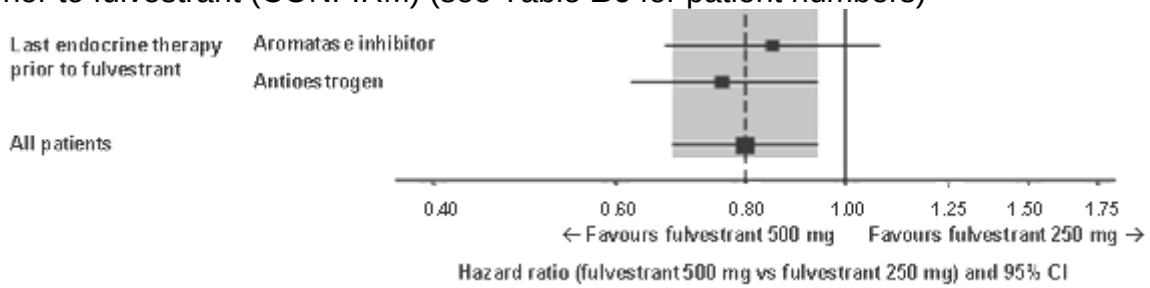
Table B1 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	Population – post menopausal women with locally advanced or metastatic breast cancer who had previously received anti-oestrogen treatment either for early or advanced breast cancer, ER+ status Interventions – fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate Outcomes – overall survival, progression free survival, time to progression, tumour response, response rate, adverse events, health related quality of life Study design – RCTs Language restrictions - none
Exclusion criteria	Population – men, pre-menopausal women, sample populations where all participants had one or more visceral lesions, patients who had not previously received anti-oestrogen therapy Interventions – trials that did not have at least one arm with the comparator of interested as identified at the scoping workshop (fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate) Outcomes Study design – anything study design other than a phase II or III RCT Language restrictions – none, other than the fact that results had to be presented in a format that was understandable without translating article for example, results presented in an English abstract or tabulated with standard abbreviations e.g. TTP = time to progression

The theoretical basis for this search was based on the license population for fulvestrant 500 mg, in other words, postmenopausal, oestrogen receptor positive women who had received prior anti-oestrogen treatment. Study populations where all participants had one or more visceral lesions were excluded due to the different prognosis compared to those without.

Challenges were encountered even prior to conducting the search. The primary trial that supports the use of fulvestrant 500 mg, the CONFIRM trial, consists of a mixed population that has either received prior anti-oestrogen (AO) treatment or prior aromatase inhibitor (AI) treatment. A decision was taken at this stage to include all the CONFIRM and FINDER I and II trial data, post AO and post AI treatment.

Figure 5: Forest plot of subgroup analysis of TTP by last endocrine therapy prior to fulvestrant (CONFIRM) (see Table **B6** for patient numbers)

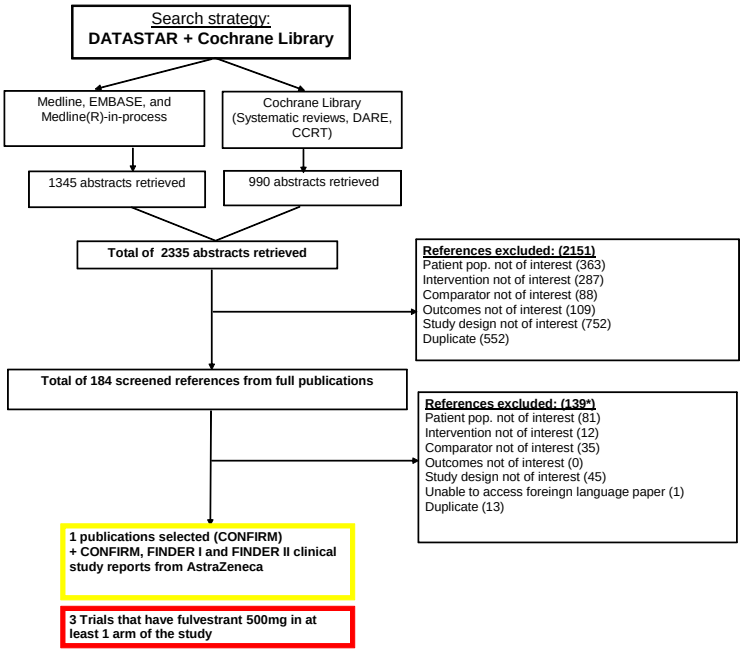


As the marketing approval for fulvestrant 500 mg is currently limited to patients who have progressed on an anti-oestrogen, the results of the last prior endocrine therapy subgroups in the forest plot are of particular interest. In this subgroup analysis, the treatment effect favouring fulvestrant 500 mg was consistent in patients who had progressed on an aromatase inhibitor compared to patients who had progressed on an anti-oestrogen (hazard ratio [95% CI]=0.85 [0.67 to 1.08] and 0.76 [0.62 to 0.94], respectively).

The inclusion of the post AI group did not alter the result in favour of fulvestrant 500 mg and considering that CONFIRM was the licensing trial and powered for the total population it was considered most appropriate to include the total population.

5.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

Figure 6: A flow diagram of the numbers of studies included and excluded in search strategy



5.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Table B2: Fulvestrant 500 mg studies and primary data sources and supporting papers

Trial no (acronym)	Primary data source	Supporting papers
CONFIRM [20]	Clinical Study report	None used[1]
FINDER I[21,22]	Clinical study report	Ohno, Rai, Iwata et al. Annals of Oncology 2010, ePub. doi: 10.1093/annonc/mdq249
FINDER II [23,24]	Clinical study report	Pritchard, Rolski, Papai et al. Breast Cancer Res Treat 2010. 123 (2): 453-461

[1] Please note that at time of writing the Manufacturer's Submission for fulvestrant, the CONFIRM study had not yet been published. It has now been published in the Journal of Clinical Oncology and is available at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2010.28.8415.

Complete list of relevant RCTs

5.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B3: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
CONFIRM	Fulvestrant 500 mg	Fulvestrant 250 mg	• Histological/cytological confirmation of breast cancer • Documented ER+ status of primary or metastatic tumour tissue, according to the local laboratory parameters • Prior treatment with an endocrine agent • Measurable disease as per Response Evaluation Criteria In Solid Tumours (RECIST) criteria OR bone lesions, lytic or mixed (lytic and sclerotic), in the absence of measurable disease as defined by RECIST • Postmenopausal woman • WHO performance status 0, 1 or 2.	Clinical study report[20]
FINDER I	Fulvestrant 500 mg	Fulvestrant 250 mg Fulvestrant 250 mg Loading dose	• Histological/cytological Confirmation of breast cancer (from either primary or metastatic tumour) • Documented ER+ status of primary or metastatic tumour tissue, defined as ≥10% positive staining by Immunohistochemistry • Requiring prior hormonal treatment • Measurable disease as per RECIST criteria • Postmenopausal women • WHO performance status 0, 1 or 2.	Clinical study report[22]
FINDER II	Fulvestrant 500 mg	Fulvestrant 250 mg Fulvestrant 250 mg Loading dose	• Histological/cytological Confirmation of breast cancer (from either primary or metastatic tumour) • Documented positive ER status (ER +ve) of primary or metastatic tumour tissue, defined as ≥10% positive staining by immunohistochemistry • Requiring prior hormonal treatment • Measurable disease as per RECIST • Postmenopausal women • WHO performance status 0, 1 or 2	Clinical study report[24]

5.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

CONFIRM, FINDER I and FINDER II all compare fulvestrant 500 mg with fulvestrant 250 mg, which was identified as an appropriate comparator.

5.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable.

List of relevant non-RCTs

5.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

None.

5.3 Summary of methodology of relevant RCTs

5.3.1 **As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, the information should be tabulated.**

Methods

5.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table B4: Comparative summary of methodology of the RCTs

Study ID	Location	Design	Duration of study	Method of randomisation	Method of blinding	Intervention(s)	Primary outcomes	Secondary outcomes	Duration of follow-up
CONFIRM	128 centres in 17 countries	Randomised, double-blind, parallel-group, multicentre, phase III study	Treatment was to continue until disease progression occurred, unless any of the criteria for treatment discontinuation were met first.	Patients fulfilling the eligibility criteria were randomised into the study and assigned a randomisation code (patient number). Randomisation codes were allocated strictly sequentially and each patient pack was labelled with a randomisation code.	Placebo injection added for lower dose fulvestrant so that both treatment groups received 2 injections. All study personnel were unaware of the randomised treatment until all decisions on the quality of data from all patients had been made and documented.	Fulvestrant 500 mg Fulvestrant 250 mg	Time to progression (TTP)*	Objective response rate (ORR) Clinical benefit rate (CBR) Duration of response (DoR) Duration of clinical benefit (DoCB) Overall survival (OS) Tolerability HRQoL	Treated until progression; all patients were to continue to have their survival status monitored until the final survival analysis.
FINDER I	43 centres, of which 40 recruited patients	Randomised, double-blind, parallel-group multicentre clinical study	Treatment with fulvestrant was to be continued until disease progression or until any other criterion for treatment discontinuation was met.	The Subject Registration Centre checked the eligibility of the patient, registered the patient and allocated a randomisation code to the patient in order of registration to the study and sent the information to the investigator and AstraZeneca. The investigator(s) then started administration of the investigational product to the registered patient. The investigator(s) kept the registration Confirmation form sent from the Registration Centre in the investigator's study file.	All study personnel were unaware of the randomised treatment until all decisions on the quality of the data from all patients had been made and documented. The study drug, fulvestrant, was supplied by AstraZeneca, in the form of pre-filled syringes. Each active pre-filled syringe contained 250 mg of fulvestrant at a concentration of 50 mg/ml in a volume of 5 ml, designated a fulvestrant 5% weight/volume (w/v) injection. The placebo	Fulvestrant 500 mg Fulvestrant 250 mg Loading dose fulvestrant 250 mg	Objective response rate (ORR)	Cmax, Clearance and Volume of distribution at steady state Time to progression (TTP). Clinical benefit rate (CBR) Duration of response (DoR) Tolerability Adverse events and safety	Throughout the treatment period and up to 8 weeks after the last injection of study medication.

Study ID	Location	Design	Duration of study	Method of randomisation	Method of blinding	Intervention(s)	Primary outcomes	Secondary outcomes	Duration of follow-up
					pre-filled syringe looked identical to the active pre-filled syringe and also had a volume of 5 ml.				

Study ID	Location	Design	Duration of study	Method of randomisation	Method of blinding	Intervention(s)	Primary outcomes	Secondary outcomes	Duration of follow-up
FINDER II	34 centres in 8 countries (Belgium, Canada, France Turkey, Czech Republic, Romania, Poland, Hungary)	Randomised, double-blind, parallel-group, multicentre clinical study	Treatment with fulvestrant was to continue until disease progression, or until any other criterion for treatment discontinuation was met	The first 4 digits in the E-code indicated the centre and digits 5 to 7 the enrolment order for the centre. This number was the patient's unique identifier for the study. Enrolment numbers were given in consecutive order. All screened patients were assigned an E-code irrespective of whether or not they were subsequently randomised to receive study treatment. Patients fulfilling the eligibility criteria were randomised into the study and assigned a randomisation code (patient number). If a patient discontinued from the study, the randomisation code (patient number) was not to be reused and the patient was not to be allowed to re-enter the study. If a randomisation code was assigned incorrectly, no attempt was to be made to remedy the error once study material had been dispensed. The patient was to continue with the allocated randomised code and study material. The actual treatment given to individual patients was determined by a randomisation schedule. Patients were to be allocated treatment in balanced blocks. The actual treatments were to be prepared and packed by AstraZeneca into individual patient packs	All study personnel were unaware of the randomised treatment until all decisions on the quality of data from all patients had been made and documented. The study drug was supplied by AstraZeneca in the form of pre-filled syringes. Each active pre-filled syringe contained 250 mg of fulvestrant at a concentration of 50 mg/ml in a volume of 5 ml, designated a fulvestrant 5% weight/volume (w/v) injection. The placebo pre-filled syringe looked identical to the active pre-filled syringe and had a volume of 5 ml.	Fulvestrant 500 mg Fulvestrant 250 mg Loading dose fulvestrant 250 mg	Objective response rate (ORR)	Cmax, Clearance and Volume of distribution at steady state Time to progression (TTP) Clinical benefit rate (CBR) Duration of response (DoR) Tolerability	The planned data cut-off for this study was when all patients, except withdrawals, had been followed up for at least 24 weeks.

* Please note that the definition of TTP used in CONFIRM, which includes death from any cause in the absence of progression, is also commonly termed progression free survival (PFS).

Participants

5.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B5: Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
CONFIRM	• Histological/cytological Confirmation of breast cancer • Documented ER+ status of primary or metastatic tumour tissue, according to the local laboratory parameters • Requiring endocrine therapy: - relapsing during, or within 12 months of completion of, adjuvant endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane), or - progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane)provided that this endocrine treatment was started at least 12 months after the completion of adjuvant endocrine treatment, or - progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) given as first treatment for patients with *de novo* advanced breast cancer • Fulfilling one of the following criteria: - patients with measurable disease as per RECIST criteria - patients with bone lesions, lytic or mixed (lytic and sclerotic), in the absence of measurable disease as defined by RECIST. • Postmenopausal woman, defined as a woman fulfilling any 1 of the following criteria: - age ≥60 years - age ≥45 years with amenorrhoea ≥ 12 months with an intact uterus - having undergone a bilateral oophorectomy - follicle stimulating hormone (FSH) and oestradiol levels in postmenopausal range - in patients who had previously been treated with a luteinising hormone releasing hormone (LHRH) analogue, the last depot must have been administered more than 4 months prior to randomisation, menses must not have restarted, and FSH and oestradiol levels must also have been in the postmenopausal range • WHO performance status 0, 1 or 2.	Any of the following was regarded as a criterion for exclusion from the study: • Presence of life-threatening metastatic visceral disease, defined as extensive hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases were eligible, provided their respiratory function was not compromised as a result of disease • More than one regimen of chemotherapy for advanced disease • More than one regimen of endocrine therapy for advanced disease • Extensive radiation therapy within the last 4 weeks (greater than or equal to 30% marrow or whole pelvis or spine) or cytotoxic treatment within the past 4 weeks prior to screening laboratory assessment, or strontium-90 (or other radiopharmaceuticals) within the past 3 months • Treatment with a non-approved or experimental drug within 4 weeks before randomisation • Current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix) • Any of the following laboratory values: - Platelets <100 × 10^9/L - Total bilirubin >1.5×upper limit reference range (ULRR) - ALT or AST >2.5×ULRR if no demonstrable liver metastases or >5×ULRRin presence of liver metastases • History of: - Bleeding diathesis (i.e., disseminated intravascular coagulation, clotting factor deficiency), or - long-term anticoagulant therapy (other than antiplatelet therapy and low dose warfarin • History of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil1 • Any severe concomitant condition which made it undesirable for the patient to participate in the trial or which would jeopardize compliance with the CSP, e.g., uncontrolled cardiac disease or uncontrolled diabetes mellitus.

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
FINDER I	For inclusion in the study, patients had to fulfil all of the following criteria; 1. Provision of informed consent 2. Histological/cytological Confirmation of breast cancer (from either primary or metastatic tumour) 3. Documented ER+ status of primary or metastatic tumour tissue, defined as ≥10% positive staining by immunohistochemistry 4. Requiring hormonal treatment: − relapsing during, or within 12 months of completion of, adjuvant endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane), or − progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) provided that this endocrine treatment was started at least 12 months after the completion of adjuvant endocrine treatment, or − progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) given as first treatment for patients with de novo advanced breast cancer 5. Patients with measurable disease as per RECIST criteria. 6. Postmenopausal women are defined as those women fulfilling any ONE of the following criteria: − age ≥ 60 − having undergone a bilateral oophorectomy − age <60 with an intact uterus and at least one intact ovary, amenorrhea ≥ 12 months continuous AND - if they received systemic cytotoxic anticancer therapy: (a) the last dose must have been ≥ 12 months prior to randomisation OR (b) age ≥ 45 - if they were on an LHRH analogue, the last depot must have been administered ≥ 4 months prior to randomisation AND FSH and oestradiol levels must be in the postmenopausal range (utilising ranges from the local laboratory facility) − for patients with at least one intact ovary and prior history of hysterectomy, FSH and oestradiol levels must be in the postmenopausal range AND - if they received systemic cytotoxic anticancer therapy: (a) the last dose must have been ≥ 12 months prior to randomisation OR (b) age the patient is ≥ 45 years of age - if they were on an LHRH analogue, the last depot must have been administered ≥ 4 months prior to randomisation 7. WHO performance status 0, 1 or 2.	Any of the following was regarded as a criterion for exclusion from the study: 1. Presence of life-threatening metastatic visceral disease, defined as *extensive* hepatic involvement, or any degree of brain or leptomeningeal involvement (past or present), or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases are eligible, provided their respiratory function is not clinically and significantly compromised as a result of disease. 2. More than one previous regimen of systemic anticancer therapy other than endocrine treatment for advanced disease. **Note:** Patients previously treated with one regimen of systemic anticancer therapy other than endocrine treatment *for advanced disease* are allowed as long as their last treatment is an anti-oestrogen or an AI. 3. More than one previous regimen of endocrine therapy for advanced disease. **Note:** Oophorectomy, ovarian ablation, or LH-RH analogue therapy did not count as endocrine treatments in this context and also did not render the patient ineligible for this study. 4. Extensive radiation therapy within 4 weeks prior to randomisation (greater than or equal to 30% marrow or whole pelvis or spine) or systemic anticancer therapy other than endocrine treatment within 4 weeks prior to randomisation, or radiolabelled strontium (or other radiopharmaceuticals) within 12 weeks prior to randomisation. 5. Treatment with a non-approved or experimental drug except the postmanufacturing/marketing clinical study drug within 4 weeks before randomisation. 6. Current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in-situ carcinoma of the cervix) 7. Any of the following laboratory values within 3 weeks of randomisation: - Platelets < 100×10^9/L - Total bilirubin > 1.5 × ULRR (upper limit of reference range)* - ALT or AST > 2.5 × ULRR if no demonstrable liver metastases or > 5 × ULRR in presence of liver metastases * Patients with confirmed Gilbert's syndrome may be included in the study 8. History of: - bleeding diathesis (i.e., disseminated intravascular coagulation [DIC], clotting factor deficiency), or - long-term anticoagulant therapy (other than antiplatelet therapy and low dose warfarin). 9. History of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil. 10. Any severe concomitant condition which makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the trial protocol, e.g., uncontrolled cardiac disease or uncontrolled diabetes mellitus. 11. Involvement in the planning and conduct of the study (applies to both AstraZeneca staff or staff at the study site)

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
		12. Previous enrolment or randomisation of treatment in the present study.
FINDER II	1. Histological/cytological Confirmation of breast cancer (from either primary or metastatic tumour) 2. Documented positive ER status (ER +ve) of primary or metastatic tumour tissue, defined as ≥10% positive staining by immunohistochemistry 3. Requiring hormonal treatment: − relapsing during or within 12 months of completion of adjuvant endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) − progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane), provided that this endocrine treatment was started at least 12 months after the completion of adjuvant endocrine treatment, or − progressing on an endocrine therapy (tamoxifen, toremifene or AIs such as anastrozole, letrozole and exemestane) given as 1st treatment for patients with de novo advanced breast cancer 4. Patients with measurable disease as per RECIST 5. Postmenopausal women, defined as those women fulfilling any one of the following criteria: - age ≥60 years - having undergone a bilateral oophorectomy - age <60 years with an intact uterus and at least one intact ovary, amenorrhoea for ≥12 months continuous AND if the patient had received systemic cytotoxic anti-cancer therapy, the last dose had to have been ≥12 months prior to randomisation; or the patient had to be ≥45 years old - if the patient was on a leuteinising hormone releasing hormone (LHRH) analogue the last depot must have been administered >4 months prior to randomisation and FSH and oestradiol levels had to be in the post menopausal range for patients with at least one intact ovary and prior history of hysterectomy follicle stimulating hormone (FSH) and oestradiol levels had to be in the postmenopausal range - if the patient had received systemic cytotoxic anticancer therapy then the last dose had to have been ≥12 months prior to randomisation or the patient had to be ≥45 years old; if the patient was on an LHRH analogue the last depot had to have been administered ≥4 months prior to randomisation. 6. WHO performance status 0, 1 or 2.	Any of the following was regarded as a criterion for exclusion from the study: 1. Presence of life-threatening metastatic visceral disease, defined as: extensive hepatic involvement; or any degree of brain or leptomeningeal involvement (past or present); or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases were eligible, provided their respiratory function was not clinically and significantly compromised as a result of disease. 2. More than one previous regimen of systemic anti-cancer therapy other than endocrine treatment for advanced disease. Patients previously treated with one regimen of systemic anti-cancer therapy other than endocrine treatment for advanced disease were allowed as long as their last treatment was an anti-oestrogen or an AI. 3. More than one previous regimen of endocrine therapy for advanced disease. 4. Extensive radiation therapy within 4 weeks prior to randomisation (≥30% marrow or whole pelvis or spine); or systemic anti-cancer therapy other than endocrine treatment within 4 weeks prior to randomisation; or radiolabelled strontium (or other radiopharmaceuticals) within 12 weeks prior to randomisation. 5. Treatment with a non-approved or experimental drug except the postmanufacturing/marketing clinical study drug within 4 weeks before randomisation. 6. Current or prior malignancy within the previous 3 years (other than breast cancer; adequately treated basal cell or squamous cell carcinoma of the skin; or in-situ carcinoma of the cervix). 7. Any of the following laboratory values within 3 weeks prior to randomisation: - platelets <100 x 10^9/L - total bilirubin >1.5 x ULRR (upper limit reference range) - alanine aminotransferase (ALT) or aspartate aminotransferase (AST)>2.5 x ULRR if no demonstrable liver metastases, or >5 x ULRR in the presence of liver metastases. 8. History of: - bleeding diathesis (i.e., disseminated intravascular coagulation, clotting factor deficiency), or - long-term anticoagulant therapy (other than anti-platelet therapy and low dose warfarin). 9. History of hypersensitivity to active or inactive excipients of fulvestrant and/or castor oil. Any severe concomitant condition which made it undesirable for the patient to participate in the trial or which jeopardised compliance with the trial protocol, e.g. uncontrolled cardiac disease or uncontrolled diabetes mellitus. 11. Involvement in the planning and conduct of the study (applicable to both AstraZeneca staff and staff at the study site). 12. Previous enrolment or randomisation of treatment in the present study.

5.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B6 Characteristics of participants in the RCTs across randomised groups

	Fulvestrant 500 mg	**Fulvestrant 250 mg**
CONFIRM (n = 736)	**(n=362)**	**(n = 374)**
Age, mean (standard deviation)	61.0 (11.47)	60.8 (11.94)
Weight (kg), mean (standard deviation)	69.8 (14.47)	69.3 (14.57)
Race		
- Caucasian	349	358
- Black	2	1
- Oriental	2	0
- Other	9	15

	Fulvestrant 500 mg	Fulvestrant 250 mg
Hormone receptor status		
- ER+	362	374
PgR+ve	241	266
PgR-	92	96
PgR unknown	29	12
Tumour grade		
- well differentiated	24	30
- moderately differentiated	129	125
- poorly differentiated	73	81
- undifferentiated	1	5
- unassessable	21	13
- not done	114	120
Disease characteristics		
- locally ABC only	4	11
- metastatic disease	358	363
- measureable disease	240	261
Adjuvant therapy		
- Endocrine therapy	231	249
AI	52	55
AO	202	217
- chemotherapy	185	200
- radiotherapy	214	206
Advanced disease therapy		
- Endocrine therapy	173	182
AI	101	108
AO	72	75
- chemotherapy	81	69
- radiotherapy	69	102
Last endocrine therapy received		
- AI	152	161
- AO	210	213

	Fulvestrant 500 mg	Fulvestrant 250 mg
FINDER I (n = 143)	**(n=47)**	**(n=45)**
Age, mean (standard deviation)	62.7 (9.1)	62.5 (7.4)
Weight (kg), mean (standard deviation)	54.0 (8.5)	55.6 (8.8)
Race - Japanese	47	45
WHO Performance status - 0 - 1 - 2	 40 7 0	 39 6 0
Oestrogen receptor status - positive	 47	 45
Progesterone receptor status - Positive - Negative	 30 17	 32 13
Tumour grade - grade 1 - grade 2 - grade 3 - unassessable - unknown	 3 18 13 3 10	 6 20 7 1 11
Metastatic status - locally ABC only - metastatic disease	 0 47	 1 44
Visceral involvement - yes - no	 27 20	 26 19
Previous therapy - radiotherapy - chemotherapy - endocrine therapy	 21 33 47	 15 25 45
FINDER II (n =144)	**(n=46)**	**(n = 47)**
Age, mean (standard deviation)	65.5 (9.0)	63.7 (9.9)

	Fulvestrant 500 mg	Fulvestrant 250 mg
Weight, mean (standard deviation)	70.8 (12.9)	71.6 (17.2)
Race - Caucasian - Japanese - Oriental	 46 0 0	 45 1 1
WHO performance status - 0 - 1 - 2 - missing	 31 14 1 0	 26 20 0 1
Receptor status - ER+	 46	 47
Tumour grade - I - II - III - Not assessable - unknown	 5 23 10 8 0	 7 15 16 9 0
Visceral involvement - yes - no	 37 9	 34 13
Previous treatment • Radiotherapy • Chemotherapy • Endocrine therapy	 25 26 46	 25 28 47

Outcomes

5.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B7 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
CONFIRM	Time to progression (TTP)	TTP is an endpoint that is commonly used in medical oncology practice to determine treatment decisions: patients who have progressive disease on a particular treatment are usually switched to an alternative therapy because it is believed that disease progression indicates resistance to the initial treatment.	Objective response rate (ORR) Clinical benefit rate (CBR) Duration of response (DoR) Duration of clinical benefit (DoCB) Overall survival (OS) Tolerability HRQoL	 Frequency and severity of AEs Trial Outcome Index (TOI) derived from the FACT-B questionnaire
FINDER I	Objective response	RECIST criteria. The objective response (OR) was	Pharmacokinetic characteristics	Cmax, Clearance and Volume of distribution at

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
	rate (ORR)	derived by categorising the best overall response for each patient as a responder (CR or PR) or a non-responder (SD, progressive disease or NE). ORR was defined as the proportion of responders (CR and PR).	Time to progression (TTP) Clinical benefit rate (CBR) Duration of response (DoR) Tolerability	steady state RECIST was used to determine a patient's TTP. RECIST was used to perform the objective tumour assessments DoR was calculated for those patients who had a best overall response of CR or PR based on RECIST. Adverse events (AEs), safety clinical laboratory tests and vital signs, electrocardiogram and physical examination.
FINDER II	Objective response rate (ORR)	Defined as having an objective response if they had a best overall response of either complete response (CR) or partial response (PR), evaluated according to RECIST.	Pharmacokinetic characteristics Time to progression (TTP) Clinical benefit rate (CBR) Duration of response (DoR) Tolerability	Cmax, Clearance and Volume of distribution at steady state RECIST was used to determine TTP RECIST was used to perform the objective tumour assessments and best overall objective tumour response DoR was calculated for those patients who had a best overall response of CR or PR based on RECIST Adverse events, safety clinical laboratory tests and vital signs, electrocardiogram and physical examination

Statistical analysis and definition of study groups

5.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B8 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
CONFIRM	To compare the efficacy of fulvestrant 500 mg treatment with fulvestrant 250 mg treatment in terms of time to progression (TTP)	For the primary endpoint TTP, the primary analysis was an unadjusted log-rank test and the secondary analysis was a Cox proportional hazard model, adjusted for treatment and other predefined covariates. The primary and secondary analyses were carried out on the Full Analysis Set (equivalent to intention-to-treat). Conclusions were to be based on the unadjusted analysis. If the unadjusted analysis and the adjusted analysis yielded different results, the consequences of covariate adjustment were to be explored. Further analysis of TTP was carried out on the per protocol set (PPS) using the log-rank test. Superiority was to be declared if the 2-sided p-value for the treatment comparison was ≤0.05. For the secondary endpoints, the nominal significance level of 0.05 was used. For OS, the log-rank test was to be performed when approximately 50% deaths had been reached. For ORR and CBR, a logistic regression model with treatment factor only	The sample size calculation was based on the primary variable, TTP, and assumed exponential progression times. The sample size was driven by the number of required events. In order to detect a hazard ratio of ≤0.8 (or ≥1.25) for fulvestrant 500 mg compared to fulvestrant 250 mg, at a 2-sided significance level of 5%, with 80% power, approximately 632 events were required to have occurred in the study (i.e., approximately 632 patients to have progressed or died in the absence of progression).	Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. AstraZeneca's quality assurance and internal quality control procedures provide reassurance that the clinical study programme was carried out in accordance with GCP guidelines.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		was fitted. DoR and DoCB were analysed. For HRQoL endpoints, a longitudinal model with treatment and other covariates was used. For efficacy and HRQoL endpoints, summaries and analyses were carried out according to the randomised treatment. For safety endpoints, summaries and analyses were carried out according to the treatment actually received. The following 12 subgroups were analysed: • "ER+ and progesterone receptor (PgR)+ve" vs. "ER+ and PgR- or unknown" patients • Visceral involvement (no vs. yes) • Last therapy prior to fulvestrant (aromatase inhibitor [AI] vs. anti-oestrogen [AO] therapy) • Response to last endocrine therapy received prior to fulvestrant (responsive vs. not responsive) • Age (<65 years vs. ≥65 years) • Measurable disease (no vs. yes) These subgroups, which were predefined in the SAP, were chosen to investigate the consistency of any treatment effect across 6 covariates that are potential prognostic factors for TTP.		

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
FINDER I	To assess the relationship between fulvestrant dose and efficacy, and determine the dosing regimen as a second line therapy for Japanese postmenopausal women	ORR was defined as the proportion of responders (CR and PR). A point estimate of ORR and the corresponding 2-sided 95% CI were calculated for each treatment group. Subgroup analyses were performed related to the following factors for OR and TTP: • Age (<65 vs. ≥65) • Response to first –line therapy for advanced breast cancer (i.e. response to the hormonal agent that was used first when the patient was diagnosed with advanced breast cancer) received prior to fulvestrant • Receptor status at diagnosis (both ER+ & PgR+ vs. ER+ & PgR other) • Visceral involvement (Yes/No) • Last therapy received prior to fulvestrant (AI/Anti-oestrogen Therapy) The number of patients in each category of the best objective overall response (CR, PR, SD ≥24 weeks, SD <24 weeks, PD or NE) was counted for each treatment group. Objective response by when response occurred (during study treatment or after study treatment) was also summarised. Consistency of best overall response between derived variable and investigator's assessment was checked.	A response rate of 19.2% for fulvestrant 250 mg was estimated from the result of studies 9238IL/0020 and 9238IL/0021. Since it was considered that response rate is non-decreased with an increase of dose, the response rate of 19.2% for fulvestrant 250 mg was assumed to be smallest response rate in this study. Assuming the smallest response rate of 19.2%, 43 patients per group were required to have the probability that the best dose regimen will correctly be selected was at least 90% if the difference of the objective response rate between the best and next best dose regimen was 15%. To allow for drop-out, 45 patients per group were to be recruited. Therefore, a total of 135 patients were to be recruited to this study.	Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and use of data management procedures. AstraZeneca's quality assurance and internal quality control procedures provide reassurance that the clinical study programme was carried out in accordance with GCP guidelines. The principal investigator/sub-investigator recorded data on the observations, tests and assessments specified in the CSP on the CRFs provided by AstraZeneca. The CRF was accompanied with 'Instructions for the Investigator', which were followed. These instructions provided guidance for the recording of study data in the CRF including how to change data incorrectly recorded. These instructions were an important part of quality control and standardisation across the study.
FINDER II	To assess the relationship between fulvestrant dose and efficacy	ORR was defined as the proportion of responders (CR and PR). A point estimate of ORR and the corresponding 2-sided 95% CI were calculated for each treatment group. Subgroup analyses were performed related to the following factors for OR and TTP: • Age (<65 vs. ≥65) • Response to first –line therapy for advanced breast cancer (i.e. response to the hormonal agent that was used first when the patient was diagnosed with advanced breast cancer) received prior to fulvestrant	The sample size was the same as the corresponding Japanese study (D6997C00004) and was calculated based on selection formulation. Based on the results of 2 previous phase III studies (Study 9238IL/0020 and Study 238IL/0021) the response rate for fulvestrant 250 mg was estimated to be 19.2%. It was anticipated that an increase in fulvestrant dose would not lead to a decrease in the response rate and therefore the response rate of 19.2% for fulvestrant 250 mg was assumed to be the smallest response rate in this study.	Quality of study data was assured through monitoring of investigational sites, provision of appropriate training for study personnel, and the use of data management procedures, as detailed below. CRFs were provided for the recording of data. The forms were 3 level NCR (no carbon required) paper. Data was to be recorded legibly onto the CRFs in black or blue ballpoint ink. Corrections were to be made legibly and initialled and dated by approved personnel; the reasons for significant changes had to be provided. Correction fluid or covering labels were

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		• Receptor status at diagnosis (both ER+ & PgR+ vs. ER+ & PgR other) • Visceral involvement (Yes/No) • Last therapy received prior to fulvestrant (AI/Anti-oestrogen Therapy) The number of patients in each category of the best objective overall response (CR, PR, SD ≥24 weeks, SD <24 weeks, PD or NE) was counted for each treatment group. Objective response by when response occurred (during study treatment or after study treatment) was also summarised. Consistency of best overall response between derived variable and investigator's assessment was checked.	Based on the assumption of a lowest response rate of 19.2%, 43 patients per arm were required to provide a ≥90% probability that the best dose regimen would be correctly selected, if the difference in the ORR between the best and next best dose regimen was 15%. To allow for drop out, it was planned that 45 patients per arm would be recruited. Therefore, a total of 135 patients were to be recruited into to this study.	not to be used. The top original, 1st and 2nd copy of each completed form was to be collected. The top original and the 1st copy were sent to data management personnel, the 2nd copy was retained by the monitor. The 3rd copy was to be retained at the investigator site. Any electronic data were loaded into the database and checked for validity. The method of distribution of data queries was to be documented in the study Data Management Plan. The original signed data query was to be returned to data management personnel. The monitor retained one copy and the other was retained at the investigator site. On receipt of the data query by data management the database was edited appropriately. Data management was co-ordinated by AstraZeneca R&D. The CRF data were verified against any source data before the patient CRFs were collected from the study site by an AstraZeneca monitor or AstraZeneca nominated monitor. The monitor was to collect the original edited patient CRF pages on an ongoing basis throughout the study, and return them to the relevant local AstraZeneca Marketing Company (MC) or Clinical Research Region (CRR).

5.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

The 12 pre-specified subgroups in CONFIRM were chosen to investigate the consistency of any treatment effect across 6 covariates that are potential prognostic factors for TTP.

The following 12 subgroups were analysed:

- "ER+ve and progesterone receptor (PgR)+ve" vs. "ER+ve and PgR-ve or unknown" patients
- Visceral involvement (no vs. yes)
- Last therapy prior to fulvestrant (aromatase inhibitor [AI] vs. anti-oestrogen [AO] therapy)
- Response to last endocrine therapy received prior to fulvestrant (responsive vs. not responsive)
- Age (<65 years vs. ≥65 years)
- Measurable disease (no vs. yes)

A forest plot of the predefined subgroup analysis of the primary endpoint in CONFIRM is displayed in figure 13. The treatment effect, favouring fulvestrant 500 mg compared to fulvestrant 250 mg, was shown to be consistent across all subgroups analysed. There were no patient subgroups where the treatment effect favoured fulvestrant 250 mg, as shown in table **B18** and **B19.**

For FINDER I and II, subgroup analyses for best objective overall response and objective response where planned for the following factors, however the number of patients in each subgroup was insufficient for adequate evaluation:

- age (<65 vs. ≥65),
- response to 1st line therapy for advanced breast cancer (i.e., response to the hormonal agent that was used first when the patient was diagnosed with advanced breast cancer) received prior to fulvestrant, receptor status at diagnosis (ER+ & PgR+ vs. ER+ & PgR other)
- visceral involvement (yes/no)
- last therapy received prior to fulvestrant (aromatase inhibitor/anti-oestrogen therapy).

ER receptor status was another variable that was reviewed with the regards to conducting a sub group analysis. The main trial that the manufacturer has in support of fulvestrant 500 mg, CONFIRM, has all patients categorized as ER+ and therefore in order to obtain the most like-for-like comparison, ideally all other trials should have included only ER+ patients. However, after conducting a systematic literature review it was found that only the CONFIRM and FINDER trials had all patients classified as ER+. Therefore the inclusion

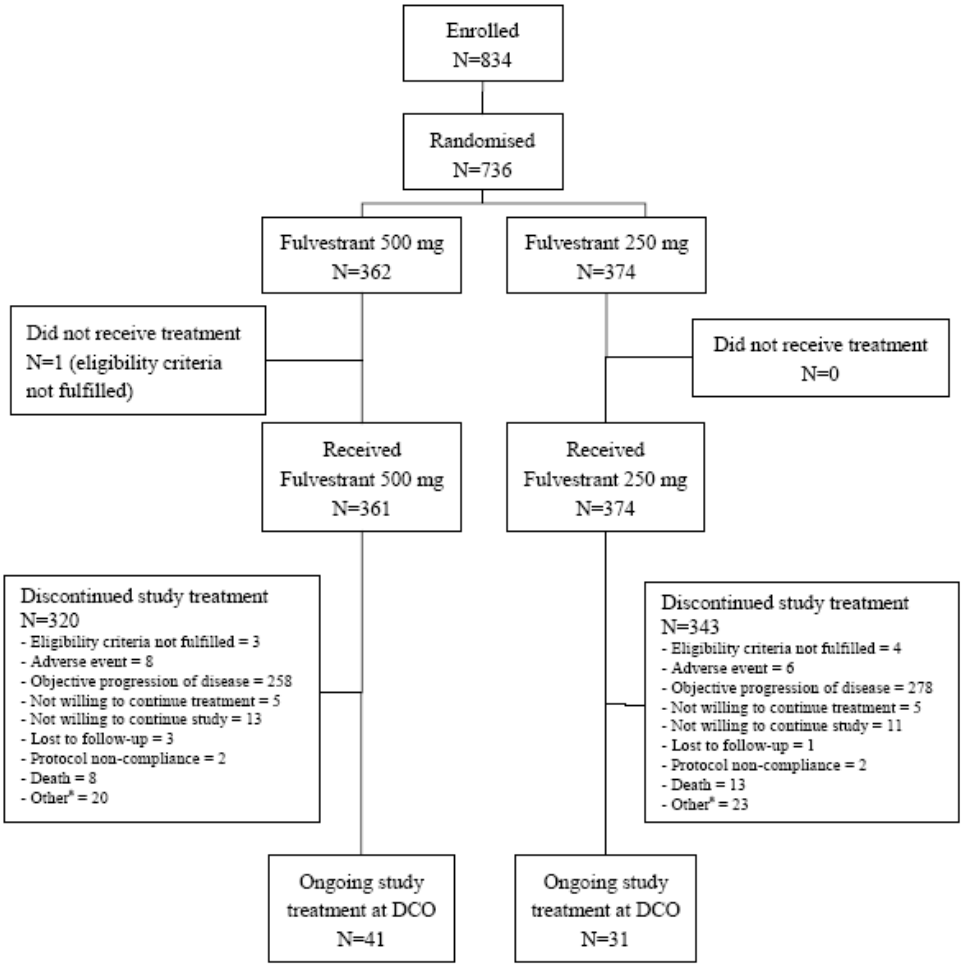
criteria were relaxed to include trials where samples contained at least 70% of patients with a documented ER+ status. The feasibility of conducting a sub-analysis for results for the ER+ subgroups in the other trials was explored, however, not all the outcomes needed for modeling were reported for this subgroup (in most cases only the primary outcome for each trial was reported for the ER+ subgroup, if at all).

Participant flow

5.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 7: CONFIRM CONSORT flowchart

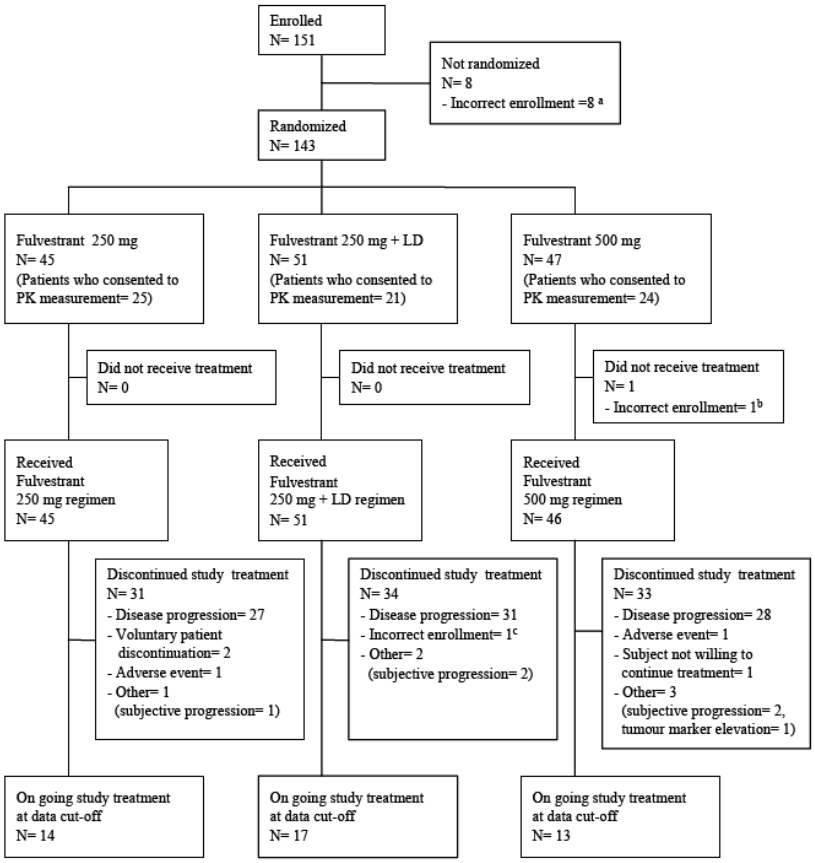
CONFIRM



[a] Examples includes: disease progression judged by evaluations other than RECIST, initiation of radiation treatment, subject moving abroad

Figure 8: FINDER I CONSORT flowchart

FINDER I

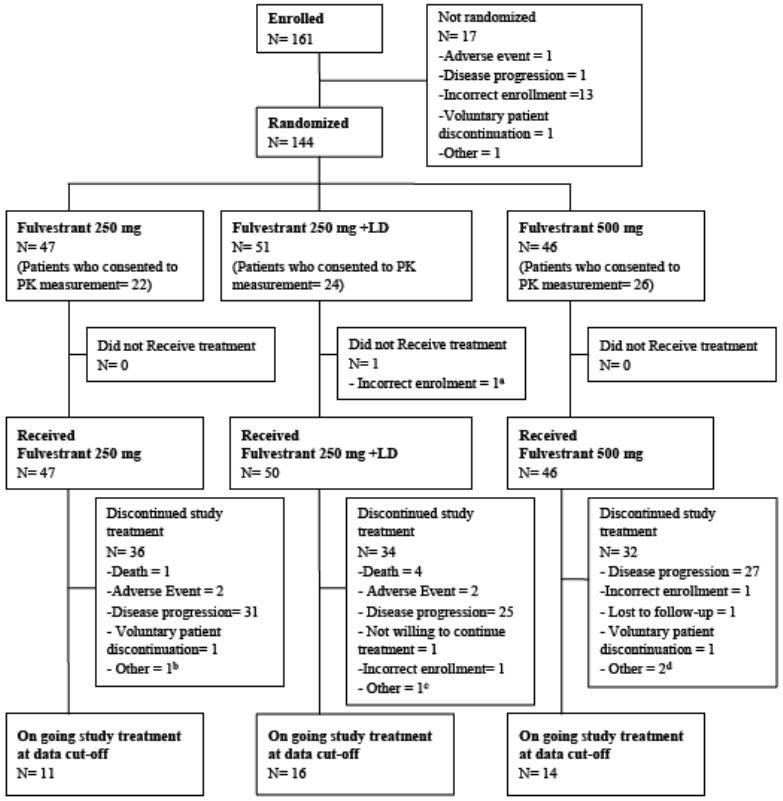


a All patients did not fulfil at least one inclusion or exclusion criterion due to the baseline evaluation.
b The patient did not receive the study treatment because she did not fulfil the inclusion criteria No. 4.
c Fallopian tube cancer was found in the patient (did not meet the inclusion criteria No. 2) during the treatment period.

Data cut-off date was 19 March 2008.

Figure 9: FINDER II CONSORT flowchart

FINDER II



[a] Patient E0012001 was randomised but did not receive study treatment as she was found to have failed inclusion criterion 4 prior to starting treatment.

[b] Patient E0032001 discontinued study treatment due to clinical progression in the opinion of the investigator.

[c] Patient E0081001 discontinued study treatment due to disease progression, however, the investigator listed this reason for discontinuation under the option 'Other' on the patient CRF.

[d] Two patients in the fulvestrant 500 mg treatment arm discontinued study treatment due to a reason listed by the investigator under the field 'Other' on the patient CRF. For Patient E0058001 the reason given by the investigator was 'dosing error'. For Patient E0081002 the reason given by the investigator was diagnosis of brain metastases after randomisation.

5.4 Critical appraisal of relevant RCTs

5.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be

validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

Please note that the critical appraisal of trials for which data were used in this submission appears in section 5.4.3, Appendix 3, and Appendix 5.

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

5.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B9 Quality assessment results for RCTs

Trial no. (acronym)	CONFIRM	FINDER I	FINDER II
Was randomisation carried out appropriately?	Yes	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Includes all randomized patients, regardless of whether any study treatment was received	Includes all randomized patients, regardless of whether any study treatment was received	Includes all randomized patients, regardless of whether any study treatment was received

5.5 Results of the relevant RCTs

5.5.1 **Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. If there is more than one RCT, tabulate the responses.**

5.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan-Meier plots.

5.5.3 For each outcome for each included RCT, the following information should be provided.

Result s from CONFIRM trial[20]

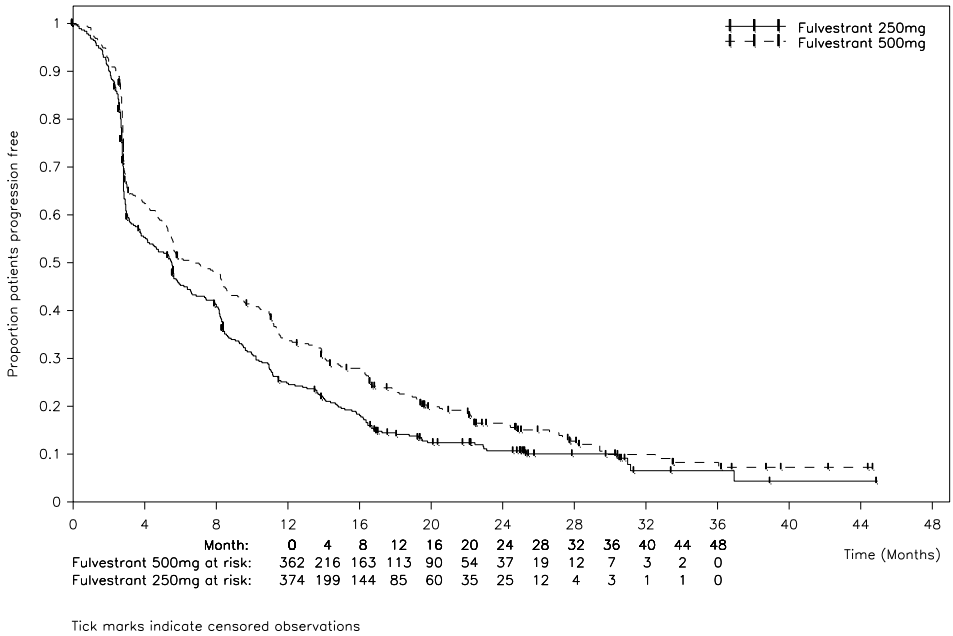
Primary Endpoint

The primary endpoint is time to progression (TTP) in Intention-To-Treat (ITT) population.

The CONFIRM study demonstrated that fulvestrant 500 mg offers a significantly longer TTP compared with fulvestrant 250 mg, according to the protocol defined criterion for statistical significance:

- hazard ratio=0.80 [95% CI 0.68 to 0.94]; 2-sided p=0.006) for the ITT population using an unadjusted log rank test;
    - this corresponds to a 20% reduction in the risk of progression
    - the Kaplan-Meier plot for TTP in the ITT population shows a separation between the 2 treatment groups from approximately 3 months, favouring the fulvestrant 500 mg group
    - median TTP was 6.5 months in the fulvestrant 500 mg group and 5.5 months in the fulvestrant 250 mg group; the Kaplan-Meier estimate of progression free survival at 12 months was 34% of patients in the fulvestrant 500 mg group compared to 25% in the fulvestrant 250 mg group.
- the treatment effect (TTP) favouring fulvestrant 500 mg was consistent across all of the subgroups analysed (see figure 13)

Figure 10: Kaplan-Meier plot of Time to Progression (ITT population)



Secondary Endpoints

- *Objective response rate (ORR)*

ORR, defined as the proportion of responders (complete response (CR) and partial response PR), was analysed in the Evaluable for Response Set. Patients were deemed to have achieved an objective response if they had a best RECIST response of CR or PR only. This means that for ORR, the Evaluable for Response population (those with measurable disease at baseline only) is the appropriate denominator (as only patients with measurable disease at baseline can possibly achieve a response of CR of PR).

Table B10 shows best objective response (BOR), according to RECIST, of patients in the fulvestrant 500 mg and fulvestrant 250 mg treatment groups.

A slightly greater proportion of patients in the fulvestrant 500 mg group had a Clinical Response (CR) than in the 250 mg group; however, a slightly lesser proportion had a Partial Response (PR).

Table B10 Summary of best objective response: Evaluable for response

Best Objective Response	Number (%) of patients	
	Fulvestrant 500 mg N=240	Fulvestrant 250 mg N=261
CR	4 (1.7)	1 (0.4)
PR	29 (12.1)	37 (14.2)
SD	98 (40.8)	103 (39.5)
PD	102 (42.5)	117 (44.8)
NE	7 (2.9)	3 (1.1)

CR: Complete response; PR: Partial response; PD: Progressive disease; SD: Stable disease.
Best response has been programmatically derived according to RECIST.
Not evaluable - no evaluable follow-up assessments after randomisation.

ORR was similar in the 2 treatment groups (13.8% in the fulvestrant 500 mg group and 14.6% in the fulvestrant 250 mg group) with no statistical difference (odds ratio=0.94 [95% CI 0.57 to 1.55]; p=0.795). See **Table B11**.

Table B11 Analysis of objective response rate: Evaluable for response set

	Fulvestrant 500 mg N=240	Fulvestrant 250mg N=261	Odds Ratio (95% CI)	p-value
ORR	13.8% (33/240)	14.6% (38/261)	0.94 (0.57-1.55)	0.795

An odds ratio >1 favours fulvestrant 500 mg whereas an odds ratio of <1 favours fulvestrant 250 mg.
OR is defined as a patient having a BOR of CR or PR.
ORR is the percentage of patients with OR.

- *Clinical benefit rate (CBR)*

Clinical Benefit Rate (CBR) defined as the proportion of responders plus those with SD ≥24 weeks, was analysed in the ITT population. Patients are deemed to have achieved clinical benefit if they have a best RECIST response of CR, PR or stable disease (SD) ≥ 24 weeks. This means that for CBR, the ITT population is the appropriate denominator.

Fulvestrant 500 mg offered patients a numerically higher CBR, (45.6%) compared to those receiving fulvestrant 250 mg (39.6%) (Odds ratio=1.28 [95% CI 0.95 to 1.71]; p=0.100). See **Table B12 and B13.**

Table B12: Summary of best objective response: ITT population

	Fulvestrant 500 mg	**Fulvestrant 250mg**
	N=362 (%)	**N=374 (%)**
CR	4 (1.1)	1 (0.3)
PR	29 (8.0)	37 (9.9)
SD ≥ 24 wks	132 (36.5)	110 (29.4)
SD change <24 wks	47 (13.0)	52 (13.9)
PD	140 (38.7)	167 (44.7)
NE	10 (2.8)	7 (1.9)

Best response has been programmatically derived according to RECIST.
Not evaluable - no evaluable follow-up assessments after randomisation.
CR: Complete response; PR: Partial response; PD: Progressive disease; SD: Stable disease.

Table B13 Analysis of clinical benefit rate: ITT population

	Fulvestrant 500 mg N=362	**Fulvestrant 250mg N=374**	**Odds Ratio (95% CI)**	**p-value**
CBR	45.6% (165/363)	39.6% (148/374)	1.28 (0.95-1.71)	0.100

An odds ratio of >1 favours fulvestrant 500 mg whereas an odds ratio of <1 favours fulvestrant 250 mg.

- *Duration of response (DoR)*

The assessment of DoR was limited to patients who had an objective response (complete and partial responses), i.e., a subset of the ITT population. The ratio of Expected Duration of Response (EDoR) between the fulvestrant 500 mg group and the fulvestrant 250 mg group favours fulvestrant 250 mg; however, this difference is not statistically significant (ratio of EDoR [95% CI]=0.89 [0.48 to 1.67]; p=0.724). See **Table B14.**

Table B14 Summary of duration of response for Response set

	Fulvestrant 500 mg	Fulvestrant 250 mg
Number of responders (%)	33 (13.8)	38 (14.6)
Median DoR (in patients with objective responses		
From randomisation (months)	19.4	16.4
From first response (months)	8.5	12.0

- *Duration of Clinical Benefit (DoCB)*

The assessment of DoCB was limited to patients who achieved clinical benefit, see **Table B15 and figure 11**.

Table B15 Summary of duration of clinical benefit: ITT population

	Fulvestrant 500 mg N=362	**Fulvestrant 250 mg N=374**
Number of patients with clinical benefit (%)	[redacted]	[redacted]
Median DoCB in patients with clinical benefit (months)	[redacted]	[redacted]

DoCB is measured from randomisation to progression.

[redacted]

The median DoCB in the fulvestrant 500 mg group [redacted] was numerically longer than in the fulvestrant 250 mg group [redacted] and the Kaplan-Meier plot [redacted]

[redacted]

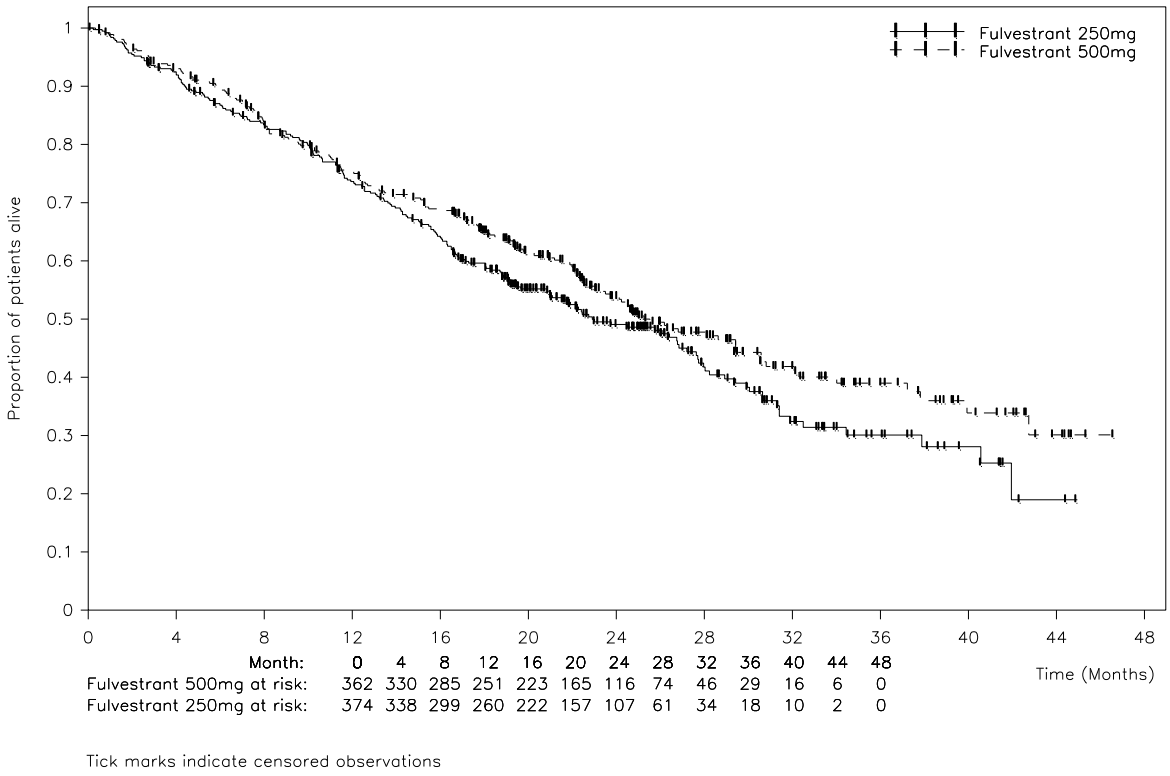
- *Quality of Life*

A total of 145 women completed a baseline FACT-B questionnaire, which represented 82.3% of the 176 women randomly assigned in the countries that participated in the QOL substudy. No significant difference was detected between the two study arms

- *Overall Survival (OS):*

OS was not formally analysed at the primary data cut-off (DCO) for TTP. At DCO, 378/736 (51.4%) of the patients had died (175 [48.3%] in the fulvestrant 500 mg group and 203 [54.3%] in the fulvestant 250 mg group). Median OS was 25.1 months in the fulvestrant 500 mg group and 22.8 months in the fulvestrant 250 mg group. The log rank analysis indicates that there is a trend for improved OS for patients in the fulvestrant 500 mg group compared with those in the fulvestrant 250 mg group, however, this does not reach statistical significance (hazard ratio=0.84 [95% CI 0.69 to 1.03]; p=0.091) corresponds to a 16% reduction in risk of death. This trend for improved survival suggests that the benefit provided by treatment with fulvestrant 500 mg until progression, is maintained past progression **(figure 12).** An exploratory analysis of OS, adjusted for the 6 predefined baseline covariates, is consistent with the unadjusted analysis (hazard ratio=0.81 [95% CI=0.66 to 0.99]; p=0.037.

Figure 12: Overall survival ITT unadjusted analysis



- *Tolerability*

Consistent with the longer TTP for patients treated with fulvestrant 500 mg, patients in this treatment group had a longer duration of exposure to fulvestrant than those in the fulvestrant 250 mg group see **Table B16**.

Table B16: Summary of duration of exposure: Safety Analysis Set

Duration (days)	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Mean (sd)	313.0 (294.64)	248.6 (244.98)
Median (range), days	174.0 (10–1441)	145.5 (7–1387)
Median (range), months	5.7 (0.3-47.3)	4.8 (0.2-45.6)

Mean time from diagnosis to randomisation in months assumes 1 month = 30.4375 days (365.25 days / 12 months).

A total of 2443 AEs were reported by 483 (65.7%) of the 735 patients in the Safety Analysis Set. Fifty-four patients (7.3%) reported a serious AE (SAE) including 11 patients (1.5%) who died due to an AE. Seventeen patients (2.3%) discontinued study treatment due to an AE. There were no notable differences between treatment groups in the incidence of AEs.

Summaries of the most commonly reported AEs, i.e., those AEs reported by ≥5% of patients in any treatment group or in total, are presented in Table B19 (by Preferred Term).

The most frequently reported AEs in the fulvestrant 500 mg group were injection site

pain (11.6% of patients), nausea (9.7% of patients) and bone pain (9.4% of patients); the most frequently reported AEs in the fulvestrant 250 mg group were nausea (13.6% of patients), back pain (10.7% of patients) and injection site pain (9.1% of patients). Overall, the incidence of AEs was well balanced across the 2 treatment groups.

Table B17: Summary of most commonly reported AEs by PT (cut-off ≥5% in either treatment group): Safety Analysis Set

	Number (%) of patients	
	Fulvestrant 500 mg N=362	Fulvestrant 250 mg N=374
Injection site pain	42 (11.6)	34 (9.1)
Nausea	35 (9.7)	51 (13.6)
Bone pain	34 (9.4)	28 (7.5)
Arthralgia	29 (8.0)	29 (7.8)
Headache	28 (7.8)	25 (6.7)
Back pain	27 (7.5)	40 (10.7)
Fatigue	27 (7.5)	24 (6.4)
Pain in extremity	25 (6.9)	26 (7.0)
Hot flush	24 (6.6)	22 (5.9)
Vomiting	22 (6.1)	21 (5.6)
Anorexia	22 (6.1)	14 (3.7)
Asthenia	21 (5.8)	23 (6.1)
Musculoskeletal pain	20 (5.5)	12 (3.2)
Cough	19 (5.3)	20 (5.3)
Constipation	18 (5.0)	13 (3.5)
Dyspnoea	16 (4.4)	19 (5.1)

Subgroup analysis of the primary endpoint (TTP) in CONFIRM

Pre-specified subgroups in CONFIRM were chosen to investigate the consistency of any treatment effect across 6 covariates that are potential prognostic factors for TTP. A forest plot of the predefined subgroup analysis of the primary endpoint in CONFIRM is displayed in figure 13.

The treatment effect, favouring fulvestrant 500 mg compared to fulvestrant 250 mg, was shown to be consistent across all subgroups analysed. There were no patient subgroups where the treatment effect favoured fulvestrant 250 mg, as shown in table B18 and B19.

Figure 13 Time to progression subgroup analysis forest plot: CONFIRM study

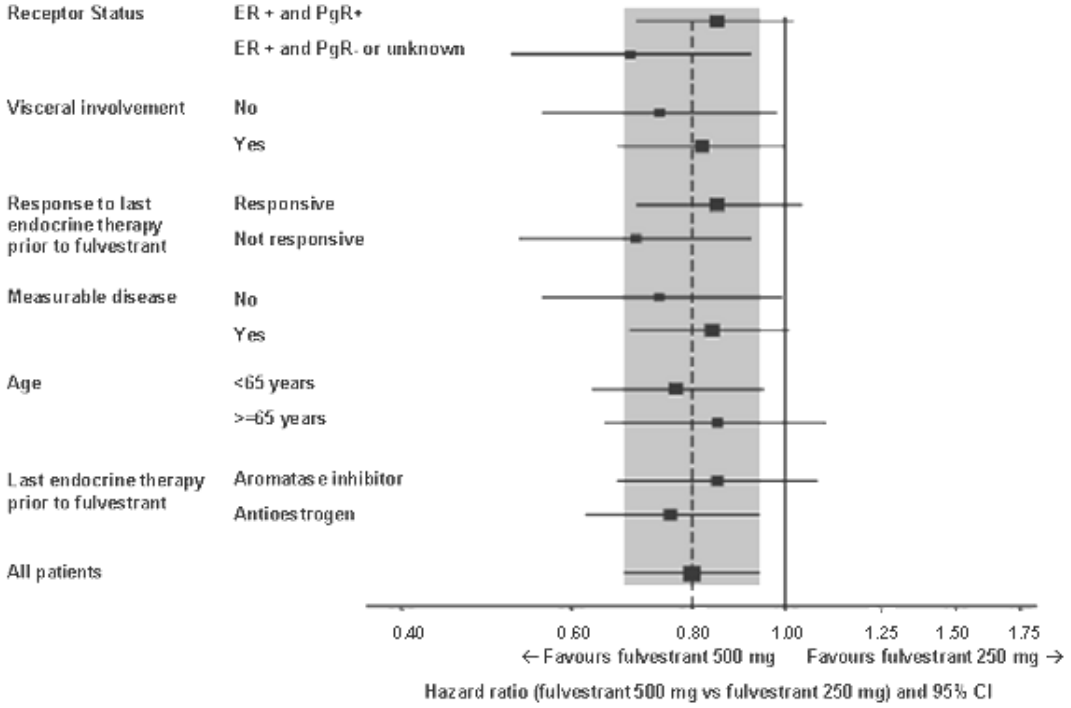


Table B18 Summary and analysis of time to progression for the receptor status, visceral involvement and response to last endocrine therapy covariates: CONFIRM ITT population

	Receptor status				Visceral involvement				Response to last endocrine therapy			
	ER+ and PgR+		ER+ and PgR- or unknown		No		Yes		Responsive		Not responsive	
	F500	F250	F500	F250	F500	F250	F500	F250	F500	F250	F500	F250
	N=241	N=266	N=121	N=108	N=123	N=142	N=239	N=232	N=229	N=249	N=133	N=125
Total number of events	199	226	98	95	93	109	204	212	190	209	107	112
Median (months)	7.0	5.5	6.5	5.4	11.1	6.5	5.2	4.1	7.0	6.6	5.8	2.9
Hazard Ratio (95% CI)	0.85(0.70-1.02)		0.69(0.52-0.92)		0.74(0.56-0.98)		0.82 (0.67-1.00)		0.85(0.70-1.04)		0.70(0.53-0.92)	

F500: fulvestrant 500 mg; F250: fulvestrant 250 mg; N: number of patients; ER: Oestrogen Receptors; PgR: Progesterone receptor

For the response to last endocrine therapy received prior to fulvestrant, patients were categorised as “responsive” if they had recurrence after 2 or more years on their last previous adjuvant endocrine therapy, or if they experienced CR, PR or SD for at least 24 weeks on first line endocrine therapy for advanced cancer. Patients were categorised as “not responsive” if they had recurrence after less than 2 years on their last previous adjuvant endocrine therapy, or if they experienced SD for less than 24 weeks or progressive disease (PD) on first line endocrine therapy for advanced breast cancer.

Table B19 Summary and analysis of time to progression for the measurable disease, age and last endocrine therapy co-variates: CONFIRM ITT population

	Measurable disease				**Age**				**Last endocrine therapy received**			
	No		**Yes**		**<65 years**		**≥65 years**		**AI**		**AO**	
	F500	**F250**	**F500**	**F250**	**F500**	**F250**	**F500**	**F250**	**F500**	**F250**	**F500**	**F250**
	N=122	**N=133**	**N=240**	**N=261**	**N=218**	**N=226**	**N=144**	**N=148**	**N=152**	**N=161**	**N=210**	**N=213**
Total number of events	**98**	**94**	**199**	**227**	**182**	**204**	**115**	**117**	**128**	**141**	**169**	**180**
Median (months)	**8.5**	**5.6**	**5.6**	**5.3**	**5.6**	**3.9**	**10.4**	**8.1**	**5.4**	**4.1**	**8.6**	**5.8**
Hazard Ratio (95% CI)	**0.74(0.56-0.99)**		**0.84(0.69-1.01)**		**0.77(0.63-0.95)**		**0.85(0.65-1.10)**		**0.85(0.67-1.08)**		**0.76(0.62-0.94)**	

AI: Aromatase inhibitor; AO: Anti-oestrogen

Results from FINDER I trial[21, 22]

Primary endpoint:

The primary endpoint was objective response rate (ORR) in an ITT population.

The ORRs with the different fulvestrant dose regimens were similar: 11.1% (95% CI 3.7–24.1), 17.6% (95% CI 8.4–30.9) and 10.6% (95% CI 3.5–23.1) for Fulvestrant 250 mg (AD), Fulvestrant Loading dose (LD) and Fulvestrant 500 mg (HD), respectively (see definitions of terms, p7 for further information on dosing regimens).

The ORR was numerically higher in the fulvestrant LD regimen, but the Confidence Intervals of all three treatment arms overlapped. The limited numbers of responders in each of the predefined subgroups meant that further subgroup analyses for efficacy parameters were not useful.

Table B20: Summary of best objective response

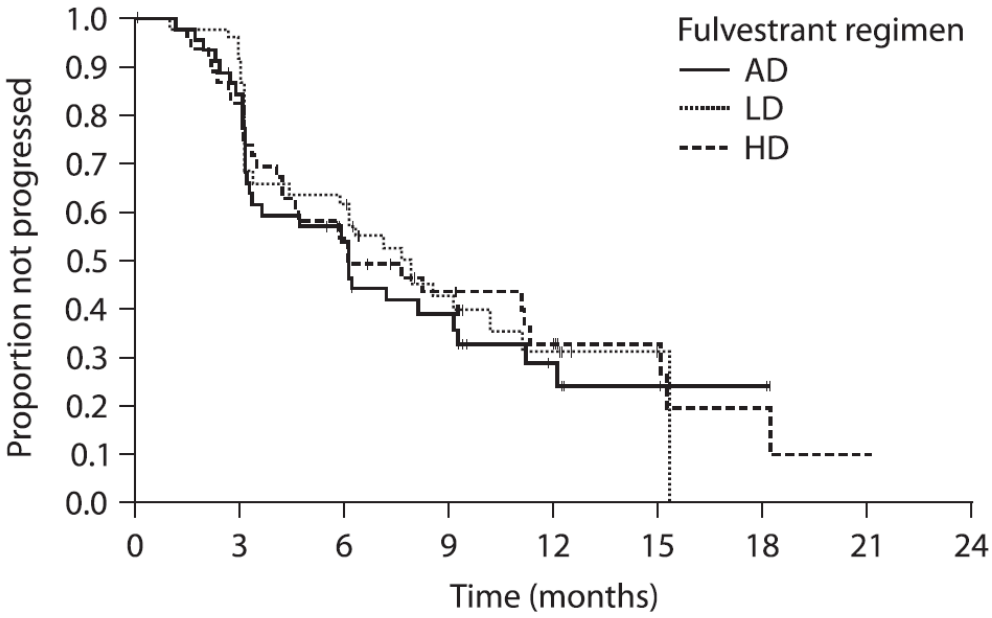
	Fulvestrant regimen		
	AD (n=45)	LD(n=51)	HD (n=47)
Complete response n (%)	2 (4.4)	0	0
Partial response n (%)	3 (6.7)	9 (17.6)	5 (10.6)
Stable disease ≥ 24 weeks, n (%)	14 (31.1)	19 (37.3)	17 (36.2)
Stable disease <24 weeks	9 (20.0)	5 (9.8)	10 (21.3)
Progression, n (%)	17 (37.8)	17 (33.3)	14 (29.8)
Not assessable, n (%)	0	1 (2.0)	1 (2.1)
Objective response rate, n (%) [95% CI]	5 (11.1) [3.7-24.1]	9 (17.6) [8.4-30.9]	5 (10.6) [3.5-23.1]
Clinical benefit rate, n (%) [95% CI]	19 (42.2) [27.7-57.8]	28 (54.9) [40.3 – 68.9]	22 (46.8) [32.1-61.9]

Secondary endpoints

- *Time to Progression (TTP)*

Median TTP was similar across the dose regimens: 6.0, 7.5 and 6.0 months for fulvestrant AD, LD and HD, respectively, with a similar number of events observed between groups: 30, 31 and 31 events respectively.

Figure 14: Kaplan-Meier plot of time to progression: ITT population



No. of patients at risk

Fulvestrant AD	45	36	22	13	6	2	2	0	0
Fulvestrant LD	51	42	29	16	7	3	0	0	0
Fulvestrant HD	47	36	24	15	8	5	2	1	0

- *Clinical benefit rate (CBR)*

CBRs were similar across the dose regimens: 42.2% (95% CI 27.7–57.8), 54.9% (95% CI 40.3–68.9) and 46.8% (95% CI 32.1–61.9) for fulvestrant AD, LD and HD, respectively.

Tolerability

A total of 765 AEs were reported by 137 (96.5%) of the 142 patients, including 8 patients (5.6%) who experienced a serious adverse event (SAE). AEs observed in ≥10% of patients were nasopharyngitis (33.8%), injection-site pain (27.5%), hot flushes (18.3%), nausea (18.3%), injection-site induration (17.6%), fatigue (14.8%), constipation (11.3%) and headache (10.6%). Notably, all injection-site AEs were ≤grade 2 intensity, with the majority grade 1, and there were no dose-dependent differences in frequency or intensity between the treatment arms. The incidence of AEs was similar among the three treatment arms.

Results from FINDER II trial[23, 24]

Primary endpoint:

The primary endpoint is objective response rates (ORR) in ITT population.

Comparison of data across the three treatment arms (similar to the treatment arms in FINDER II shows that fulvestrant 250 mg (AD), fulvestrant loading dose (LD) and fulvestrant 500 mg (HD) had similar efficacy.

The point estimate for ORR in the fulvestrant 500 mg regimen (15.2% [95% CI: 6.3%, 28.9%]) was numerically higher than in the other 2 dose regimens (8.5% [95% CI: 2.4% to 20.4%] in the fulvestrant 250 mg regimen; 5.9% [95% CI: 1.2% to 16.2%] in the fulvestrant 250 mg +LD regimen), although the CIs of all 3 treatment arms overlapped.

Table B21: Summary of best objective response (ITT population)

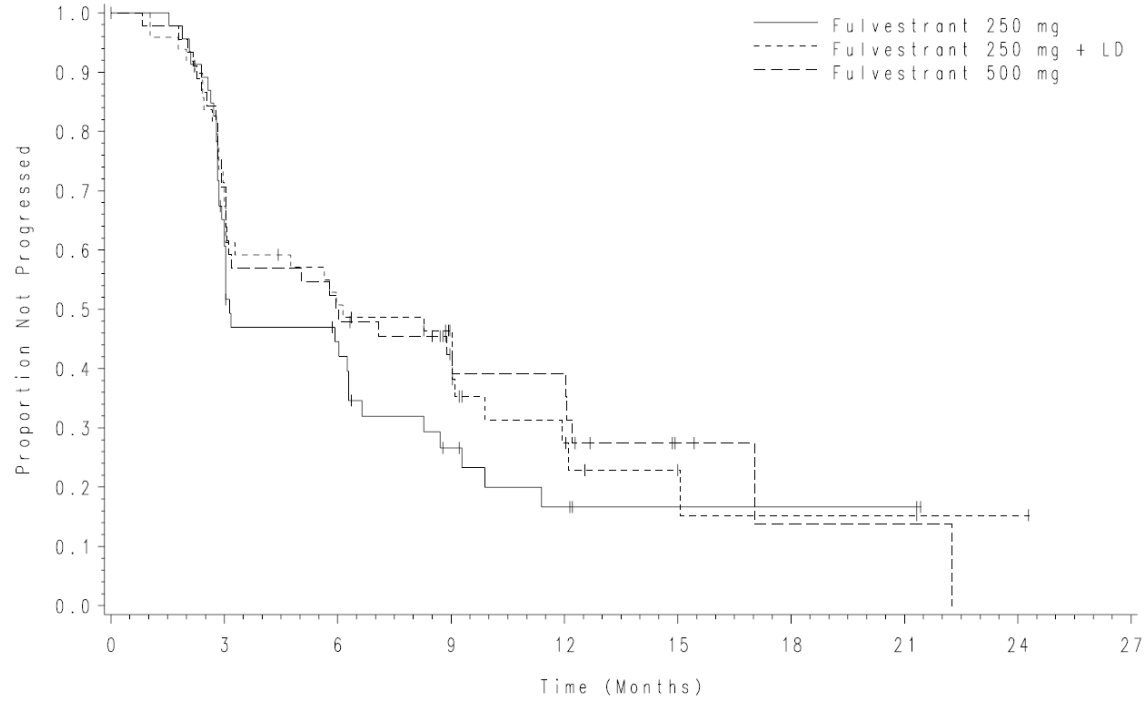
	Fulvestrant regimen		
	AD (n=47)	LD(n=51)	HD (n=46)
Complete response n (%)	0	0	0
Partial response n (%)	4 (8.5)	3 (5.9)	7 (15.2)
Stable disease ≥ 24 weeks, n (%)	11 (23.4)	21 (41.2)	15 (32.6)
Stable disease <24 weeks	7 (14.9)	5 (9.8)	3 (6.5)
Progression, n (%)	24 (51.1)	20 (39.2)	19 (41.3)
Not assessable, n (%)	1 (2.1)	2 (3.9)	2 (4.3)
Objective response rate, n (%) [95% CI]	4 (8.5) [2.4-20.4]	3 (5.9) [1.2-16.2]	7 (15.2) [6.3-28.9]
Clinical benefit rate, n (%) [95% CI]	15 (31.9) [19.1-47.1]	24 (47.1) [32.9-61.5]	22 (47.8) [32.9-63.1]

Secondary endpoint:

- *Time to progression (TTP)*

The medians for TTP in the fulvestrant 500 mg and fulvestrant 250 mg +LD treatment arms (6.0 months and 6.1 months, respectively) were numerically longer than the median TTP of the fulvestrant 250 mg treatment arm (3.1 months); however, the percentage of progression events was similar between the 3 treatment arms (67.4%, 66.7% and 74.5%, respectively).

Figure 15: Kaplan-Meier plot of TTP: ITT population



Number Of Patients At Risk:

Months	0	3	6	9	12	15	18	21	24	27
Fulvestrant 250 mg	47	29	18	9	5	2	2	2	0	0
Fulvestrant 250 mg + LD	51	35	24	17	7	4	2	2	1	0
Fulvestrant 500 mg	46	31	22	13	10	3	1	1	0	0

Tick marks indicate censored observations

- *Clinical Benefit Rates (CBR)*

The CBRs were similar across the 3 treatment arms. The point estimates for CBR in the fulvestrant 500 mg and 250 mg +LD regimen (47.8% [95% CI: 32.9%, 63.1%]; and 47.1% [95% CI: 32.9%, 61.5%], respectively) were numerically higher than the 250 mg regimen (31.9% [95% CI: 19.1%, 47.1%]), although the CIs of all 3 treatment arms overlapped.

Tolerability

The safety results of this study showed that all 3 fulvestrant dose regimens were well tolerated. There were no clear differences between the safety profiles of the 3 dose regimens. The most frequently reported AEs in this study were back pain, arthralgia, fatigue, injection site pain, nausea, dyspnoea, cough and hot flush. Overall the AEs observed in this study were consistent with the known safety profile of fulvestrant and there were no safety concerns emerging from this study.

5.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

5.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

Not applicable.

5.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

A simple meta-analysis was not considered appropriate. The reason for this was that the only comparator available if this method was to be adopted would have been fulvestrant 250 mg. Although fulvestrant 250 mg is one of the comparators identified in the scope, it was decided that a more comprehensive picture with additional comparators would be obtained if a network-meta analysis was conducted in place of a meta-analysis. A network meta-analysis is also known as a mixed treatment comparison, but it has been referred to as a network meta-analysis within the submission.

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

5.7 Indirect and mixed treatment comparisons

5.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details

of the search strategy used should be provided in section 9.4, appendix 4.

Search strategy is outlined in Appendix 4.

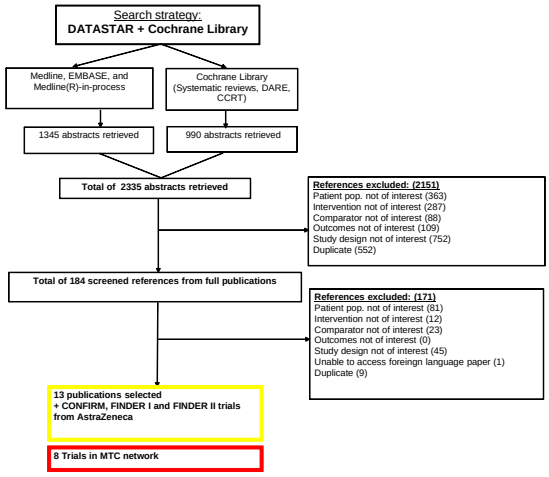
5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Table B22: Eligibility criteria used in search strategy for indirect comparison

	Clinical effectiveness
Inclusion criteria	Population – post menopausal women with locally advanced or metastatic breast cancer who had previously received anti-oestrogen treatment either for early or advanced breast cancer, documented ER+ receptor status of 70% or more Interventions – fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate Outcomes – overall survival, progression free survival, time to progression, tumour response, response rate, adverse events, health related quality of life Study design – RCTs Language restrictions - none
Exclusion criteria	Population – men, pre-menopausal women, sample populations where all participants had one or more visceral lesions, patients who had not previously received anti-oestrogen therapy Interventions – trials that did have at least one arm with the comparator of interested as identified at the scoping workshop (fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, megestrol acetate, exemestane, letrozole, medroxyprogesterone acetate) Outcomes Study design – anything study design other than a phase II or III RCT Language restrictions – none, other than the fact that results had to be presented in a format that was understandable without translating article for example, results presented in an English abstract or tabulated with standard abbreviations e.g. TTP = time to progression

5.7.2.1 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 5.2.4.

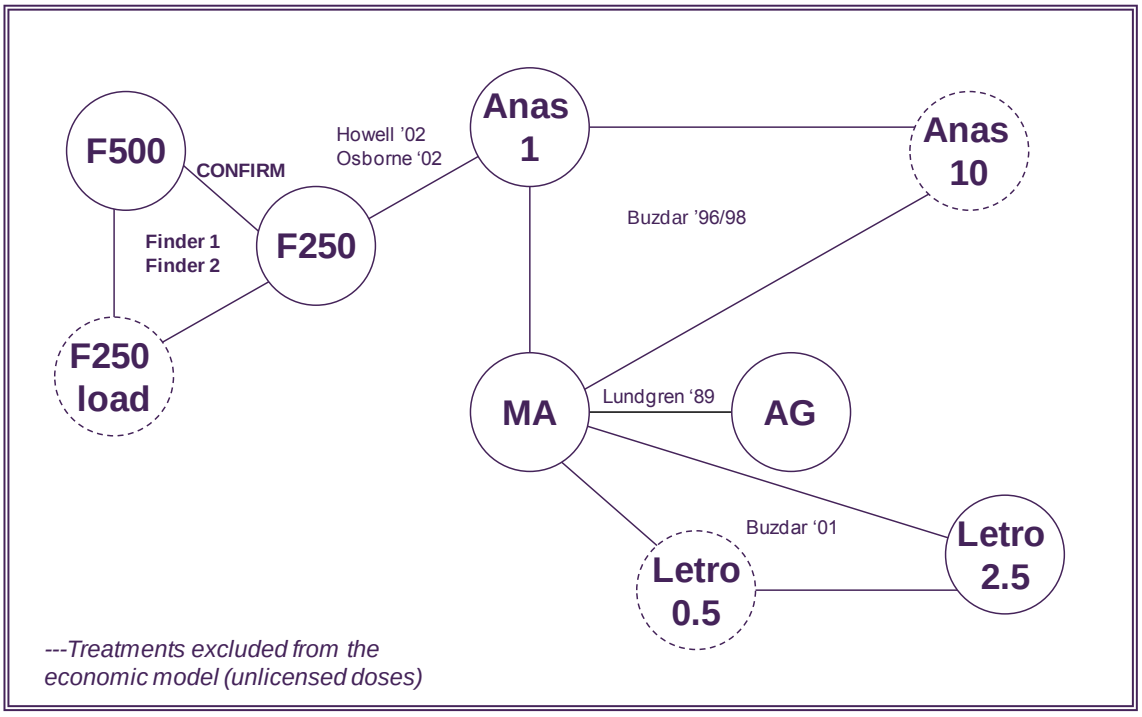
Figure 16A: QUOROM flow diagram of excluded and included fulvestrant studies



Once the search had been conducted, other issues were encountered. CONFIRM, FINDER I and FINDER II were the only trials identified that had the entire sample documented as ER+. It was decided that some flexibility was required concerning ER+ status as due to practical reasons it was necessary to have a comparator, other than fulvestrant 250 mg, for use in the submission. Key Opinion Leaders and clinicians were consulted on this issue and no firm criteria with a solid rationale based on evidence could be decided on. A number of issues were discussed

including: only including trials from recent years (it was decided that as the understanding of the role of ER status in outcomes developed over time it was not possible to identify a date that was not completely randomly chosen), excluding trials that had a certain percentage of documented ER- status patients. As no evidence based rationale could be found for an alternative criteria together with the fact that ER status is definitely a variable that effects outcomes the inclusion criteria would be relaxed to 'at least 70% of the sample with a documented ER+ receptor status' and reassessed if substantial heterogeneity was detected.

Figure 16B: Resulting network.



F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Anas 10=Anastrazole 10mg; Letro 0.5=Letrozole 0.5mg; Letrozole 2.5=Letrozole 2.5mg; AG=Aminoglutethimide 250mg

As a result of the exclusion criterion related to the ER+ status, the following studies were excluded from the base-case analysis:

- Dombernowsky 1998[25]
- Gershanovich 1998[26]
- Kaufmann 2000[10]
- Rose 2003.[27]

5.7.2.2 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Table B23: Primary data sources and supporting papers for studies included in indirect comparison

Trial no (acronym)	Primary data source	Supporting papers
Buzdar 1996/1998	Buzdar_1998[28]	Buzdar 1996 [29]
		Jonat_1996[30]
		Buzdar_1997 (Cancer)[31]
		Buzdar_1997 (J Steroid Biochem Molec Biol)[32]
Howell_2002	Howell_2002[8]	Robertson_2003[33]
		Mauriac_2003 [34]
		Howell_2005 [16]
Osborne_2002	Osborne_2002[9]	Robertson_2003[33]
		Mauriac_2003 [34]
		Howell_2005 [16]
Ludgren_1989	Ludgren_1989[35]	No others
Buzdar_2001	Buzdar_2001[36]	No others

Complete list of relevant RCTs

5.7.2.3 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Table B24: List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Buzdar 1996/1998[28]	Anastrozole 1 mg once daily Anastrozole 10mg once daily	Megestrol acetate 40mg four times daily	To enter the trials, patients were required to have: - progressed while receiving tamoxifen or other anti-oestrogen therapy for ABC or relapsed during or after receiving adjuvant tamoxifen treatment be postmenopausal - post menopausal - have a World Health Organization (WHO) performance status score 2.	Cancer, 1998, 83 (6), 1142-52.
Trial 20 Howell_2002[8]	Fulvestrant (250 mg once monthly intramuscular injection: Trial 20 – 1x5m)	Anastrozole (1 mg as a once-daily oral treatment)	• Postmenopausal women • Locally advanced or metastatic breast cancer with • Objective evidence of disease recurrence or progression on adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease • Histological or cytological proof of breast cancer, • Presence of at least one measurable or evaluable lesion, tumours with evidence of hormone sensitivity (i.e. prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity) • Life expectancy of >3 months • World Health Organization (WHO) performance status of ≤ 2 • No prior fulvestrant or aromatase inhibitor therapy.	Eur J Cancer, 2003, 39: 1228-33 and Clinical Study Report
Trial 21 Osborne_2002[9]	Fulvestrant Initially, patients were given fulvestrant 125 mg (2.5 ml) im monthly plus anastrozole placebo orally daily; fulvestrant 250 mg (2x2.5 ml) im monthly plus anastrozole placebo orally daily; or anastrozole 1 mg orally daily plus fulvestrant placebo 2.5 ml im monthly or fulvestrant placebo 2x2.5 ml im monthly. Patients	Anastrozole (1 mg as a once-daily oral treatment)	• Postmenopausal women • Locally advanced or metastatic breast cancer with • Objective evidence of disease recurrence or progression on adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease • Histological or cytological	J Clin Oncol, 2002; 20 (16):3386-95 and Clinical Study Report

	randomized to treatment after the 125-mg treatment group was discontinued were given either the fulvestrant 250-mg regimen or the anastrozole regimen as described.		proof of breast cancer, • Presence of at least one measurable or evaluable lesion, tumours with evidence of hormone sensitivity (i.e. prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity) • Life expectancy of >3 months • World Health Organization (WHO) performance status of ≤ 2 • No prior fulvestrant or aromatase inhibitor therapy.	
Lundgren_1989[35]	Megestrol acetate (160mg od)	Aminoglutethimide (treatment schedule for first 2 weeks was 250m b.i.d. and cortisone acetate 50mg b.i.d. thereafter it was 250 mg AG q.i.d and cortisone acetate b.i.d.)	Women with ABC who had been previously treated with tamoxifen either in the advanced or adjuvant setting	Breast Cancer Res Treat, 1989; 14: 201-6.
Buzdar_2001[36]	Letrozole (0.5mg and 2.5 mg everyday)	Megestrol acetate (40mg qid)	Postmenopausal women Histologically or cytologically confirmed breast cancer who presented with either locally advanced or locoregionally recurrent disease or had metastatic disease Tumors were required to be either oestrogen receptor (ER) and/or progesterone receptor (PgR) positive. Unknown status of ER and PgR was acceptable for study entry if no assay had been conducted Patients had either relapsed while receiving continuous adjuvant anti-oestrogen therapy (e.g., tamoxifen) or had relapsed within 12 months of stopping adjuvant anti-oestrogen therapy that had been administered for at least 6 months. Patients were also eligible if they progressed while receiving first-line anti-oestrogen therapy for advanced disease.	J Clin Oncol, 2001; 19: 3357-66

Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

None. Therefore, an indirect comparison will be conducted.

5.7.2.4 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

Not applicable.

List of relevant non-RCTs

5.7.2.5 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 5.8 and key details should be presented in a table; the following is a suggested format.

None.

5.7.2.6 Summary of methodology of relevant RCTs

Methods

5.7.2.7 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

Table B25 Comparative summary of methodology of the RCTs

Study ID	Location	Design	Duration of study	Method of randomisation	Method of blinding	Intervention(s)	Primary outcomes	Secondary outcomes	Duration of follow-up
Buzdar 1996/1998	Two trials, one in North America (49 centres), the other in Europe, Australia and South Africa (73 centres)	The two trials were randomized, double-blind for anastrozole, open-label for megestrol acetate, parallel-group, and multi-center studies.	Median follow up approximately 6 months	Randomization scheme was stratified for center in each trial. In addition, treatments were allocated in blocks of size three in the North American trial and six in the European trial, such that treatment groups were balanced after every three or six patients at each center.	Double blind for anastrozole, open label for megestrol acetate Anastrozole was supplied as film-coated, white tablets that contained either 1 or 10 mg of drug. Megestrol acetate was supplied as white, circular, scored tablets that contained 40 mg of drug.	Anastrozole and megestrol acetate	Time to disease progression, tumor response, and tolerability.	Time to treatment failure, response duration, and survival.	Median follow up approximately 6 months
Trial 20 Howell_2002	Trial 0020 – Europe, Australia and South Africa	Trial 20 was an open-label, multicentre, randomised, parallel group study	Patients were recruited between May 1997 and September 1999	Trial 20 - The treatment given to individual patients was determined for each centre by a randomization schedule prepared by the Biostatistics Group, AstraZeneca. The randomisation schedule and associated code breaks were produced by computer software that incorporates a standard procedure for generating random numbers. A separate randomisation schedule was produced for each centre, but all the schemes were held and administered by a central randomisation centre at Covance	Trial 20 – open label	Fulvestrant Anastrozole	Time to disease progression.	Objective response rate Time to treatment Failure Time to death, Duration of response, Symptomatic response Quality of life.	All patients were followed up for progression and thereafter until death (unless the patient refused).

Study ID	Location	Design	Duration of study	Method of randomisation	Method of blinding	Intervention(s)	Primary outcomes	Secondary outcomes	Duration of follow-up
Trial 21 Osborne_2002	Trial 21 – North America	Trial 21 was a double-blind, double-dummy, multicentre, randomised, parallel group study	Patients were recruited between May 1997 and September 1999	Trial 21 - randomization schedule and associated code breaks were produced by computer software that incorporated a standard procedure for generating random numbers. A separate randomization schedule was produced for each center. Patients were allocated to treatment in balanced blocks by MEDEX Clinical Trial Services Incorporated	Fulvestrant administered with anastrozole placebo (identical in presentation and administration to anastrozole), and anastrozole was administered with fulvestrant placebo (identical in presentation and administration to fulvestrant). Treatment remained blinded to all conducting the trial (i.e., patients, investigators, AstraZeneca personnel) except for one statistician	Fulvestrant Anastrozole	Time to disease progression.	Objective response rate Time to treatment Failure Time to death, Duration of response, Symptomatic response Quality of life.	All patients were followed up for progression and thereafter until death (unless the patient refused).
Lundgren_1989	Norway	Prospective randomised study without stratification	Not stated	Not stated	Not stated	Megestrol acetate (MA) Aminoglutethimide (AG)	Objective response rate	Number and duration of stable diseases Disease progression Tolerability	Not stated
Buzdar_2001	120 centres throughout the US, Canada and Europe (7 countries in total)	Randomised, double-blind, parallel-group, multicentre, international, comparative phase II trial	Enrolment occurred over a 30 month period	Randomisation was performed for each country without stratification by centre.	Double blind – patients received either one tablet letrozole 0.5mg or letrozole 2.5 mg once daily in the morning and one placebo capsule (matching a MA tablet) qid, or one 40mg capsule MA plus one placebo tablet (matching a letrozole tablet) once daily	Letrozole 0.5mg Letrozole 2.5 mg MA 160mg	Objective response rate	Duration of response Duration of clinical benefit TTF TTP Time to death HRQL Tolerability	On discontinuation from the study patients were followed until death or until lost to follow up for a period of 60 months from their first study visit

Participants

5.7.2.8 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Table B26 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Buzdar 1996/1998	- patients were required to have progressed while receiving tamoxifen or other anti-oestrogen therapy for ABC or relapsed during or after receiving adjuvant tamoxifen treatment - be postmenopausal, defined as having nonfunctioning ovaries through natural menopause or surgical, radiation, or chemical castration (women > 50 years of age who did not menstruate during the preceding 12 months were considered postmenopausal, whereas women < 50 years of age had to have a follicle-stimulating hormone concentration > 40 IU/L to enter - have a World Health Organization (WHO) performance status score 2.	- oestrogen receptor-negative breast cancer (except when the patient had shown a previous response to tamoxifen treatment) - exposure to more than one previous course of cytotoxic therapy for advanced disease (except adjuvant chemotherapy) - exposure to more than one previous hormonal therapy for ABC - any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results
Trial 20 Howell	• Postmenopausal women • Locally advanced or metastatic breast cancer with • Objective evidence of disease recurrence or progression on adjuvant endocrine therapy or following first-line endocrine therapy for advanced disease • Histological or cytological proof of breast cancer, • Presence of at least one measurable or evaluable lesion, tumours with evidence of hormone sensitivity (i.e. prior sensitivity to hormonal therapy or known ER or progesterone receptor positivity) • Life expectancy of >3 months • World Health Organization (WHO) performance status of ≤ 2 • No prior fulvestrant or aromatase inhibitor therapy.	• Life-threatening metastatic visceral disease (defined as extensive hepatic involvement) • Symptomatic pulmonary lymphangitic spread (patients with discrete pulmonary parenchymal metastases were eligible for inclusion, provided their respiratory function was not compromised as a result of the disease.)
Trial 21 Osborne_2002	• histologic or cytologic confirmation of breast cancer; • objective evidence of recurrence or progression of disease not considered amenable to curative treatment - locally advanced disease was included if considered not amenable to curative therapy; • postmenopausal, defined as any of the following: (i) aged 60 years or older,	• presence of life-threatening metastatic visceral disease (defined as extensive hepatic involvement) or any degree of brain or leptomeningeal involvement (past or present) or symptomatic pulmonary lymphangitic spread (Patients with discrete pulmonary parenchymal metastases were eligible provided their respiratory function was not compromised as a

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	(ii) aged 45 years or older with amenorrhea for longer than 12 months and an intact uterus, (iii) follicle-stimulating hormone (FSH) levels within the postmenopausal range (defined by the testing laboratory), or (iv) patient had a bilateral oophorectomy; • no more than 1 prior hormonal therapy for breast cancer with second-line hormonal treatment required because patient had a relapse after adjuvant endocrine therapy with an anti-oestrogen or a progesterone, or the patient's disease progressed after treatment with either an anti-oestrogen or progesterone as first-line treatment for advanced disease; • evidence of hormone sensitivity, defined as (i) at least 12 months of adjuvant hormonal treatment before relapse, or (ii) tumor remission or stabilization resulting from hormonal therapy for at least 3 months before progression in advanced disease, or (iii) oestrogen-receptor-positive (ER+) or progesterone receptor-positive (PgR+) status; • presence of at least 1 measurable or evaluable (nonmeasurable) lesion; (7) World Health Organization (WHO) performance status of 0, 1, or 2 (Ref WHO 1979); • life expectancy longer than 3 months	result of disease.); • previous treatment with fulvestrant or aromatase inhibitors; 2 or more regimens of endocrine therapy for advanced disease (excluding oophorectomy, ovarian radiation, or luteinizing hormone-releasing hormone [LH-RH] analogue therapy), radiation, or chemotherapy within 4 to 6 weeks of baseline tumor assessment; or oestrogen replacement therapy or investigational drug therapy within 4 weeks of randomization; • previous or current systemic malignancy within 3 years (other than breast cancer or adequately treated in-situ carcinoma of the cervix uteri or basal or squamous cell carcinoma of the skin); • evidence of severe or uncontrolled systemic disease

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Lundgren_1989	• Progressive ABC • <75 years • Karnofsky index >50 • Previously treatment with tamoxifen either in the advanced or adjuvant setting	• Single osteoblastic bone metasasis • CNS manifestations only • Life expectancy of less than 2 months • Rapid progression on tamoxifen
Buzdar_2001	• Postmenopausal women (women ≥ 50 years of age who had not menstruated during the preceding 12 months or had castrate follicle-stimulating hormone levels (. 40 IU/L), women less than 50 years of age who had castrate follicle-stimulating hormone) • levels, or women who had undergone a bilateral oophorectomy • histologically or cytologically confirmed breast cancer who presented with either locally advanced or locoregionally recurrent disease or had metastatic disease • tumors were required to be either oestrogen receptor (ER) and/or progesterone receptor (PgR) positive. Unknown status of ER and PgR was acceptable for study entry if no assay had been conducted • either relapsed while receiving continuous adjuvant anti-oestrogen therapy (e.g., tamoxifen) or had relapsed within 12 months of stopping adjuvant anti-oestrogen therapy that had been administered for at least 6 months. Patients were also eligible if they progressed while receiving first-line anti-oestrogen therapy for advanced disease • at the start of the study, patients were required to have the bulk (> 50%) of their tumor burden measurable and/or assessable. This criterion was found to unduly restrict patient enrollment, so inclusion criteria were amended to require patients to have at least one measurable and/or assessable tumor lesion • discontinued any systemic anticancer treatment at the time of study entry. Any radiation therapy was completed at least 14 days before study entry. • estimated to have, in the opinion of the investigator, a life expectancy of at least 6 months • Karnofsky performance status score of ≥ 50% • all laboratory results were required to be within the limits defined by the study protocol, which included creatinine less than 1.5 times the upper limit of normal (ULN), total bilirubin less than 1.5 times ULN, transaminases less than 2.6 times ULN, WBC count ≥ 3,000/mm3, granulocyte count ≥ 1,500/mm3, hemoglobin ≥ 8.5 g/dL, platelet count ≥ 75,000/mm3, and total calcium less than 11.6 mg/dL.	• existence of malignancies at other sites ≤ 5 years before study entry or concurrent with study participation, with the exception of cone-biopsied in situ carcinoma of the cervix or uterus and adequately treated basal and squamous cell carcinoma of the skin • inflammatory breast cancer • extensive hepatic metastases, defined as more than 33% of the liver replaced by metastases noted on sonogram and/or computed tomography scan • metastases to the CNS • pulmonary lymphangitic metastases involving more than 50% of the lung • history of deep venous thrombosis or pulmonary embolism within 3 years unless the thrombosis was known to be directly related to tumor obstruction of circulation • severe uncontrolled cardiac disease (e.g., congestive heart failure of the New York Heart Association ≥ Class III) • crescendo angina • myocardial infarction within 6 months before study entry • uncontrolled diabetes mellitus.

5.7.2.9 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Table B27 Characteristics of participants in the RCTs across randomised groups

	Fulvestrant 250 mg	Anastrozole 1 mg	Anastrozole 10mg	Megestrol Acetate	AG	MA 160mg od	Letrozole 0.5mg	Letrozole 2.5 mg
Buzdar 1996/1998		**(n = 263)**	**(n = 248)**	**(n = 253)**				
Age, mean (range)		65 (29-97)	66 (41-91)	65 (39-90)				
Ethnicity - Caucasian - Oriental - Other		Not provided	Not provided	Not provided				
WHO Performance status score0 • 0 • 1 • 2 • 3 • 4		 138 91 34 0 0	 109 101 34 4 0	 116 103 32 1 1				
Previous treatment • surgery • cytotoxic chemo • radiotherapy		 346 98 153	 230 92 146	 237 89 156				
Receptor status - ER+, PR+ - ER+, PR- - ER+, PR unknown - ER-, PR+ - ER-, PR- - Unknown		 134 45 14 4 4 62	 115 34 17 4 12 66	 119 34 20 5 11 64				
Trial 20 Howell	**(n =222)**	**(n =229)**						
Age, median (range)	64 (35-86)	65 (33-89)						
Weight, median (range)	67 (41-124)	67 (40-110)						
Race • white • black • Hispanic • Asian • Other • Not given	 214 0 0 1 2 5	 218 0 1 2 2 6						
Previous treatment • surgery	 204	 200						

	Fulvestrant 250 mg	Anastrozole 1 mg	Anastrozole 10mg	Megestrol Acetate	AG	MA 160mg od	Letrozole 0.5mg	Letrozole 2.5 mg
• cytotoxic chemo • radiotherapy • anti-oestrogen	94 168 216	98 162 225						
Receptor status - ER+; PgR+ - ER+; PgR- - ER+; PgR unknown - ER-; PgR+ - ER-; PgR- - ER-; PgR unknown - ER unknown; PgR unknown	 86 35 35 7 6 2 51	 95 43 35 10 7 2 37						
Performance status - 0 - 1 - 2 - 3	 104 93 25 0	 104 98 27 0						
Disease site - breast - skin - bone - liver - lung - lymph nodes - other	 21 40 115 48 56 78 27	 30 35 117 56 60 83 18						
Trial 21 Osborne_2002	**(n =206)**	**(n =194)**						
Age, mean (range)	63 (33-89)	62 (36-94)						
Weight, mean (range)	72 (37-127)	73 (43-134)						
Previous treatment • cytotoxic chemo • endocrine for advanced disease • adjuvant endocrine	 129 110 122	 122 97 116						
Receptor status - ER+ - ER- - ER Unknown	 170 23 13	 156 22 16						
Performance status - 0	 90	 84						

	Fulvestrant 250 mg	Anastrozole 1 mg	Anastrozole 10mg	Megestrol Acetate	AG	MA 160mg od	Letrozole 0.5mg	Letrozole 2.5 mg
- 1 - 2 - missing	94 21 1	95 15 0						
Extent of metastatic or recurrent disease - soft tissue only - bone only - visceral only - lymph node only - not recorded - mixed	12 47 39 15 1 92	13 43 45 17 2 74						
Lundgren_1989					**(n =76)**	**(n =74)**		
Age, mean (range)					62.0	62.7		
Menopausal status - premenopausal - postmenopausal					3 73	2 72		
Previous treatment					14	11		
Receptor status - ER+ - ER Unknown					50 26	57 17		
Main metastatic localisation - soft tissue only - bone only - visceral only					33 11 32	33 23 18		
Buzdar_2001						**(n=201)**	**(n =202)**	**(n =199)**
Age, median						65.9	66.5	65.5
Weight, mean (range)							Not supplied	
Stage of disease at diagnosis - I/ II - III - IV						7 11 183	6 11 185	7 11 181
Previous treatment • cytotoxic chemo • endocrine for advanced disease • adjuvant endocrine						86 49 62	72 119 99	82 87 129

	Fulvestrant 250 mg	Anastrozole 1 mg	Anastrozole 10mg	Megestrol Acetate	AG	MA 160mg od	Letrozole 0.5mg	Letrozole 2.5 mg
Receptor status - ER+ - ER- - ER Unknown						 161 0 40	 168 3 31	 160 0 39
Dominant site - soft tissue - bone - visceral						 51 53 97	 44 57 101	 36 68 95
Number of prior endocrine therapies • none (adjuvant only) • 1 • >1						 78 120 3	 83 116 3	 70 126 3

Outcomes

5.7.2.10 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

Table B28 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Buzdar 1996/1998	Assessments of tumour response included the evaluation of both measurable and non-measurable disease. Measurable disease was defined as the presence of metastatic lesions measurable in one or two dimensions using physical or radiographic methods (including computed tomography scan) and osteolytic bone lesions. Nonmeasurable disease was defined as single metastatic lesions smaller than 0.5 cm, malignant pleural effusion or ascites, positive bone scan, and osteoblastic bone lesions The best objective response over	For measurable lesions, only physical or radiologic measurements were recorded. To ensure consistency and objectivity in the assignment of response categories, a computerized algorithm was used to assign responses based on the measurements. The program strictly applied the protocol definition of response based on Union Internationale Cont. For non-measurable lesions, partial responses were not permitted to be assigned, in accordance with the strict criteria for assessment. Therefore, responses were assigned only in the categories of complete response, stable disease, or progressive disease.re le Cancer (UICC) criteria.' °	Time to treatment failure was the time to earliest occurrence of progression, death, or withdrawal. Time to death represented the number of days until death from any cause. Duration of response, which was recorded for those with either a complete or partial response, was the time to objective progression or death.	

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
	time was determined on the basis of objective responses at each visit. Complete or partial responses were assigned only when noted on successive visits at least 4 weeks apart. Measurable lesions of bone, chest, and abdomen were assessed at 12-week intervals. A best response of stable disease was assigned when responses of stable disease or better were observed for at least 24 weeks. If such responses had been observed for less than 24 weeks because a patient did not have measurements for 24 weeks at the time of data cut-off, then a best response of stable disease for less than 24 weeks was recorded. Time to progression, time to treatment failure, time to death, and duration of response were calculated from the date of randomization. Time to progression represented the time to objective disease progression or death, whichever occurred first. Patients who had not reached progression at the time of data cut-off were right-censored in the analysis at the time of their latest visit.			
Trial 20 Howell_2002	TTP. TTP was defined as the time from randomization until objective disease progression. Death was regarded as a progression event in those who died before disease progression. Subjects whose disease had not progressed at the time of analysis were right-censored using the last assessment date.	Treatments were compared using the Cox proportional hazards regression model (including the covariates age, performance status, measurable compared with non-measurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease). A global test was performed to determine whether there were significant treatment-by-baseline covariate interactions. The estimate of	TTF. TTF was defined as the number of days from randomization until the earliest occurrence of disease progression, death from any cause, or withdrawal from trial treatment for any reason. Patients whose treatment had not failed at the time of analysis were right censored in the analysis at the time of their last assessment. Any patient who did not receive any trial therapy	Statistically, TTF was analyzed in the same way as TTP.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
		the treatment effect is expressed as an HR (fulvestrant/anastrozole), together with the corresponding CI and *P* value. TTP was also summarized using Kaplan-Meier curves for each treatment group, and the median TTP was calculated.	was assigned an uncensored TTF of zero days. OR rate. Responders were defined as those patients with a CR or PR. To qualify as a responder, the patient had to satisfy the criteria for CR or PR on one visit with no evidence of disease recurrence or death within 4 weeks after assessment. DOR. The DOR was defined for responding patients only as the period of time from randomization to the first observation of disease progression. Clinical benefit. Clinical benefit was defined as the sum of CR + PR + SD ≥ 24 weeks. TTD.	 Treatment differences in OR was assessed by comparing the proportion of responders using a logistic regression model (with the same covariates as for TTP). The estimate of the treatment effect is expressed as an odds ratio (fulvestrant/ anastrozole), together with the corresponding CI and P value. In addition, an estimate of the difference in response rates (fulvestrant/ anastrozole) and corresponding CI was also produced. The DOR was summarized using Kaplan-Meier curves for each treatment group, and the median DOR was also calculated for each group. Patients who died before reaching progression were classified as completing their response at time of death. No statistical comparison was performed for DOR in only those patients responding to treatment, because this is not a randomized comparison. Rather, all patients were included in a statistical analysis of DOR, defined for responders as the time from onset of response to disease progression and for non-responders as zero. These data were also summarized using Kaplan Meier curves. As specified in the protocol, TTD (overall survival) will be analyzed when more than 50% of the patients have died. At the time of this data analysis, only 34.5% of patients had died; therefore, no formal statistical analyses were conducted.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Trial 21 Osborne_2002	TTP. TTP was defined as the time from randomization until objective disease progression or death from any cause before progression. Subjects who had not progressed at the time of analysis were right-censored using the last assessment date.	Treatments were compared using Cox's proportional hazards regression model (including the covariates age, performance status, measurable compared with non-measurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease). A global test was performed to determine whether there were significant treatment-by-baseline covariate interactions. The estimate of the treatment effect was expressed as an HR (fulvestrant/anastrozole), together with the corresponding CI and P value. TTP was also summarized using Kaplan-Meier curves for each treatment group, and the median TTP was calculated.	TTF. TTF was defined as the number of days from randomization until the earliest occurrence of disease progression, death from any cause, or withdrawal from trial treatment for any reason. Patients whose treatment had not failed at the time of analysis were right censored in the analysis at the time of their last assessment. Any patient who did not receive any trial therapy was assigned an uncensored TTF of zero days. OR rate. Responders were defined as those patients with a CR or PR. To qualify as a responder, the patient had to satisfy the criteria for CR or PR on one visit with no evidence of disease recurrence or death within 4 weeks after assessment. DOR. The DOR was defined for responding patients only as the period of time from randomization to the first observation of disease progression. Clinical benefit. Clinical benefit was defined as the sum of CR + PR+ SD ≥ 24 weeks.	Statistically, TTF was analyzed in the same way as TTP. Treatment differences in OR was assessed by comparing the proportion of responders using a logistic regression model (with the same covariates as for TTP). The estimate of the treatment effect is expressed as an odds ratio (fulvestrant/ anastrozole), together with the corresponding CI and P value. In addition, an estimate of the difference in response rates (fulvestrant/ anastrozole) and corresponding CI was also produced. The DOR was summarized using Kaplan-Meier curves for each treatment group, and the median DOR was also calculated for each group. Patients who died before reaching progression were classified as completing their response at time of death. No statistical comparison was performed for DOR in only those patients responding to treatment, because this is not a randomized comparison. Rather, all patients were included in a statistical analysis of DOR, defined for responders as the time from onset of response to disease progression and for non-responders as zero.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			TTD.	As specified in the protocol, TTD (overall survival) will be analyzed when more than 50% of the patients have died. At the time of this data analysis, only 34.5% of patients had died; therefore, no formal statistical analyses were conducted.

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Lundgren_1989	Objective response rate		Response duration Number and duration of stable diseases Tolerability	
Buzdar_2001	Objective response rate	Tumour response was evaluated by the investigator at the site according to International Union Against Cancer criteria specified by the protocol and by a designated central radiologist at each site who remained blinded. Measurable disease, whether bi- or unidimensional, was assessed either by palpation or on radiologic assessment (x-ray, abdominal ultrasound, or computed tomography scan). Non-measurable, assessable tumours were not measurable by ruler or calliper but were assessed and evaluated by physical or radiologic evaluation. Response or increasing disease could only be estimated. Methodology for tumour assessment was to remain consistent throughout the course of the study. Full tumour evaluation, including the above procedures, was performed at baseline and at months 6 and 9. All evaluations of objective tumour response (CR or PR) required Confirmation after at least 4 weeks.	Duration of response Duration of clinical benefit TTP	Duration of response was defined as the time from the date of randomization to the earliest date of documented disease progression or death from cancer or unknown cause. The time was censored at the cut off date for analysis for patients still in response. Duration of clinical benefit was calculated only for those patients who had a confirmed objective tumour response or stable disease for >= 6 months. In these patients, duration of clinical benefit was calculated in the same manner as duration of response. TTP was defined as the time from randomization to the earliest date of disease progression, cancer-related death, or death from an unknown cause during therapy, or the time was censored at the cut off date for analysis for patients without progressive disease. All deaths for which the reason was neither unknown cause nor malignant cause were reviewed before the treatment codes were unblinded so that the censoring mechanism could be identified on the database for analysis. TTP was censored if the patient remained on trial treatment at the date of the last patient's last visit (data cut off date) without any evidence of disease progression, or if she was withdrawn from the trial for any reason other than unsatisfactory therapeutic effect or death from cancer or unknown cause. TTF was defined as the time from the date of

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			TTF	randomization to the earliest date of disease progression, discontinuation of therapy for any other reason, or death, or the time was censored at the cut off date for analysis for patients still on therapy without evidence of disease progression.
			Time to death	TTD was defined as the time from the date of randomization to the date of last known alive or death from any cause.
			HRQL (EORTC QLQ-C30 version 2.0)	
			Safety National Institutes of Health/National Cancer Institute common toxicity criteria and selected laboratory parameters to score severity of adverse experiences	

Statistical analysis and definition of study groups

5.7.2.11 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

Table B29 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Buzdar 1996/1998	To compare the efficacy and tolerability of anastrozole (1 and 10 mg once daily), a selective, oral, nonsteroidal aromatase inhibitor, and megestrol acetate (40 mg four -times daily), in postmenopausal women who progressed following tamoxifen treatment.	Efficacy analyses were analyzed on the basis of the treatment to which the patients were randomly assigned (intention-to-treat basis). Cox's proportional hazards model was used to analyze time to disease progression, time to treatment failure, and time to death. Logistic regression was used to analyze response data. All efficacy analyses were adjusted for the covariates of previous treatment status (adjuvant or for advanced disease) and hormone receptor status. The combined estimate of the treatment effect for a time-to-event variable for either dose of anastrozole compared with megestrol acetate was derived by fitting a Cox proportional hazards model with trial and treatment as covariates and then testing for significance of treatment. Log hazards ratios and standard errors were estimated and were used to calculate confidence intervals on the hazards ratio. Upper confidence limits c 1.25 for a hazards ratio of either dose of anastrozole to megestrol acetate would allow an inference that the effects of anastrozole were not substantially inferior to the effects of megestrol acetate (i.e., an upper confidence limit of 1.25 was considered to represent equivalence between anastrozole and megestrol acetate). Additional analyses were performed to assess the effects of the prognostic factors of prior hormonal treatment history, presence or absence of measurable disease, and presence or absence of visceral disease on time to progression and time to treatment failure. Likelihood ratio tests were performed to rule out qualitative interactions when treatment by prognostic factor interactions existed. Because the two anastrozole groups were compared with the megestrol acetate group, Bonferonni adjustments were made for the analyses of each end point. For tumor response data, an approach similar to the method outlined earlier was used. The incidence of adverse events was compared	A population of 300 patients (100 in each treatment group) in each trial was deemed sufficient to detect a treatment difference of approximately 14 weeks in median time to progression with 80% power and a two-sided alpha level of 0.05, assuming a median time to progression of 26 weeks and a minimum follow-up time of 6 months.	Patients were withdrawn from active treatment for a serious adverse event, noncompliance with protocol procedures, unwilling or inability to continue the trial, withdrawal by an investigator, or clinically significant breast cancer progression. All patients who were withdrawn were monitored for survival.

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		between patients treated with anastrozole 1 mg and those treated with megestrol acetate and between those treated with anastrozole 10 mg and those given megestrol acetate. Fisher's exact test was used for the statistical comparisons; a two-sided alpha level of 0.01 was used to allow for multiple comparisons. Interim analyses of each trial were performed in 1994 to enable independent data-monitoring committees to evaluate periodically efficacy and safety data from the two trials and recommend that the trials be continued or stopped, or recommend a change to the study design. In the North American trial, two interim analyses of objective response and time to progression were performed, whereas in the European trial one interim analysis was performed. In each trial, the O'Brien and Fleming adjustment was used in the analysis of both objective response and time to progression; the significance level for all end points was adjusted using the Bonferroni method. After reviewing interim results, the independent committees monitoring the two trials recommended that each of the trials be continued.		

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Trial 20 Howell	Originally, the primary objective of the trial was to compare the effects of 2 doses of long-acting (LA) intramuscular (im) fulvestrant (125 or 250 mg, administered every 28 ± 3 days), with oral anastrozole (1 mg daily) in terms of time to progression, in postmenopausal women with advanced breast cancer. Effective 27 April 1998, the primary objective was amended because a protocol-defined preliminary data summary showed no objective responses in the first 30 patients (across this trial and Trial 9238IL/0021 treated with fulvestrant 125 mg, and this treatment arm was therefore discontinued because of insufficient evidence of clinical activity. The revised primary objective was therefore amended to the following: to compare the effect of LA im fulvestrant (250 mg) with oral anastrozole	The final efficacy analyses (of the primary and secondary endpoints) included all randomized patients and compared treatment groups on the basis of treatment to which patients were randomly assigned, regardless of treatment actually received (i.e., an intention-to-treat [ITT] approach). These analyses were considered the primary statistical analyses of the endpoints. Secondary 'per-protocol' analyses were also performed for the primary endpoint of time to progression and the secondary endpoints of time to death, objective response rate, and time to treatment failure. These were conducted according to treatment received, and excluded patients with major protocol violations and deviations (see Section 3.3). If the results from the secondary analyses led to different conclusions from the primary (ITT analyses), the results were evaluated to identify the reasons for the difference. Analyses were scheduled to occur after 340 endpoint events (disease progression or death before disease progression) were recorded across the 2 remaining treatment groups (fulvestrant 250 mg and anastrozole 1 mg). The nominal level of significance was set at 5%, except for the primary endpoint of time to progression and the secondary endpoint of objective response rate. For these 2 analyses, the significance level was adjusted to 4.86% because of the preliminary data summary of objective response and the interim analysis of time to progression, and 95% confidence intervals were adjusted as appropriate. The analysis for time to death was scheduled to occur after 50% of patients (i.e., 196 if 392 patients were recruited) across the treatment groups had died. The effects of centre and treatment-by-centre interaction were not investigated. No analyses were performed for individual centers or for any subgroup of centers. All significance levels were 2-sided.	To detect a hazard ratio, for fulvestrant treatment compared with anastrozole treatment, of greater than or equal to 1.43 or less than or equal to 0.70, at a significance level of 5% with 90% power, 490 endpoint events (disease progression or death before progression) had to occur in the trial (i.e., 490 patients had to progress or die; this was equal to a change of 60 days in the median time to progression for patients treated with fulvestrant). This trial had an estimated accrual time of 24 months, with a 6-month follow-up period, and this equated to 196 patients per treatment group being required Therefore, a total of at least 588 patients were required for the trial, unless 1 treatment group of the trial was dropped. If 1 treatment group was dropped, 196 patients would be required in each of the remaining 2 groups, and the analysis would be performed when 340 endpoint events (disease progression or death before disease progression) occurred across the remaining 2 groups. Because the 125 mg treatment group was discontinued, effective 27 April 1998, the number of patients required was changed, and recruitment continued until 196 patients were enrolled in each of the remaining 2 treatment groups, i.e., fulvestrant 250 mg and anastrozole 1 mg. Thus the total number of patients required to be recruited was revised to a minimum of 392 evaluable patients.	This was accurately reported in the clinical study report
Trial 21	To compare the efficacy and	The trial was designed to detect the superiority of	The final analysis was scheduled to	Patients who withdrew from trial

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Osborne_2002	tolerability of fulvestrant with anastrozole in the treatment of ABC in patients whose disease progresses on prior endocrine treatment	fulvestrant 250 mg in terms of efficacy and tolerability compared with anastrozole 1 mg in postmenopausal women with ABC. The efficacy analyses were performed according to randomized treatment (i.e., "intention to treat") using a nominal significance level of 5%. However, for the TTP and OR analyses, the significance level was adjusted to 4.86% because of the preliminary data summary of OR and the interim analysis of TTP. As a result, the 95% confidence intervals (CIs) were adjusted accordingly to 95.14%. All significance levels are two-sided. Although not described in the protocol, fulvestrant was retrospectively compared with anastrozole for non inferiority for OR, TTP, and TTF. Because of the interim analysis, a one-sided CI of 97.57% was used for the evaluation of TTP and OR. For the analysis of TTF, a one-sided CI of 97.5% was used. These limits are identical to using the upper limit of the 95.14% two-sided CI from the analysis of TTP, the lower limit of the 95.14% two-sided CI for the difference in response rates for OR, and the upper limit of the 95% two-sided CI for TTF.	occur when 340 events (i.e., objective disease progression or death) had occurred across the two groups. This provided 90% power to detect a hazard ratio (HR) ≥1.43 or ≤ 0.70 for fulvestrant treatment compared with Anastrozole treatment, at a significance level of 5%. It was therefore planned to recruit 392 patients (196 in each treatment group) to achieve the required number of events.	treatment before progression were followed up until objective disease progression and death. Documented, can be seen in patient flow diagram
Lundgren_1989	To compare the clinical response and toxicity of MA and AG as second-line treatment in patients with metastatic breast cancer	Differences in rates between the two groups were tested with chi square or Fischer's exact test. Survival rates were computed by the life table method, and possible differences in survival distribution were tested for by the log-rank test. The effects of different prognostic factors were analysed by the Cox regression method. Statistical significance is indicated by $p \leq 0.05$	Not provided	Documented – can be seen in patient flow diagram
Buzdar_2001	To compare two doses of letrozole (0.5mg and 2.5 mg every day) and MA (40mg qid)as endocrine therapy in postmenopausal women with ABC previously treated with anti-oestrogens	All statistical tests performed were two-sided, with a .05 level of significance. Two-sided 95% confidence intervals for the odds ratio for each treatment comparison were also presented. No adjustments for multiple comparisons or multiple end points were made. The primary efficacy variable was the confirmed best overall objective tumor response rate and was analyzed using a logistic regression procedure both adjusted and unadjusted for prognostic baseline covariates (disease-free interval, dominant site of disease, prior anti-oestrogen therapy, stage of disease, and locally advanced, locoregionally recurrent, or metastatic breast cancer at study entry). Although there were two letrozole arms, the statistical	The sample size for this trial was computed as the number of patients needed within one letrozole (0.5 mg or 2.5 mg daily) treatment group to detect at least a 13% difference from the megestrol acetate 160 mg treatment group for the confirmed ORRs (CR + PR). The sample size was calculated assuming 80% power, alpha level of 0.05, and two-sided, to show that either one of the two letrozole treatment groups was superior to the megestrol acetate treatment group, assuming a	

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
		significance was based only on pair comparison. Cochran Mantel-Haenszel tests were performed to compare ORRs according to the covariates that were thought to have an effect on overall objective response (disease-free interval, dominant site of disease, stage of disease at study entry, and history of anti-oestrogen therapy). A Cox proportional hazards regression analysis was performed on the intent to-treat population for the median time to event and 95% confidence intervals for variables, including duration of response, duration of clinical benefit, time to response, TTP, TTF, and TTD. No adjustments for multiple comparisons or multiple end points were made. A longitudinal analysis on quality of life was performed using a pattern mixture model. The criterion for the pattern classification was based on whether the patient was receiving the study drug 6 months or longer. Adverse experiences were summarized in terms of the number of patients who experienced an event in each treatment arm, and by relationship to treatment, severity of the event, and duration of exposure to study medication.	response rate for letrozole equal to 28% and a response rate for megestrol acetate equal to 15%. A total of 513 patients (171 per treatment arm) were required. Therefore, approximately 590 patients were planned in order to obtain the required 513 completed patients.	

Participant flow

5.7.2.12 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 17: Budzar_1996/1998 CONSORT flowchart

Buzdar_1996/1998

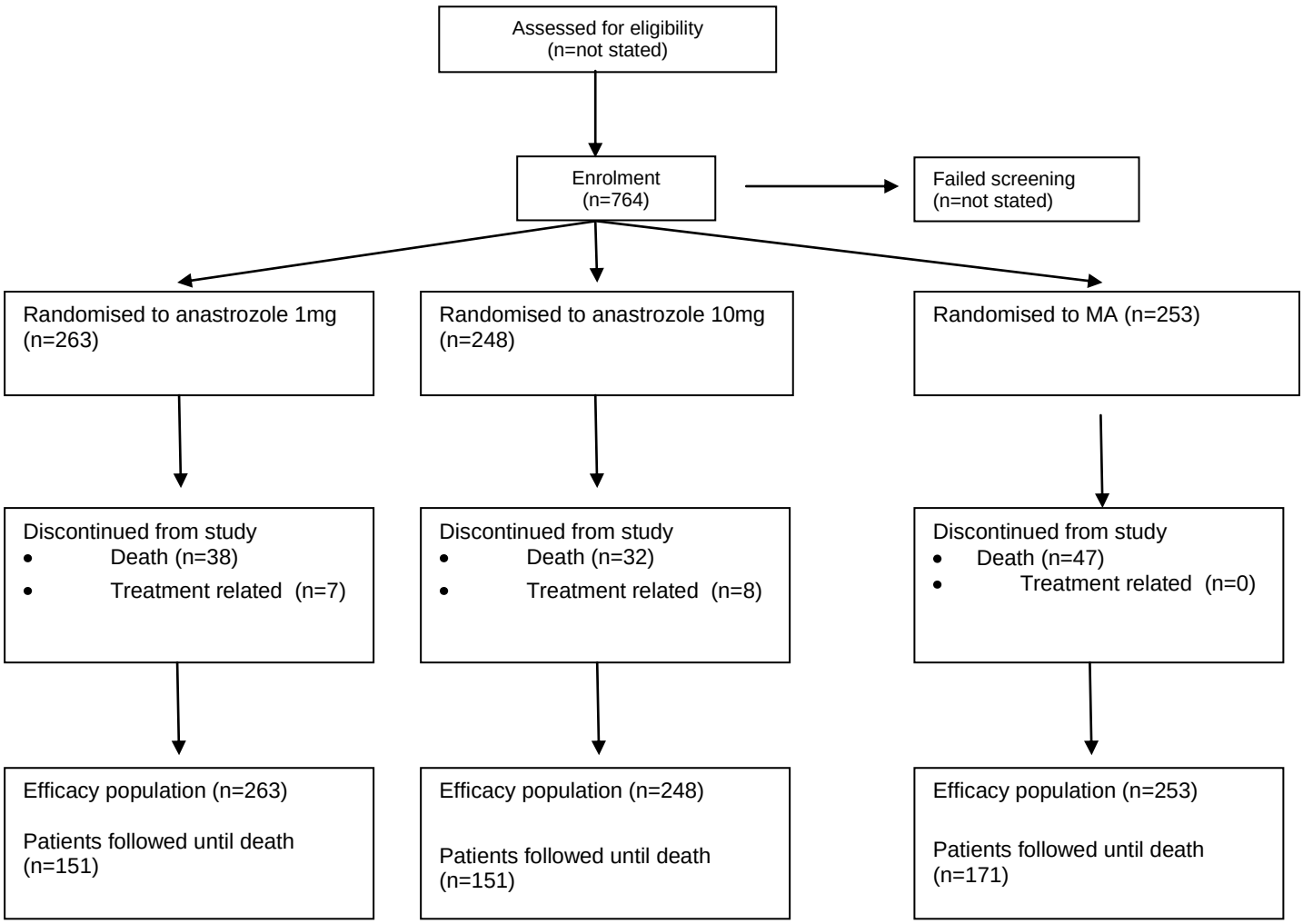


Figure 18: Howell_2002 CONSORT flowchart

Howell_2002

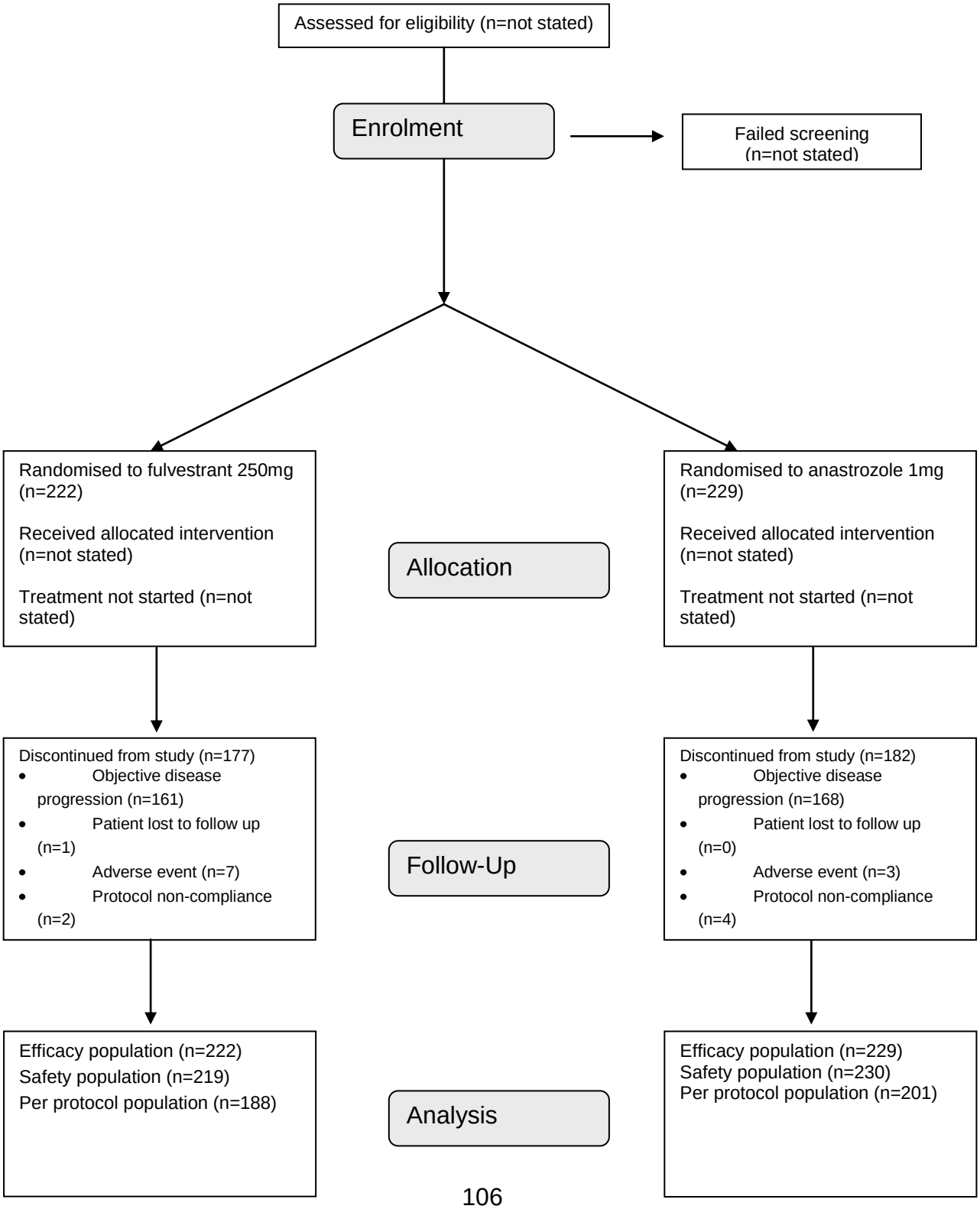


Figure 19: Osborne_2002 CONSORT flowchart

Osborne_2002

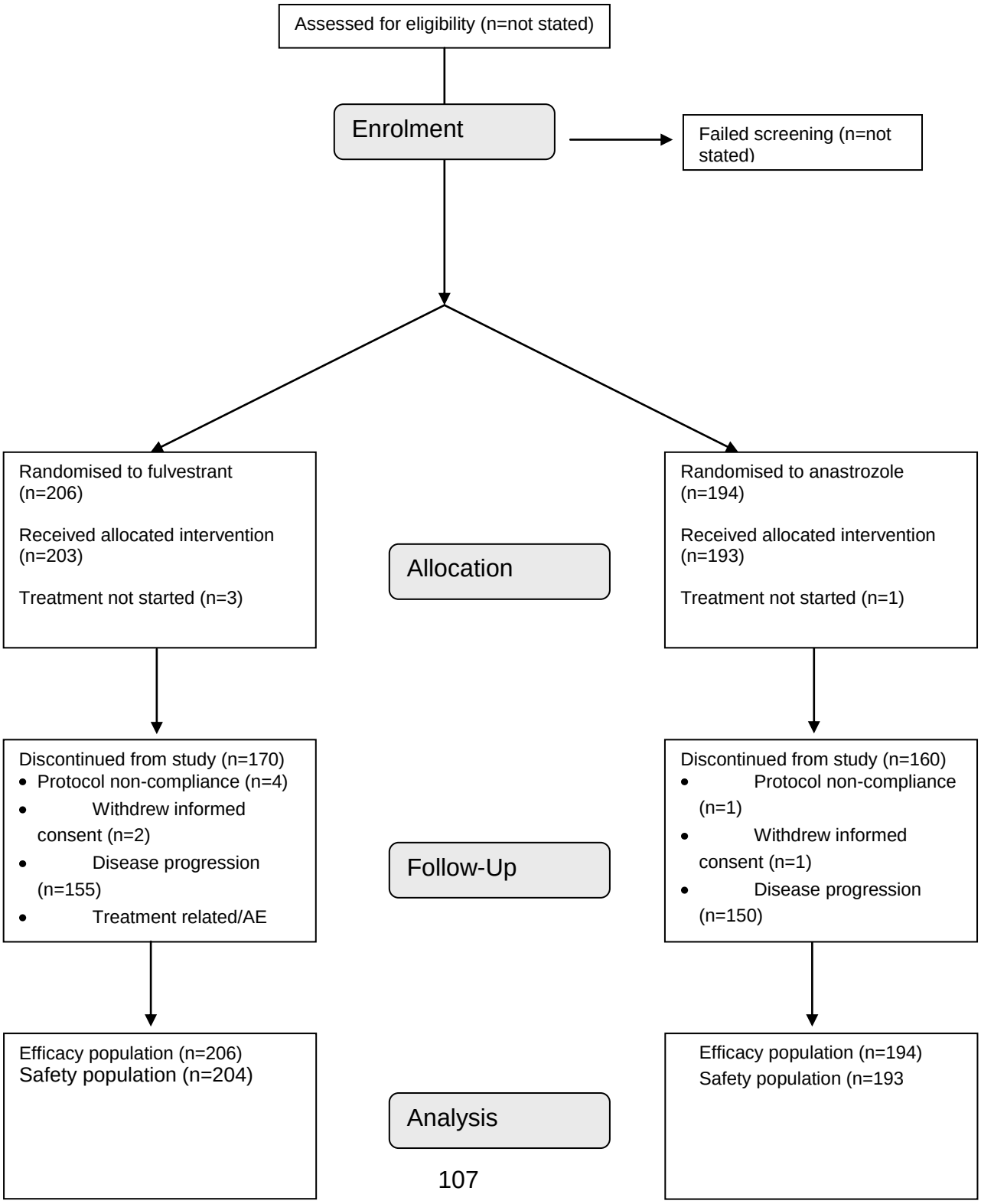


Figure 20: Lundgren_1989 CONSORT flowchart

Lundgren_1989

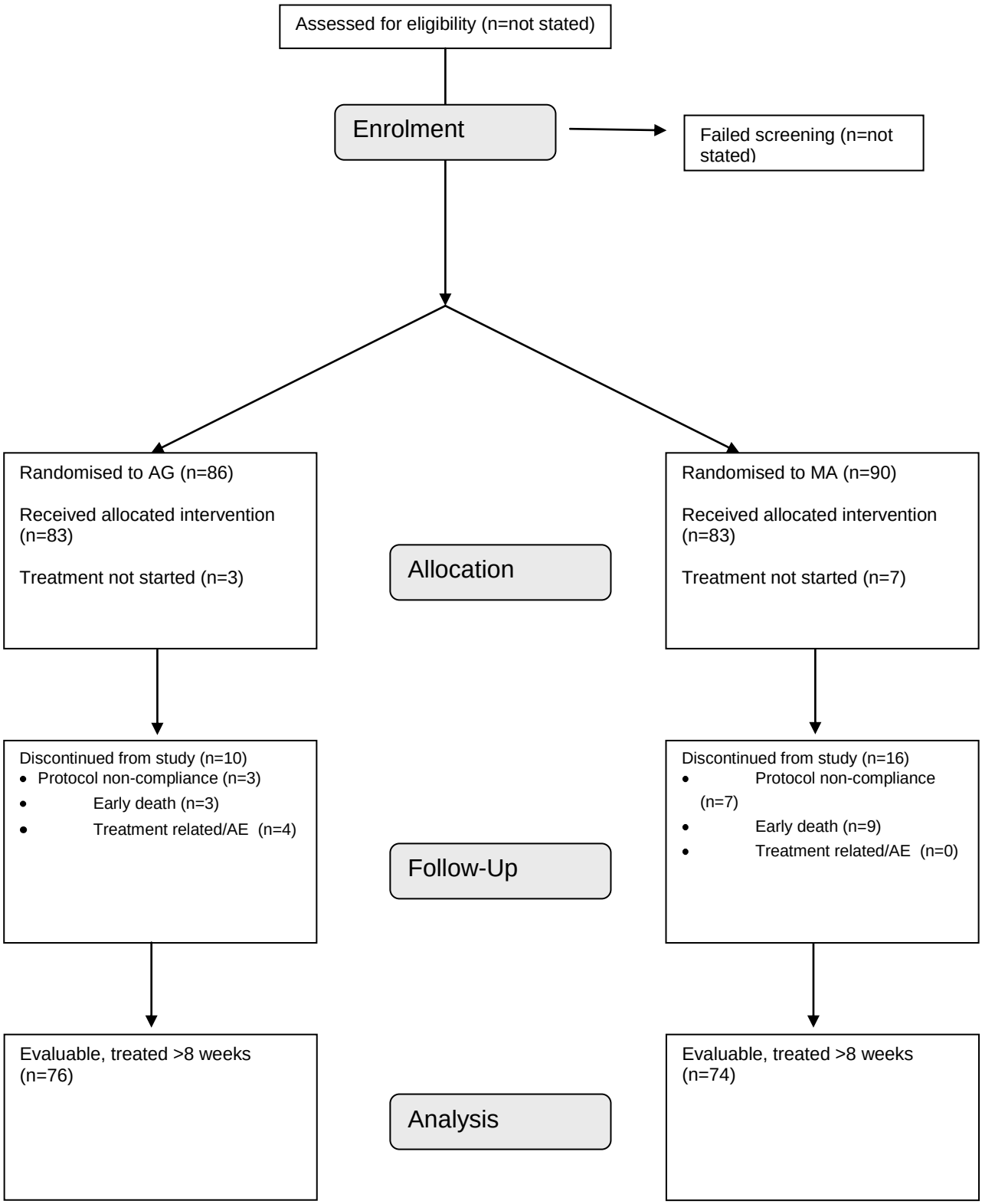
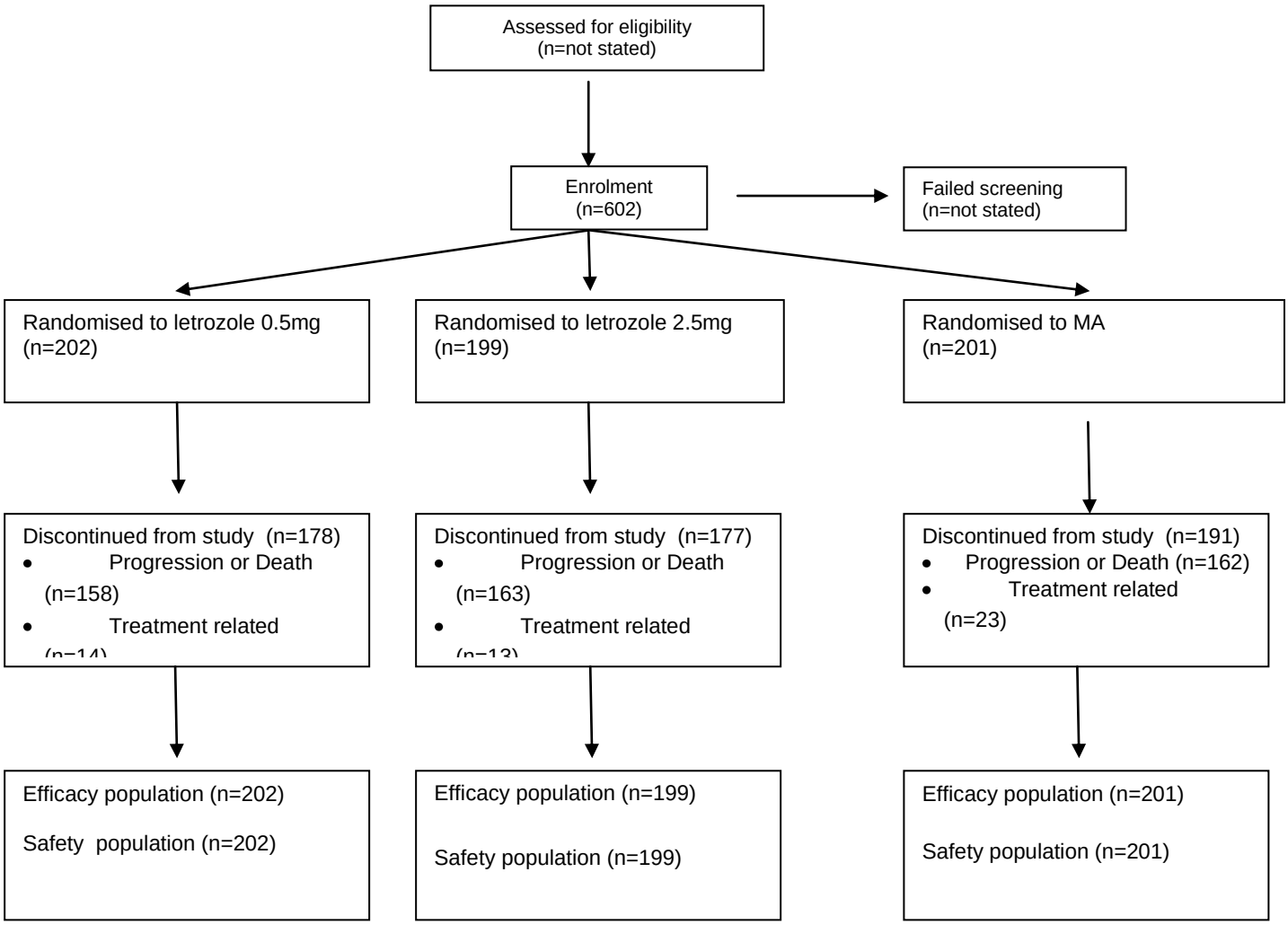


Figure 21: Buzdar_2001 CONSORT flowchart

Buzdar_2001



5.7.2.13 Critical appraisal of relevant RCTs

5.7.2.14 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See section 9.3, appendix 3.

5.7.2.15 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Table B30 Quality assessment results for RCTs

Trial no. (acronym)	Buzdar 1996/1998	Trial 20 Howell	Trial 21 Osborne_2002	Lundgren_1989	Buzdar_2001
Was randomisation carried out appropriately?	Yes	Yes	Yes	Not stated	Yes
Was the concealment of treatment allocation adequate?	No -Open label for megestrol acetate, in addition to the fact that the dosing schedule differed for MA and anastrozole	No – open label study	Yes	Not stated	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes - Groups formed were well balanced with respect to demographic and pre-treatment characteristics. There appeared to be an imbalance in treatment allocation for the three groups however it was believed to be an artifact related to the large proportion of centres in the European trial in which the total number of patients was not divisible by six (allocated in blocks of 6 in European trial, compared with blocks of 3 in the US trial)	Yes	Yes	Yes	
Were the care providers, participants and outcome assessors blind to treatment allocation?	No – open label study	No – open label study	Yes	Not stated	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No	No	There are differences but the numbers are small so difficult to assess whether real differences or due to chance	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No	No	No	No	No

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Calculations based on number randomised	The primary statistical analyses of the efficacy endpoints were conducted using all randomized patients on an intention-to-treat basis, and used response data as defined by the computer algorithm	The primary statistical analyses of the efficacy end points were conducted on an intention-to-treat basis, included all randomized patients, and used response data as defined by the computer algorithm. Secondary (supportive) statistical analyses were conducted on a per-protocol population (according to treatment received) and an intention-to-treat basis with a model that excluded baseline covariates	No - Calculations only involved evaluable patients who had been treated for > 8 weeks	ITT defined as the set of randomised patients who took at least one dose of trial medication. All patients, regardless of their length of treatment were included in the ITT analysis.

5.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

Table B31 Summary of the trials used to conduct the indirect comparison

No. trials	References of trials	Fulvestrant 500 mg	Fulvestrant 250 mg	Fulvestrant 250 mg Loading dose	Anastrozole 1 mg	Anastrozole 10mg	MA 160mg	AG 500 mg	Letrozole 0.5mg	Letrozole 2.5 mg
1	CONFIRM	X	X							
2	FINDER I FINDER II	X	X	X						
1	Buzdar 1996/1998				X	X	X			
2	Howell_2002 Osborne_2002		X		X					
1	Lundgren_1989						X	X		
1	Buzdar_2001						X		X	X
	Adapted from Caldwell et al. (2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900									

5.7.4 For the selected trials, provide a summary of the data used in the analysis.

The review identified eight RCTs for which 7 trials reported sufficient data to evaluate the TTP (Table B33) and 5 trials reported sufficient data to evaluate OS (Table B32). Please note that the RCTs by Buzdar in 1996 and 1998 are based on the same trial. There was insufficient OS data in the following studies, which were excluded from the network meta-analysis as indicated by the grey font and the "x" in Table B32: FINDER 1, FINDER 2, and Lundgren 1989. In the case of TTP, there was insufficient data for the study by Lundgren 1989. The asterisks in Tables B32 and B33 indicate the comparators that were excluded from the economic model which included only the licensed doses for the relevant comparators.

Table B32. Evidence available for OS

No. trials	Reference	F500	F250	F250 LD*	Anas 1	Anas 10*	MA	Letro 0.5*	Letro 2.5	AG
1	CONFIRM	☑	☑							
2	FINDER 1	☒	☒	☒						
3	FINDER 2	☒	☒	☒						
4	Howell 2002	·	☑		☑					
5	Osborne 2002		☑		☑					
6	Buzdar 1996				☑	☑	☑			
6	Buzdar 1998				☑	☑	☑			
7	Buzdar 2001						☑	☑	☑	
8	Lundgren 1989						☒			☒

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Anas 10=Anastrozole 10mg; Letro 0.5=Letrozole 0.5mg; Letrozole 2.5=Letrozole 2.5mg; AG=Aminoglutethimide 250mg

Table B33. Evidence available for TTP

No. trials	Reference	F500	F250	F250 LD*	Anas 1	Anas 10*	MA	Letro 0.5*	Letro 2.5	AG
1	CONFIRM	☑	☑							
2	FINDER 1	☑	☑	☑						
3	FINDER 2	☑	☑	☑						
4	Howell 2002	·	☑		☑					
5	Osborne 2002		☑		☑					
6	Buzdar 1996				☑	☑	☑			
6	Buzdar 1998				☑	☑	☑			
7	Buzdar 2001						☑	☑	☑	
8	Lundgren 1989						☒			☒

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Anas 10=Anastrozole 10mg; Letro 0.5=Letrozole 0.5mg; Letrozole 2.5=Letrozole 2.5mg; AG=Aminoglutethimide 250mg

5.7.5 Please provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

Since there was OS and TTP data available from multiple trials across the comparators, it was necessary to pool the available data as well as to extrapolate the curves for both OS and TTP. In the absence of any head-to-head studies for the comparisons of interest of fulvestrant 500 mg versus the alternatives, it was necessary to perform a network meta-analysis. The tables in section 5.7.4 illustrate that the hormonal therapy alternatives can be indirectly compared to fulvestrant 500 using fulvestrant 250 as a common comparator. Fulvestrant 250 was selected as the baseline comparator for the economic model because patient-level data was available from the CONFIRM study for both TTP and OS and this pivotal study represented the largest study with the longest duration.

The network meta-analyses of OS and TTP used a Bayesian approach which involves the formal combination of a prior probability distribution that reflects a prior belief of the possible values of the pooled relative effects with a likelihood distribution of the pooled effect based on the observed data in the different studies to obtain a posterior distribution of the pooled relative treatment effect. Model parameters were estimated using a Markov Chain Monte Carlo (MCMC) method called Gibbs sampling as implemented in the WinBUGs software package. The WinBUGs sampler was run for 30,000 iterations for the models and these were discarded as 'burn-in' and the model was run for a further 70,000 iterations upon which inferences were based.

OS extrapolation and network meta-analysis using Weibull distribution
In the case of OS, the Weibull distribution was selected (see section 6.3.7 and appendix 16 for goodness of fit versus alternative distributions) and the hazard ratios in the CONFIRM study were constant over time (the shape parameters were very similar for both the baseline and comparator treatment; see Figure 22); therefore it was possible to perform a network meta-analysis by pooling the hazard ratios across the interventions and extrapolating the OS using a Weibull distribution.

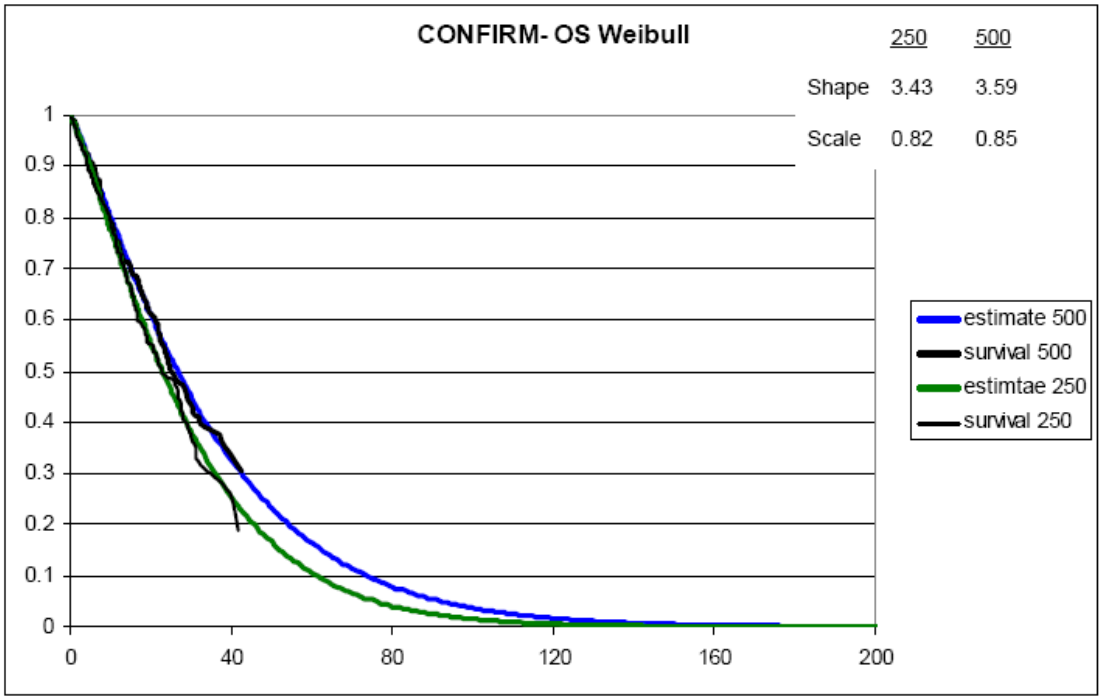
The baseline OS curve was fit based on fulvestrant 250 using the CONFIRM individual patient study data and the pooled hazard ratios resulting from the meta-analysis were applied to the baseline curve. Since no additional data was available for fulvestrant 250 Figure 22 represents the baseline curve used in the economic model for fulvestrant 250, which is based on a 2-parameter Weibull survivor function S(t) given by equation 1:

$$S(t) = \exp(-\lambda t^{\gamma}) \qquad \text{eq.1}$$

where λ = scale parameter, t = time and γ = shape parameter.

The data sets analyzed (including for scenario analysis) for the hazard ratios are presented in Appendix 16, which was incorporated in the economic model using a Cholesky decomposition.

Figure 22. Overall survival (OS) from CONFIRM study using Weibull distribution



TTP extrapolation and network meta-analysis using log normal distribution

For TTP, since the log normal distribution was selected (see section 6.3.7 and appendix 17 for goodness of fit versus alternative distributions) it was not appropriate to pool the hazard ratios given that the proportionality and constancy of the hazard ratios cannot be assumed from a theoretical perspective. Alternatively, based on the methodology developed by Ouwens et al[37](Ouwens et al, 2011), a simultaneous extrapolation and network meta-analysis of TTP curves for all of the comparators were derived from the available RCTs. This was achieved by relating the TTP Kaplan Meier curves of each of the competing interventions directly to parameters of the log normal survival curves.

The 2-parameter log normal survivor function S(t) is given by the equation:

$$S(t) = 1 - \Phi\left(\frac{\ln(t) - \mu}{\sigma}\right) \qquad \text{eq.2}$$

where μ = scale parameter, t = time and σ = shape parameter.

For all other studies except the CONFIRM study (where patient-level data was available), the reported Kaplan-Meier curves were digitized (Engauge

Digitaliser v4.1) for each treatment arm in each study by using the survival percentages for the time points where the numbers at risk were provided. For studies where no numbers at risk were provided, the monthly TTP percentages were extracted from the Kaplan Meier and a conservative estimate of uncertainty was derived for these TTP percentages using information regarding the duration of follow-up and death (see Appendix 17). A fixed effects model was used to simultaneously extrapolate Kaplan-Meier curves over time by means of lognormal curves, to synthesize and to indirectly compare the different treatments. The scale and the shape for the baseline comparator (fulvestrant 250 mg) were calculated as the average of μ_1 and μ_2 of all studies evaluating fulvestrant 250 mg, and were used as the anchor to obtain estimates for the shape and scale for the other interventions. The pooled TTP curves for each treatment were produced and the corresponding area under the curves was calculated to obtain the mean TTP with each treatment. With this approach the possible differences in both shape and scale of the log normal curves within trial is taken into account without breaking randomization. Please see Appendix 17 for more details on the network meta-analysis methodology and data sets analyzed (including for scenario analysis).

Please note that the correlation matrices for the shape and scale parameters of the TTP curves are presented in Appendix 17, which was incorporated in the economic model using a Cholesky decomposition.

Please also note that selected comparators, such as letrozole 0.5 mg, were included in the network meta-analysis, although the results were not included in the economic model since this dose is not licensed. In addition, megestrol acetate was included in the network meta-analysis in order to connect letrozole to the network, but was not included in the economic evaluation given the comparators specified in the scope.

5.7.6 Please present the results of the analysis.

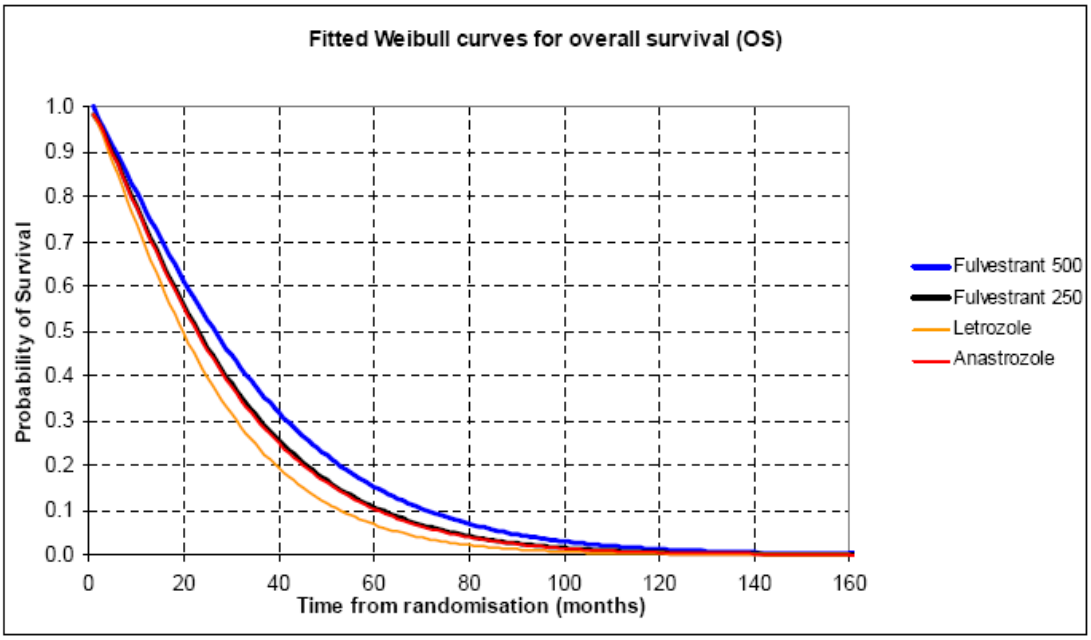
Overall survival

Table B34. Network meta-analysis OS results: Hazard Ratios relative to fulvestrant 250 mg

Treatment	HR	2.5th percentile	97.5th percentile
Fulvestrant 500 mg	0.84	0.69	1.03
Anastrozole 1 mg	1.02	0.88	1.19
Megestrol acetate*	1.31	0.98	1.75
Letrozole 0.5 mg*	1.03	0.71	1.51
Letrozole 2.5 mg	1.20	0.83	1.74

*Excluded from the economic model

Figure 23 Overall OS as estimated with fixed effects Weibull network meta-analysis model



Time to progression

Table B35. Network meta-analysis TTP results: Fulvestrant 250 mg (baseline comparator)

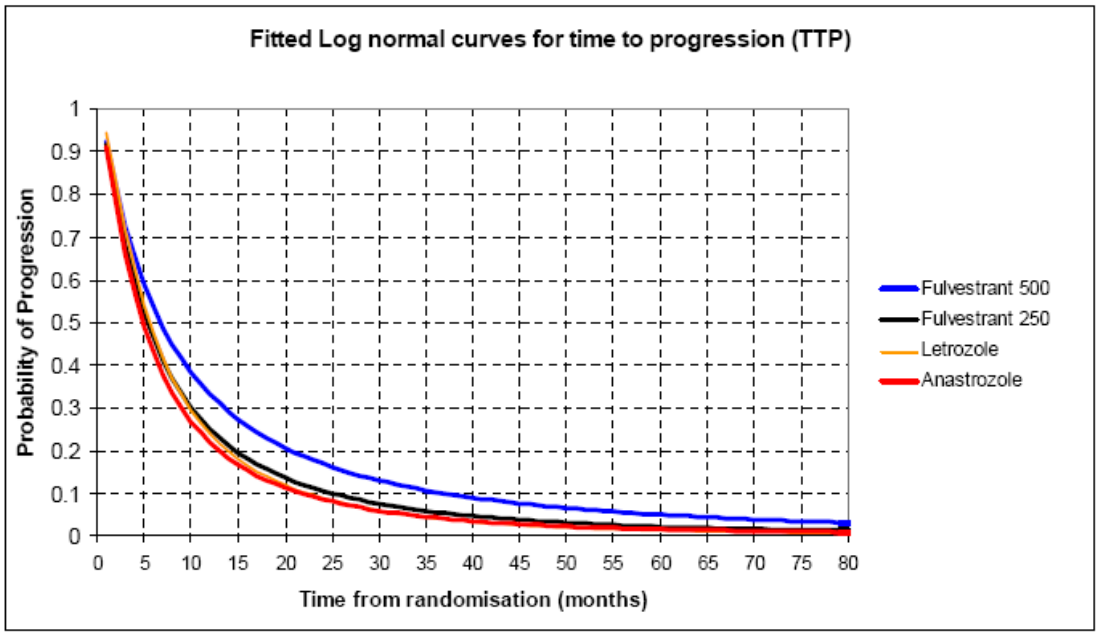
Treatment	Scale			Log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250	1.676	1.600	1.750	-0.185	-0.344	-0.062

Table B36. Network meta-analysis TTP results: Difference in log normal parameters for treatment alternatives versus fulvestrant 250 mg

Treatment	Difference in scale			Difference in log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250 mg LD*	0.209	-0.047	0.503	-0.067	-0.639	0.402
Fulvestrant 500 mg	0.229	0.167	0.293	-0.102	-0.185	-0.020
Anastrozole 1 mg	-0.094	-0.189	-0.004	0.029	-0.109	0.173
Megestrol acetate 160 mg*	-0.017	-0.162	0.131	0.222	0.033	0.405
Letrozole 0.5 mg*	0.281	0.089	0.468	-0.004	-0.267	0.244
Letrozole 2.5 mg	0.045	-0.140	0.231	0.108	-0.139	0.348

*Excluded from the economic model; LD=Loading dose

Figure 24. Overall TTP as estimated with fixed effects lognormal network meta-analysis model



5.7.7 Please provide the statistical assessment of heterogeneity undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

In the methods used for the base case and scenario analyses for OS and TTP, the studies used in the Network Meta-Analysis were too few in number to be able to carry out a meaningful quantitative analysis of heterogeneity.

5.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

None

5.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

Not applicable.

5.8 Non-RCT evidence

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

Not applicable – only RCTs were used.

5.9 Adverse events

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.8 and 9.9, appendices 8 and 9.

Not applicable.

5.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

The EPAR for fulvestrant 500 mg (see section **1.4**) states that no clinically relevant differences with respect to tolerability and toxicity have demonstrated comparing the 500 mg and the 250 mg doses. Therefore no table has been provided due to the regulatory procedure being type II variation. A network meta-analysis was conducted on serious adverse reactions and the results can be found at section **6.3** and Appendix **18**

5.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

A pooled analysis of safety included data from 560 patients treated with fulvestrant 500 mg (mean exposure: 261.89 days) and 567 patients treated

with fulvestrant 250 mg (mean exposure: 218.43 days). In addition to this, 101 patients were treated with fulvestrant 500 mg in the FIRST study (mean exposure: 283.86 days).

In the pooled database, the most frequently reported AE was injection site pain with 13.9% vs. 10.2% of patients in the fulvestrant 500 mg and 250 mg groups, respectively. This was followed by nausea, fatigue, hot flush and headache with 10.2% vs. 13.9%, 9.6% vs. 7.1%, 8.8% vs. 8.6% and 8.0% vs. 7.2%, respectively, in the 500 mg and 250 mg groups, respectively. There were no important differences between the treatment groups in the reporting of these AEs **(see Table B37).**

Table B37 Commonly reported AEs in CONFIRM and pooled data (incidence ≥5% in either pooled group): Safety analysis set

MedDRA preferred term[a]	Number (%) of patients, by treatment[b]			
	Fulvestrant 500 mg		Fulvestrant 250 mg	
	CONFIRM	Pooled	CONFIRM	Pooled
	500 mg (N=361)	500 mg (N=560)	250 mg (N=374)	250 mg (N=567)
Patients with any AE	243 (67.3)	393 (70.2)	240 (64.2)	387 (68.3)
Injection site pain	42 (11.6)	78 (13.9)	34 (9.1)	58 (10.2)
Nausea	35 (9.7)	57 (10.2)	51 (13.6)	79 (13.9)
Fatigue	27 (7.5)	54 (9.6)	24 (6.4)	40 (7.1)
Hot flush	24 (6.6)	49 (8.8)	22 (5.9)	49 (8.6)
Headache	28 (7.8)	45 (8.0)	25 (6.7)	41 (7.2)
Back pain	27 (7.5)	40 (7.1)	40 (10.7)	54 (9.5)
Arthralgia	29 (8.0)	38 (6.8)	29 (7.8)	36 (6.3)
Bone pain	34 (9.4)	37 (6.6)	28 (7.5)	30 (5.3)
Vomiting	22 (6.1)	33 (5.9)	21 (5.6)	32 (5.6)
Anorexia	22 (6.1)	32 (5.7)	14 (3.7)	20 (3.5)
Pain in extremity[c]	25 (6.9)	32 (5.7)	26 (7.0)	38 (6.7)
Cough	19 (5.3)	31 (5.5)	20 (5.3)	32 (5.6)
Diarrhoea	17 (4.7)	30 (5.4)	11 (2.9)	24 (4.2)
Asthenia	21 (5.8)	29 (5.2)	23 (6.1)	31 (5.5)
Hypertension	16 (4.4)	24 (4.3)	15 (4.0)	29 (5.1)
Nasopharyngitis	5 (1.4)	24 (4.3)	12 (3.2)	33 (5.8)

a Patients with multiple occurrences of the same event were counted only once per event.
b Pooled data: CONFIRM, NEWEST, FINDER1 and FINDER2.
c Following data queries to the investigational sites, it was confirmed that pain in extremity was not linked to injection site pain but was a distinct and separate AE.
Preferred-terms are in order of decreasing frequency for the pooled data in the 500 mg group then alphabetically.
MedDRA: Medical Dictionary for Regulatory Activities.
Note on table B37: NEWEST study does not feature in the indirect comparisons as the study population is outside the licence for Faslodex. The NEWEST study was a phase II randomised, neoadjuvant trial comparing fulvestrant 500 mg vs. 250 mg in postmenopausal women with locally advanced, oestrogen receptor-positive breast cancer.

There were no particularly severe adverse events associated with fulvestrant or any of the other comparators identified in the scope. In most cases, “common” adverse events were reported, or alternatively adverse events occurring in ‘x%’ of the population were reported. This method of reporting highlights the fact that the adverse events associated with the treatments

were relatively mild as adverse events are often reported in terms of grades 3 and 4 for oncology treatments and was not the case in most the publications reviewed as there were simply not enough severe adverse events to report in this format. This has implications on the adverse event costing and modelling (see section 6.3.1 for details of inclusion of adverse events in economic model).

5.10 Interpretation of clinical evidence

5.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Fulvestrant 500 mg has demonstrated a clear clinically meaningful benefit to the currently approved fulvestrant 250 mg dose. Previously fulvestrant 250 mg was shown to have a comparable efficacy and tolerability to anastrozole (Osborne et al, 2002, Howell et al, 2002, Robertson et al, 2001)[2,8,9]. In the pivotal phase III CONFIRM study, there was a statistically significant prolongation of the time to progression with a 20% reduction in the risk of progressing for patients receiving fulvestrant 500 mg. Fulvestrant 500 mg's advantage to fulvestrant 250 mg applies to the broad inclusive population of ABC patients who received prior treatment with an anti-oestrogen.

From the pooled analysis of safety data, the risks associated with fulvestrant 500 mg are relatively minor and can be effectively managed by information in the SmPC. Injection site reaction and hypersensitivity (predominantly pruritus) are the only adverse drug reactions for which there is evidence of an increased risk for fulvestrant 500 mg compared to fulvestrant 250 mg.

The improved efficacy, and similar safety and tolerability that fulvestrant 500 mg offers compared fulvestrant 250 mg clearly indicate that there is an improved benefit-risk profile for fulvestrant 500 mg in postmenopausal women with ABC who have recurred or progressed after previous endocrine therapy. Furthermore, the improved efficacy for fulvestrant 500 mg compared with 250 mg was seen in all patient subgroups analysed. Taken together, these findings support the use of fulvestrant 500 mg as per its marketing authorisation after treatment with an anti-oestrogen for oestrogen-receptor positive postmenopausal women with ABC.

5.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Table B38 Summary of strengths and limitations of the clinical evidence base

CONFIRM Trial	
Strengths	Limitations
Confirmed oestrogen positive breast cancer is one of the key deciding factors for choosing endocrine therapy in clinical practice. 100% of the population in CONFIRM is ER positive reflecting current clinical practice.	The population of the CONFIRM trial contains a high, 60%, amount of patients with visceral metastases. Patients with visceral metastasis have a poorer prognosis than those with other types of metastasis, bone for example, and are commonly treated with chemotherapy in the UK.
Currently in the UK ABC patients progressing on adjuvant therapy is split approximately 20/80 between aromatase inhibitors and anti-oestrogens. The CONFIRM trial reflects UK adjuvant initiations with the last endocrine therapy received by patients being 42.5% and 57.5% for aromatase inhibitors and anti-oestrogens respectively	The position of the median quartile for TTP in the CONFIRM trial does not represent the scale of the significant difference seen in AUC on the Kaplan-Meier curves as represented by the 0.80 hazard ratio.
In clinical practice clinicians use length of response to previous endocrine therapy to judge continued endocrine sensitivity. In the CONFIRM trial 60% of the population had a response to prior endocrine therapy	The comparator in the CONFIRM trial does not reflect current clinical practice. NICE guidelines recommend the use of an AI after adjuvant AO and there are no guidelines after adjuvant AI. However clinical practice is to use a steroidal AI after adjuvant therapy with a non-steroidal AI or fulvestrant

FINDER I	
Strengths	Limitations
Confirmed oestrogen positive breast cancer is one of the key deciding factors for choosing endocrine therapy in clinical practice. 100% of the population in FINDER I is ER positive reflecting current clinical practice.	Population for this trial was entirely of Japanese ethic origin and does not represent the demographics of the UK
	Sample size was calculated on dose selection formulation rather than hypothesis testing formulation. As a result the trial is not optimally powered to show differences in efficacy.

FINDER II	
Strengths	Limitations
The population of this trial was almost entirely of Caucasian ethic origin and therefore more representative of the UK population	
Confirmed oestrogen positive breast cancer is one of the key deciding factors for choosing endocrine therapy in clinical practice. 100% of the population in FINDER I is ER positive reflecting current clinical practice.	Sample size was calculated on dose selection formulation rather than hypothesis testing formulation. As a result the trial is not optimally powered to show differences in efficacy.

5.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

The evidence base discussed in this submission is directly relevant to ABC patients seen in UK clinical practice.

Relevance of clinical endpoints to UK clinical practice

Objective response is not routinely assessed in England and therefore was not considered clinically relevant to include in the model. In addition progression free survival in the model is based on TTP from the CONFIRM trial which included death. This definition of progression is commonly referred to as progression-free survival (Saad et al, 2010) [19]

Comparators

The positioning of fulvestrant 500 mg in the current treatment paradigm means that it could potentially displace aromatase inhibitors and therefore the Manufacturer believes the choice of comparators reflects UK clinical practice as set out in the Advanced Breast Cancer clinical guidelines published by NICE[1]. See **section 2.4** for treatment algorithm.

5.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable

based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

As discussed in section 2.5, fulvestrant is currently used in UK clinical practice as 3rd or 4th line endocrine therapy and the scope of this appraisal positions fulvestrant 500 mg as second line therapy after prior anti-oestrogen therapy. Steger and his colleagues were able to show that earlier use of fulvestrant in the treatment algorithm of ABC resulted in better clinical benefit rates (Steger et al, 2005) [17]. Therefore it could be concluded that the current UK clinical experience will be different to the position with which this appraisal is looking at.

At least one comparator arm of the fulvestrant studies discussed in this submission are at the UK licensed dose of 500 mg monthly with an additional 500 mg dose given two weeks after the initial dose.

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 9.10, appendix 10.

A systematic literature review was conducted in January 2010 to identify potentially relevant economic evaluation studies for ABC that have been published. The search was conducted in a number of bibliographic databases, conference proceedings and health technology assessment.

Databases searched for published cost-effectiveness studies

The following bibliographic databases were searched for relevant cost-effectiveness study publications using the search strategy listed in section 9.10, appendix 10: MEDLINE, EMBASE, MEDLINE--in process, EconLIT, National Health Service Economic Evaluation Database (NHSEED) and Health Economic Evaluation Database (HEED).

Conference websites searched for published cost-effectiveness studies

The following conference and congress websites were also searched for relevant publications in the past two years:

- ISPOR Europe, 2008 and 2009
- ISPOR US, 2008 and 2009
- International health economics association (IHEA)*
- 6th World Congress, 2007
- 7th World Congress, 2009
- 2008 American Society of Clinical Oncology (ASCO) Annual Meeting
- 2008 San Antonio Breast Cancer Symposium
- 2009 ASCO Annual Meeting
- 2009 Breast Cancer Symposium

Systematic review: Inclusion and exclusion criteria

The primary objective of the systematic literature review was to identify published economic evaluation studies for fulvestrant and other hormonal

therapies in patients with ABC. A secondary objective of the literature review was to search for cost-effectiveness studies of chemotherapy agents for ABC to retrieve publications that could inform the methodological approach for the modelling. However, given the large number of papers retrieved for chemotherapy agents, the publications considered of relevance was restricted to those conducted in the UK. No country restrictions were applied to economic evaluation publications on hormonal therapies as part of the primary objective.

Table B39: Inclusion criteria were used for the cost effectiveness systematic review:

Type of study	Economic evaluation
Population	Adult women with advanced breast cancer, defined as including either stage III or stage IV (metastatic) breast cancer.
Geographical location	Economic evaluation studies of hormonal therapy: Any country Economic evaluation study of chemotherapies: UK only
Interventions	Hormonal and/or chemotherapy in 1st or sequential lines of treatments for ABC.
Outcomes of interest	QALYs and expected costs

Table B40: Exclusion criteria were used for the cost effectiveness systematic review:

Type of study	Cost-minimisation studies, reviews, discussion papers, or letters related to economic models.
Other	Early breast cancer.
Language	Non-English language.

Description of identified studies

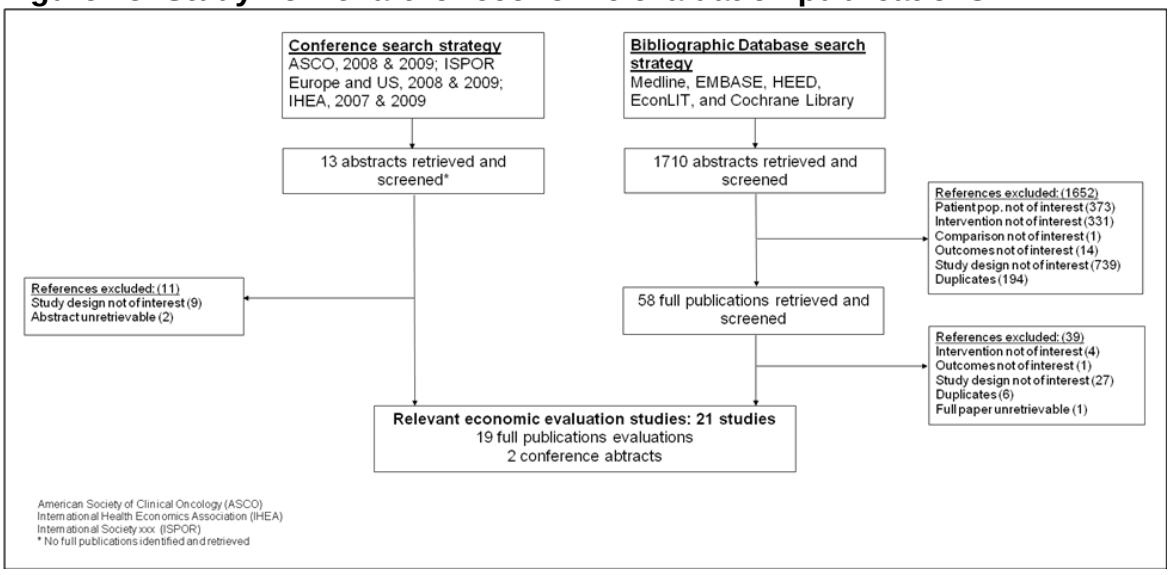
6.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more

than one study is identified, please present in a table as suggested below.

From the initial search of the bibliographic databases, a total of 1,710 abstracts were retrieved and screened. A total of 1,652 references were excluded in the first screening (see Figure 25). A further 58 full-paper publications were retrieved and assessed on quality and against the inclusion and exclusion criteria. Of these publications, 19 were considered relevant to the decision problem and met the inclusion criteria, while 39 were excluded (see Figure 25 for a summary of the reasons for exclusion). Of the 19 relevant studies identified, this included 14 cost-effectiveness studies of hormonal therapies conducted in any country and five publications for chemotherapy agents that were conducted in the UK. A brief overview of the 19 published economic evaluation studies identified in the systematic review of the bibliographic databases are summarised in Table B41.

From the additional search of conference and congresses, a further 13 potentially relevant abstracts were identified. No full-papers of these abstracts were identified and retrieved. Based on the conference abstracts available, two abstracts met the inclusion and exclusion criteria (see figure 25). A brief overview of the two conference abstracts identified are summarised in Table B42.

Figure 25: Study flow chart for economic evaluation publications



In summary, the systematic literature review of published economic evaluation studies identified 21 relevant publications, which included 19 full-papers and two conference papers. No published economic evaluation studies were identified that evaluated the cost-effectiveness of fulvestrant 500 mg as a hormonal therapy for advanced breast cancer.

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
An Economic Evaluation of Docetaxel and Paclitaxel Regimens in MBC in the UK[38]	Benedict	2009	UK	Markov model	Docetaxel vs. paclitaxel in different regimens (Pac3w (every 3 weeks), Pac1w (weekly), and Nab-P)	2nd-line therapy: MBC patients who had progressed after treatment on an anthracycline	*Docetaxel:* 1.18 QALYs *Pac3w:* 0.85 QALYs *Pac1w:* 0.89 QALYs *Nab-P:* 0.96 QALYs	*Docetaxel:* £17,321 *Pac3w:* £13,301 *Pac1w:* £15,973 *Nab-P:* £14,116 (£GBP, 2005-06)	ICERs for docetaxel were: £12,032/QALY gained vs. Pac3w, £4,583/QALY gained vs. Pac1w and £14,694/QALY gained vs. Nab-P
Cost Effectiveness of Treatment Options in ABC in the UK[39]	Brown	2001	UK	Updated Markov model	Docetaxel vs. paclitaxel Docetaxel vs. vinorelbine	2nd -line therapy: ABC patients with disease progression following failure of adjuvant or 1st-line chemo with anthracyclines	*Docetaxel:* 0.7347 *Paclitaxel:* 0.6485 *Vinorelbine:* 0.4822	*Docetaxel:* £7,817 *Paclitaxel:* £7,645 *Vinorelbine:* £4,268 (£GBP, 1998)	In the base-case analysis, the incremental cost-utility ratio for docetaxel vs. paclitaxel was £1,995 per QALY gained and for docetaxel vs. vinorelbine was £14,055 per QALY gained

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Economic evaluation of fulvestrant as an extra step in the treatment sequence for ER+ ABC[40]	Cameron	2008	UK	Markov model	Starting with first-line hormonal therapy followed by subsequent lines of therapy (with or without fulvestrant)	2nd -line therapy: Postmenopausal women with ER+ ABC	*2nd-line use of fulvestrant:* Cohort A (with fulvestrant): 1.18 QALY per patient Cohort B (without fulvestrant): 1.14 QALY per patient *3rd-line use of fulvestrant:* Cohort A (with fulvestrant): 1.178 QALY per patient Cohort B (without fulvestrant): 1.142 QALY per patient	*2nd-line use of fulvestrant:* Cohort A (with fulvestrant): £11,725 per patient Cohort B (without fulvestrant): £11,424 per patient 3rd-line use of *fulvestrant:* Cohort A (with fulvestrant): £11,055 per patient Cohort B (without fulvestrant): £11,424 per patient	ICER Cohort with fulvestrant versus Cohort without fulvestrant (2nd-line use): £ 7300 / QALY ICER Cohort with fulvestrant versus Cohort without fulvestrant (3rd-line use): Cohort with fulvestrant dominates cohort without fulvestrant

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
A Bayesian Approach to Markov Modelling in CEA: Application to Taxane Use in ABC[41]	Cooper	2003	UK	Probabilistic Markov model	Docetaxel vs. doxorubicin	2nd -line therapy: Postmenopausal patients with advanced breast cancer.	*n/a* Mean incremental utility between 0.036-0.047 depending on methodology used	*n/a* Mean incremental cost between £4,438-5,250 depending on methodology used (£GBP, 1999)	At given £100,000 per additional QALY gained threshold, the probability that taxanes are more cost effective than the standard treatment is 0.49 for the Bayesian 'informative prior distribution analysis' and 0.48 for the classical analysis
CUA of second-line hormonal therapy in ABC: a comparison of two aromatase inhibitors to megestrol acetate{{; 1951 Dranitsaris,G. 2000}}	Dranitsaris	2000	Canada	Decision analysis model	Letrozole vs. megestrol acetate (MA) Anastrozole vs. MA	2nd -line therapy: Postmenopausal women with ABC who are ER/PR+, anthracycline naive and have failed first-line hormonal therapy with tamoxifen	*Letrozole:* 0.80/0.78 *Anastrozole:* 0.80/0.72 *MA:* 0.80/0.67 (from public volunteers/ healthcare workers)	*Letrozole:* $2,966 *Anastrozole:* $3,149 *MA:* $2,949 ($Can, 1999)	Baseline average cost-effectiveness ratio (with utilities from women in general public) was $7,400 for MA, $7,200 for Letrozole, and $7,500 for Anastrozole per QALY gained

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Cost-utility analysis of first-line hormonal therapy in ABC. Comparison of two aromatase inhibitors to tamoxifen[42]	Dranitsaris	2003	Canada	Decision analytic model	Anastrozole vs. tamoxifen Letrozole vs. tamoxifen	2nd -line therapy: Postmenopausal women with ER/PgR+ breast cancer who are anthracycline naïve and have not received first-line hormonal therapy in the advanced setting	*Quality adjusted progression-free benefit (years)* *Anastrozole: 0.47* *Letrozole: 0.49* *Tamoxifen 0.44*	*Anastrozole:* $Can 2,847, Letrozole: $Can 2,883 Tamoxifen: $Can 2,258	n/a

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
nab-Paclitaxel weekly or every 3 weeks compared to standard docetaxel as 1st-line therapy in patients with MBC: an economic analysis of a prospective randomized trial[43]	Dranitsaris	2010	UK	Hazard-rate driven model	nab-Paclitaxel in 3 doses vs. docetaxel	1st-line therapy: Mean age per trial arm: nab-Paclitaxel 100 mg/m2 (weekly) (n=76) is 55.4 (SD9.6); nab-Paclitaxel 150 mg/m2 (weekly) (n=74) is 53.2 (SD9.2); nab-Paclitaxel 300 mg/m2 (every 3 weeks) (n=76) is 51.7 (SD9.5); and Docetaxel 100 mg/m2 (every 3 weeks) (n=74) is 55.4 (11.6) Depending on arm, between 64.5% and 81.6% of women were classified as postmenopausal	*nab-Paclitaxel 100mg/m2 weekly (QW):* 12.8 PF months *nab-Paclitaxel 150 mg/m2 weekly (QW):* 12.9 PF months *nab-Paclitaxel 300mg/m2 every 3 weeks (q3w):* 11.0 PF months *Docetaxel 100mg/m2 every 3 weeks (q3w):* 7.5 PF months	*nab-Paclitaxel 100mg/m2 QW:* £15,396 *nab-Paclitaxel 150 mg/m2 QW:* £27,222 *nab-Paclitaxel 300mg/m2 q3w:* £15,809 *Docetaxel 100mg/m2 q3w:* £12,923 (£GBP, 2007)	Incremental cost per PFY of £5,600, £31,800 and £9,900 for nab-paclitaxel 100, 150 g/m2 QW and 300mg/m2 q3w, respectively When expressed on a monthly basis, the incremental cost per progression-free month was £500, £2,700 and £800 for nab-paclitaxel 100, 150mg/m2 weekly and 300mg/m2 q3w

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Cost-effectiveness implications of increased survival with anastrozole in the treatment of ABC[44]	Drummond	1999	UK	Cox's proportional hazards model	Anastrozole vs. megestrol acetate	2nd-line therapy: Postmenopausal women with ABC who had progressed whilst receiving tamoxifen or other anti-oestrogen therapy for their disease	n/a	*Anastrozole: In UK daily cost of (*£2.97) Megestrol acetate: £0.97	ICER (anastrozole to megestrol acetate) for the primary analysis was £1,608 per LYG for the UK; the Weibull model was slightly more conservative giving an ICER of £1.761 per LYG for the UK; Kaplan-Meier estimates were less conservative giving a ration of £1,056 per LYG in UK
Cost-effectiveness analysis of exemestane compared with megestrol in patients with ABC[45]	Hillner	2001	USA	Hazard-rate driven model	Exemestane vs. megestrol	2nd-line therapy: Patients with postmenopausal, tamoxifen-refractory ABC	*Exemestane:* Average survival of 746 days *Megestrol acetate;* 688 days	*Exemestane:* US$ 1517 *Megestrol acetate;* US$ 235 (US$, 2001)	The baseline (1000 days) incremental cost effectiveness (CE) ratio using exemestane was $10,600 per life year gained (estimated 95%CI, $6,200-209,000). Using a 5-year projection, the CE ratio for exemestane was $5,900 per life year.

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
A new decision model for cost-utility comparisons of chemotherapy in recurrent MBC[46]	Hutton	1996	UK	Markov model	Docetaxel vs. paclitaxel.	2nd-line therapy: Patients with anthracycline-resistant MBC	*Docetaxel:* 0.6016 *Paclitaxel:* 0.5111	*Docetaxel:* £8,233 *Paclitaxel:* £8,013 (£GBP, 1994)	Incremental cost-utility ratio for docetaxel vs. paclitaxel of £2431 per QALY (£7 per healthy day)

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
A trial-based cost-effectiveness analysis of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for postmenopausal advanced breast cancer[47]	Karnon	2003	UK	A trial based CEA	Letrozole vs. Tamoxifen	1st and 2nd-line therapy: Postmenopausal women with ABC	QALYs per 1000 patients: 1st-line letrozole followed by 2nd-line tamoxifen: 1,171 1st-line tamoxifen followed by 2nd-line letrozole: 1,012	£, year unknown per 1000 pts: 1st-line letrozole followed by 2nd-line tamoxifen: 4,765,088 1st-line tamoxifen followed by 2nd-line letrozole: 3,417,939	Base-case analysis: 1st-line letrozole followed by 2nd-line tamoxifen versus 1st-line tamoxifen followed by 2nd-line letrozole: ICER of £ 8514 / QALY 95% CI (6,083 – 23,558)
A Stochastic Economic Evaluation of Letrozole vs. Tamoxifen as a 1st line HT for ABC in Postmenopausal Patients[48]	Karnon	2003	UK	Markov model	Letrozole vs. tamoxifen.	1st-line therapy: Postmenopausal patients with ABC that is ER and/or PgR positive or of unknown receptor status.	*Letrozole:* 4.182 years *Tamoxifen:* 3.468 years	*Letrozole:* £11,303 Tamoxifen: £9,631 (£GBP, 2000)	Mean incremental cost per LYG of £2,342 and a mean cost per QALY gained between £2,927 and £3,969 for letrozole

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Cost-Effectiveness Analysis of Exemestane Compared with Megestrol in ABC A Model for Europe and Australia[49]	Lindgren	2002	Australia and Europe (Belgium, France, Germany, Italy, The Netherlands, Spain and UK)	Hazard-driven model	Exemestane vs. megestrol.	2nd-line therapy: Postmenopausal women with progressive ABC after therapy with tamoxifen.	*Exemestane*: 758.5 days (1,080 days) 1,102.8 days (lifetime) *Megestrol*: 696.3 days (1080 days) 929.3 days (lifetime)	*Exemestane*: €16,366 (1080 days) €23,293 (lifetime) *Megestrol*: €14,359 (1080 days) €19047 (lifetime) (€EUR, 1999)	When running the model for 1080 days, the CE of exemestane varied between about €5,000 and €13,000 per LYG; the total expected CE (until no survivors left) ranged from €3,700 Germany) to €9,100 (Netherlands)
Cost-utility analysis for advanced breast cancer therapy in Germany: results of the fulvestrant sequencing model[50]	Lux	2009	Germany	Markov model	Starting with 1st-line hormonal therapy followed by subsequent lines of therapy (with or without fulvestrant)	2nd-line therapy: Postmenopausal women with HR+ metastatic / ABC	Cohort A (with fulvestrant): 1.15 QALY per patient Cohort B (without fulvestrant): 1.13 QALY per patient	Cohort A (with fulvestrant): €13,356 per patient Cohort B (without fulvestrant): £13,920 per patient	The cohort with fulvestrant dominates the cohort without fulvestrant

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Cost Utility and Budget Impact of Third-Generation Aromatase Inhibitors for ABC: A Literature-Based Model Analysis of Costs in the Italian national Health Service[51]	Marchetti	2004	Italy	Markov model	Anastrozole vs. tamoxifen Letrozole vs. tamoxifen	1st-line therapy: Postmenopausal women with ER+ metastatic breast cancer.	*Anastrozole:* 18.80 quality-adjusted months *Letrozole:* 18.73 quality-adjusted months *Tamoxifen:* 16.10 quality-adjusted months	*Anastrozole:* €22,505 *Letrozole:* €23,777 *Tamoxifen:* €20,076 (€, 2003)	Baseline analysis produced ICERs of €10,795 (95% CI, €7,737-€12,899) for anastrozole and €16,886 (95% CI, €9,117-€15,465) per QALY gained for letrozole
Cost Effectiveness of Letrozole in the Treatment of ABC in Postmenopausal Women in the UK[52]	Nuijten	1999	UK	Semi-Markov model	Letrozole vs. megestrol.	2nd-line therapy: postmenopausal women with ABC who had previously failed to respond or relapsed following 1st-line or adjuvant anti-oestrogen therapy	*Letrozole:* 2.1 years (25.3 months) *Megestrol:* 1.9 years (21.5 months)	*Letrozole:* £7,547 *Megestrol:* £6,820 (£GBP, 1996)	ICER of £3,588 per LYG

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Economic Evaluation of Letrozole in the Treatment of ABC in Postmenopausal Women in Canada [53]	Nuijten	2000	Canada	Modified Markov model	Letrozole vs. megestrol acetate (MA)	2nd-line therapy: Postmenopausal women with ABC with hormone receptor-positive tumours	*Letrozole:* 28.26 months *MA:* 25.74 months	*Letrozole:* $20,068 *MA:* $19,007 ($Can, 1996)	The ICER for letrozole 2.5 mg with respect to MA was $5,051 per LYG
Cost-Effectiveness of Anastrozole vs. Tamoxifen as First-Line Therapy for Postmenopausal women with ABC [54,55]	Simons	2003	USA	Trial-based model	Anastrozole vs. tamoxifen	1st-line therapy: Women aged >65 years	*Anastrozole:* 8.8 months/ 9.7 months *Tamoxifen:* 4.6 months/ 5.1 months (QATTP with uniform utility weight of 0.5/QATTP with utility weight graded by severity)	*Anastrozole:* $18,843 Indemnity $22,917 PPO $21,587 POS $18,431 HMO *Tamoxifen:* $28,521 Indemnity $37,189 PPO $34,301 POS $27,495 HMO ($US, 2000)	Incremental cost reductions in total costs ranged from $9,064 (HMO) to $14,273 (PPO) in favour of anastrozole depending on the type of health care insurer

Table B41 Summary list of other cost-effectiveness evaluations identified in search of bibliographic databases									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Economic evaluation of antiaromatase agents in the second-line treatment of MBC[55]	Verma	2003	Canada	Markov model	Anastrozole vs. megestrol Exemestane vs. megestrol Letrozole vs. megestrol Anastrozole vs. exemestane Anastrozole+ exemestane vs. letrozole	2nd-line therapy: Postmenopausal patients with hormone-sensitive MBC who had failed tamoxifen	*Anastrozole:* 130.46 weeks *Exemestane:* 130.46 weeks *Letrozole:* 123.39 weeks *Megestrol:* 123.39 weeks	*Anastrozole:* $41,000 *Exemestane:* $41,000 *Letrozole:* $39,500 *Megestrol:* $39,800 ($Can, 2000)	Exemestane and anastrozole patients experienced higher costs and increased survival compared to megestrol patients, at a cost of $9,000 per LYG; letrozole cost $300 per patient less than megestrol, with the same benefit (letrozole patients spent longer in the less-expensive hormonal care phase, while megestrol patients spent longer in the more-expensive ongoing care phase)
Abbreviations: ABC – advanced breast cancer; CT- chemotherapy; ER+ - oestrogen receptor positive; ICER - incremental cost-effectiveness ratio; Indemnity - indemnity plan; LYG - life year gained; HMO - health maintenance organization; HT - hormonal therapy; MBC – metastatic breast cancer; PF - progression free; PgR+ - progesterone receptor positive; POS - point of service; PPO - preferred provider organizations; PT - palliative therapy; QALY(s) - quality-adjusted life year(s); QATTP - quality-adjusted time to progression.									

Table B42 Summary list of cost-effectiveness evaluations identified from systematic review of conference proceedings									
Study	**Author**	**Year**	**Country where study performed**	**Summary of model**	**Intervention vs. comparator**	**Patient population**	**QALYs (or LYG)**	**Costs**	**ICER (per QALY gained)**
Economic evaluation of fulvestrant as an additional endocrine step in the treatment sequence for hormone-receptor positive advanced and metastatic breast cancer in Israel[56]	Greenberg D, et al.	2009	Israel	Markov model	With fulvestrant (2nd or 3rd line therapy) vs. without fulvestrant	Postmenopausal women with ER+ ABC or MBC	*Addition of fulvestrant (2nd line) vs. without fulvestrant:* 0.04 QALY gain *Addition of fulvestrant (3rd line) vs. without fulvestrant:* 0.03 QALY gain	*Addition of fulvestrant (2nd line) vs. without fulvestrant:* NIS8,000 cost-saving per patient *Addition of fulvestrant (2nd line) vs. without fulvestrant:* NIS13,000 cost-saving per patient	Not reported
A cost-utility analysis of fulvestrant in treating recurrent metastatic breast cancer[57]	Park SY, et al.	2009	Korea	Markov model	Cohort A (Fulvestrant as sequenced treatment) vs.cohort B (without fulvestrant as a sequenced treatment)	Postmenopausal women with hormone receptor-positive local advanced or recurrent metastatic breast cancer	*At 10-years:* *Cohort A (with Fulvestrant);* 1.037 QALY *Cohort B (without Fulvestrant):* 0.822 QALY	*At 10-years:* *Cohort A (with Fulvestrant);* US$16,265 *Cohort B (without Fulvestrant):* US$13,562	ICER of cohort A vs. cohort B; $9,513 per QALY

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[2] or Philips et al. (2004)[3]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

The critical appraisal of the 19 relevant full-text cost-effectiveness studies that have been identified and summarized in section 6.1.2 was conducted using the Drummond and Jefferson (1996) checklist. See section 9.11 in appendix 11 for the individual critical appraised summaries.

A comprehensive critical appraisal of the two conference abstracts that were identified in the search of conference websites and congresses was not possible due to insufficient information contained with the published abstracts.

6.2 De novo analysis

Patients

6.2.1 What patient group(s) is (are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.4 and 5.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient group presented in the base-case analyses the cost-effectiveness of fulvestrant 500 mg as a second-line hormonal treatment in postmenopausal women with oestrogen positive, locally advanced or metastatic breast cancer for disease relapse on or after adjuvant anti-oestrogen therapy, or disease progression on therapy with anti-oestrogen, - as per the marketing authorisation for fulvestrant 500 mg (see section 1.5).

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[2] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[3] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

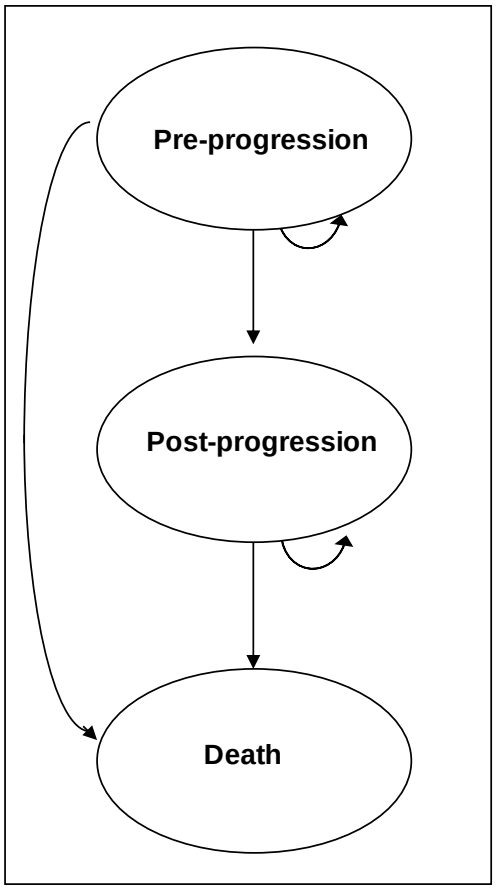
With respect to the evidence base specific to the decision problem, the patient population in clinical trial for fulvestrant 500 mg, CONFIRM, consists of a mixed population that had either received prior anti-oestrogen (57.5%) or post-aromatase inhibitor (42.5%) therapy as their last therapy. The entire population was used in the network meta-analysis and the results generated have been incorporated into the base-case analysis in the cost-utility model. The primary reason for this was that when a subgroup analysis was conducted on the CONFIRM results by post-oestrogen or post-aromatase inhibitor treatment, no significant difference was found in the TTP (see section 5.2 for further information).

Model structure

6.2.2 Please provide a diagrammatical representation of the model you have chosen.

An excel-based cost-utility model, based on a time-in-state model structure, has been developed to analyse the differences in health benefits (measured in QALYs) and costs between the relevant competing interventions. Figure 26 provides a diagrammatical representation of the health states and the patient pathways in the model.

Figure 26: Schematic for cost-utility model for the second-line hormonal treatment of advanced breast cancer patients



After reviewing the relevant published cost-effectiveness studies (see section 6.1) and evaluating the chronic nature of ABC, a time-in-state model structure was selected. The transition between the pre-progression to post-progression health state is based the clinical end point, TTP. Within the CONFIRM trial, TTP was defined as the time from randomisation to the time of the earliest evidence of objective disease progression or death from any cause prior to the documented progression. This definition of progression is commonly referred to as progression-free survival (Saad et al, 2010)[19]

Using the time-in-state approach, the proportion of patients transiting to the post-progression health state within a given cycle was estimated as the difference between the proportion of patients being alive at that time point and the proportion of patient being progression-free – i.e. the difference between OS and TTP. Given that there is an unproven relationship between TTP and OS for both fulvestrant 500 mg and the lower dose (250 mg) that was previously marketed, the time-in-state approach allows both TTP and overall survival to be incorporated independently without requiring additional assumptions. If a Markov model structure had been used, for example, it would have been necessary to derive information regarding the probability of transitioning between health states. However, based on the clinical data for TTP, it is normally not possible to differentiate how patients transition to death from pre-progression or post-progression. Therefore, if a Markov structure had been used it would have only been possible to model death after post-progression. On the other hand, the time-in-state approach allows the amount of time spent in each health state to be modelled explicitly, thereby avoiding this assumption.

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The model structure is predominantly based on the clinical guideline recommendation for the sequential systematic therapy for women that was published as part of the NICE advanced breast guidelines in 2009 (see section 2.4). Within the guidelines, it is recommended that those women that are postmenopausal and where rapid tumour response is not needed should be considered for endocrine therapy. Based on licensed use for fulvestrant 500 mg, the decision problem for fulvestrant 500 mg in the context of this economic evaluation is after patients have previously been treated with tamoxifen in either the adjuvant or advanced setting and subsequently progressed – this represents the initial pre-progression health state and this is considered and referred to as second-line hormonal treatment in the context of this submission. All patients within the cost-utility model begin in the pre-progression health state.

When patients leave the pre-progression health state, they may either die or progress and move to the post-progression health state. For those patients that progress while on second-line hormonal treatment, they subsequently move into the post-progression health state where their second-line hormonal therapy is stopped and they are considered for a further line of hormonal

therapy, up to three sequential lines of chemotherapy and then supportive palliative care. This has been incorporated into a single health state as these subsequent health states do not represent the decision problem.

For an ABC patient that has progressed while on a second-line hormonal therapy, the clinical decision as to whether the patient should be prescribed a further line of hormonal therapy is dependent on a number of factors. One factor of particular interest is the extent and duration of any previous response to endocrine therapy, as this is likely to be an indicator as to whether the patient will respond to another hormonal treatment. As such, there are a number of patients that will not be considered appropriate for a further line of hormonal therapy. This 'treatment skipping' has been incorporated into the cost-utility modelling within the post-progression health state. Further treatment skipping has also been incorporated to the subsequent lines of chemotherapy treatment, although all patients that progress while on treatment will receive supportive palliative care. This is discussed in more detail in section 6.5.5.

A small number of the relevant economic evaluation studies identified in the systematic literature review modelled the pre-progression health state as two distinct health states based on whether the patients experience an objective response. These would be represented as a pre-progression (stable disease) health state and pre-progression objective response health state. This approach was not considered appropriate for this decision problem, given that objective response is not routinely assessed and considered clinically relevant in the UK. Furthermore, it was expected this approach would increase uncertainty for the clinical results due to the smaller sample size associated with responders and the non-responder sub-groups.

6.2.4 Please define what the health states in the model are meant to capture.

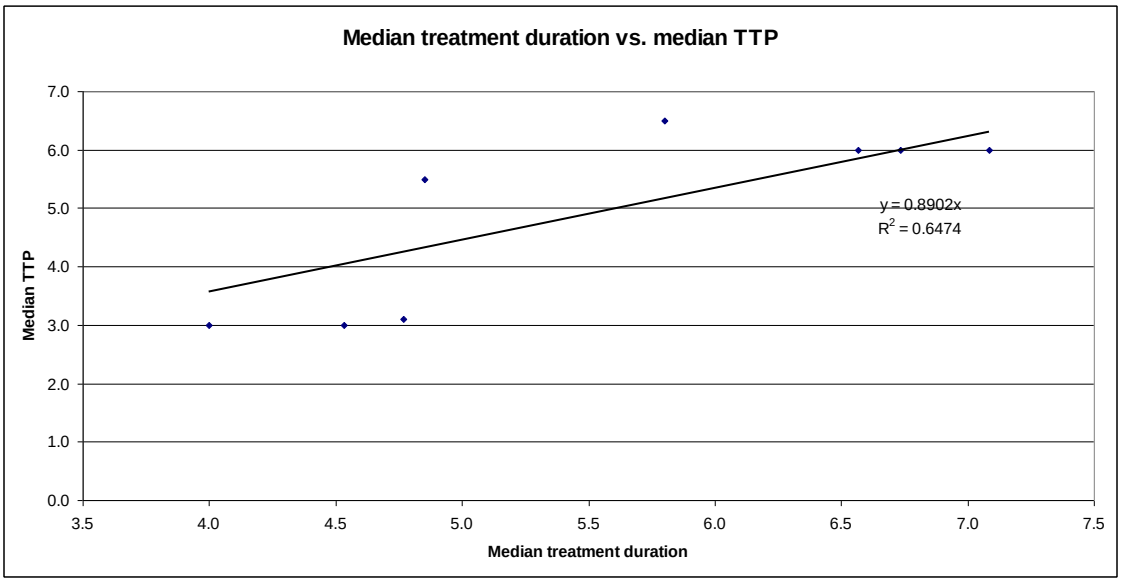
There are three mutually exclusive health states represented in the model: pre-progression, post-progression and death.

The pre-progression health state represents those patients that receive second-line hormonal therapy and are stable or responding to therapy. This health state represents the decision problem outlined in the scope and is the starting point in the model and where patients are initiated on fulvestrant 500 mg therapy (in-line with the current marketing authorisation) or its competing alternatives, anastrozole, exemestane and letrozole.

Patients in the pre-progression health state can then either die or if their disease progresses while on second-line hormonal therapy, they move to the post-progression health state. The duration of second-line hormonal treatment was assumed to be the same as the amount of time spent in the pre-progression health state given that the average duration of treatment was not consistently reported in the clinical trials. This assumption was based on the

positive relationship between the median TTP and the median treatment duration, which is illustrated in Figure 27 for the studies included in the base case analysis where median treatment duration was reported (Buzdar 2001, FINDER study 1, FINDER study 2, and CONFIRM study).

Figure 27 Relationship between median treatment duration and median TTP



Source: Buzdar 2001, FINDER study 1, FINDER study 2, and CONFIRM study

Table B43 Comparison for CONFIRM trial mean duration versus mean TTP used in the economic model

Treatment	Mean duration (months) reported in CONFIRM trial (<5 patients with no TTP event at 36 months)	Mean TTP at 36 months in economic model for CONFIRM study alone (with half-cycle correction)	Difference
Fulvestrant 250 mg	8.3	9.0	9%
Fulvestrant 500 mg	10.4	11.3	9%

As illustrated in the Table B43, the average duration of the hormonal treatment reported in the CONFIRM trial is similar to the average TTP at 36 months in the economic model for the CONFIRM study alone for both doses of fulvestrant. When a lifetime horizon is used in the economic model, the average discounted TTP values are 9.96 and 13.64 months for fulvestrant 250 mg and fulvestrant 500 mg, respectively.

In-line with the advanced breast cancer guidelines published by NICE (2009)[1], the post-progression health states captures a series of subsequent therapies the patient may receive. These can be broadly described in the following three groups:

1. Third-line hormonal therapy

2. Chemotherapy, which is based on the patients receiving up to three lines of therapy
    a. First-line chemotherapy (docetaxel)
    b. Second-line chemotherapy
    c. Third-line chemotherapy
3. Supportive Palliative Care

As explained in section 6.2.3, treatment skipping rules (where some patients may receive not receive all of the above therapies), has been applied to these sequential lines of line of therapies, to reflect clinical practice in England.

Patients in the post-progression state are assumed to remain in this state until death. The final absorbing health state in the model is death, which patients can move to from either the pre-progression or the post-progression health state. This captures death from any cause.

6.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The model structure selected captures the chronic nature of the disease and reflects the poor survival rates of ABC patients by the inclusion of overall survival data and death health state. With respect to the management of patients with ABC in the NHS in England and the decision problem, patients are considered for several sequential lines of therapies, which include hormonal treatments and chemotherapy. This has been captured within the pre-progression and post-progression health states, and is predominantly based on the recommended treatment pathway outlined in the NICE advanced breast cancer guidelines. Further information with respect to this can be found in section 6.2.3.

Advanced breast cancer is characterised by stable disease, response or progression. Disease progression has been incorporated within the model structure for the intervention of interest and its relevant comparators using TTP results from a network meta-analysis. Within the model, when a patient progresses while on second-line hormonal treatment within the pre-progression health state, they move to the post-progression health state.

6.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table B44 Key features of analysis

Factor	Chosen values	Rationale/Reference
Time horizon	Lifetime (13 years)	NICE Reference Case; 10-year survival rates for patients diagnosed at stage IV ABC is 7.4% (West Midlands Cancer Intelligence Unit, 2009)[13]
Cycle length	Monthly	Clinically relevant, given dosing schedule of treatments of the interventions of interest and standard monitoring practices in the NHS
Half-cycle correction	Yes, half-cycle correction applied	Cohort transits halfway through cycles in model [58]
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE Reference Case
Discount of 3.5% for utilities and costs	3.5% for utilities and costs	NICE Reference Case
Perspective (NHS/PSS)	NHS	NICE Reference Case
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years		

A monthly cycle length was adopted as this reflects the maximum length of time between doses of hormonal therapies and was also considered the shortest interval over which clinicians would observe a change in the course of the disease or symptoms in clinical practice

Technology

6.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

For the base-case analysis, fulvestrant 500 mg's comparators (as defined in the scope), anastrozole and letrozole have been implemented as per their marketing authorisations for ABC (table B45). Exemestane is excluded from the base-case analysis as there is no published clinical trial data based on the inclusion criteria used for the network meta-analysis where 'at least 70% of the sample had a documented ER+ receptor status' (see section 5.7.2.1). The

table below summarises the relevant ABC indication included in the marketing authorisation for these drugs.

Table B45: Summary of licensed indications for fulvestrant 500 mg, anastrozole, exemestane and letrozole.

Drug	**SPC wording (Electronic Medicines Compendium, March 2011)**
Fulvestrant 500 mg	See section 1.5
Anastrozole 1 mg	"*Treatment of advanced breast cancer in postmenopausal women. Efficacy has not been demonstrated in oestrogen receptor negative patients unless they had a previous positive clinical response to tamoxifen."*
Exemestane 25 mg	Exemestane "*is indicated for the treatment of advanced breast cancer in women with natural or induced postmenopausal status whose disease has progressed following anti-oestrogen therapy.*"
Letrozole 2.5 mg	"*First-line treatment in postmenopausal women with advanced breast cancer."* *"Advanced breast cancer in postmenopausal women in whom tamoxifen or other anti-oestrogen therapy has failed.*"

Within the model, fulvestrant 500 mg has been implemented in the model as per its marketing authorisation, with the exception of the clinical trial data included within the scope of the network meta-analysis (see Section 5). For the network meta-analysis, the entire population in the fulvestrant 500 mg trial, CONFIRM, was used. The CONFIRM population consists of a mixed that had either received prior anti-oestrogen or post-aromatase inhibitor patients, where 42.5% of patients had received prior aromatase inhibitor while the remaining patients had received prior post-anti-oestrogen therapy. The primary reason for this was that when a subgroup analysis was conducted on the CONFIRM results by post-anti-oestrogen or post-aromatase inhibitor treatment, no significant difference was found in the TTP (see section 5.2 and 6.2.1 for further information).

The scope has specified that fulvestrant 250 mg is a relevant comparator for this decision problem, however, this dose of fulvestrant is no longer licensed. Fulvestrant 250 mg was originally licensed in 2004 by the EMA, but was subsequently withdrawn when the EMA granted the marketing authorisation for fulvestrant 500 mg. Fulvestrant 250mg has been implemented into the model based on the indication in the latest SPC prior to its withdrawal, which was the same as the current indication for fulvestrant 500 mg.

A secondary analysis implemented in the cost-utility model broadens the decision problem to postmenopausal women whose disease has progressed following post-anti-oestrogen or post-aromatase inhibitor therapy in order to evaluate the cost-effectiveness of fulvestrant 500 mg versus exemestane (see section 6.7.9). This is because there is no clinical trial data for the licensed dose of exemestane in a post-anti-oestrogen population only where 'at least 70% of the sample had a documented ER+ receptor status' (see section

5.7.2.1 for inclusion criteria used for the network meta-analysis for TTP and OS) and therefore it was not possible to include this in the base-case network meta-analysis. This analysis differs from the existing marketing licenses for fulvestrant 500 mg, exemestane and letrozole and the prior marketing authorisation for fulvestrant 250 mg. The rationale for this secondary analysis was to inform the decision problem outlined by the scope.

6.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy alongside the base-case interventions and comparators. Consideration should be given to the following.

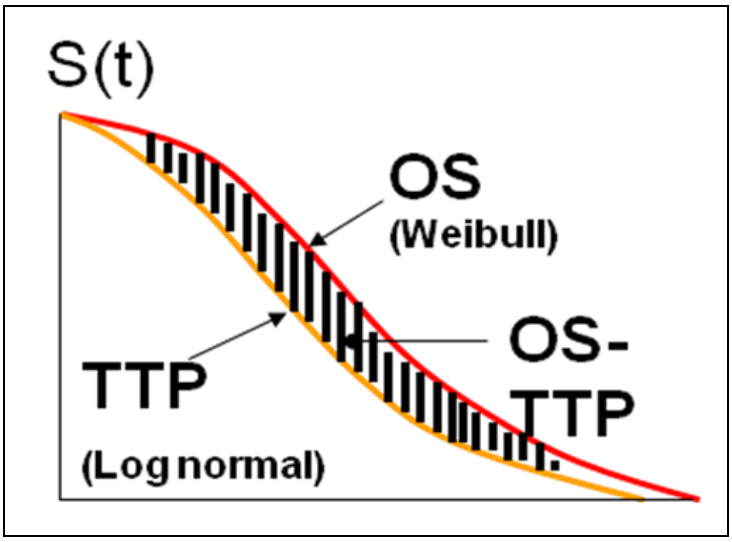
A treatment continuation rule has not been assumed

6.3 Clinical parameters and variables

6.3.1 Please demonstrate how the clinical data were implemented into the model.

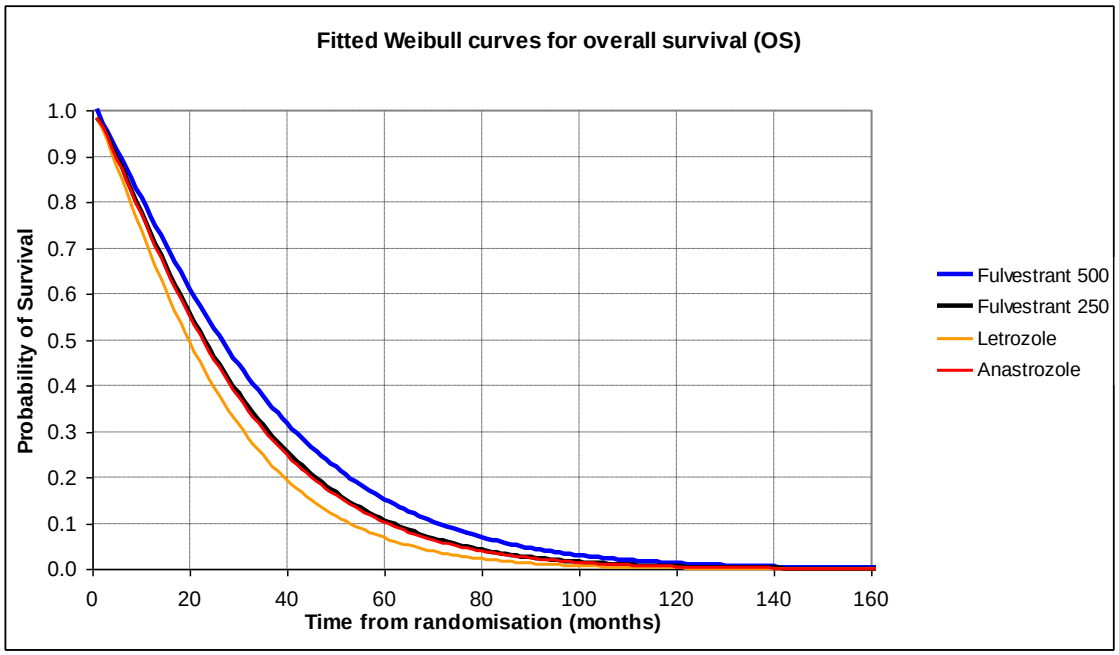
The clinical data for TTP and OS were incorporated into the model as a distribution, using the best-fitting distribution for TTP and OS (see section 6.3.7). Figure 28 illustrates how the survival curves for TTP and OS for patients receiving second line hormonal therapy were used directly to estimate the average time spent in each health state. The TTP survival curves were used to determine the distribution of patients in the 'pre-progression' health state over time. The OS curves were used to determine the proportion of patients that were in the 'Death' health state at any point in time for each arm. The difference between the OS curve and TTP curves provided the proportion of patients in the post-progression health state.

Figure 28: Time-in-state model structure and health states



Using patient-level CONFIRM trial data, the Weibull distribution was identified as the best-fitting distribution for OS (see section 6.3.7). As such, the baseline treatment, fulvestrant 250 mg, was extrapolated using the Weibull distribution. Given the hazard ratios in the CONFIRM trial were constant over time, supported by the similar values for the shape parameters for the baseline (fulvestrant 250 mg) and comparator treatment (fulvestrant 500 mg), the relative treatment effects of the alternative treatments were applied to the baseline treatment (fulvestrant 250 mg) using a pooled hazard ratio for OS from the network meta-analysis conducted by Mapi Values (see section 5.7). The curve was then extrapolated past the 36-month up period of the CONFIRM trial. Figure 29 illustrates the OS curves resulting from the network meta-analysis that are used in the economic model. See Table B34 in section 6.3.6 for a summary of the hazard ratios for each alternative treatment.

Figure 29 Overall OS as estimated with fixed-effects Weibull network meta-analysis model



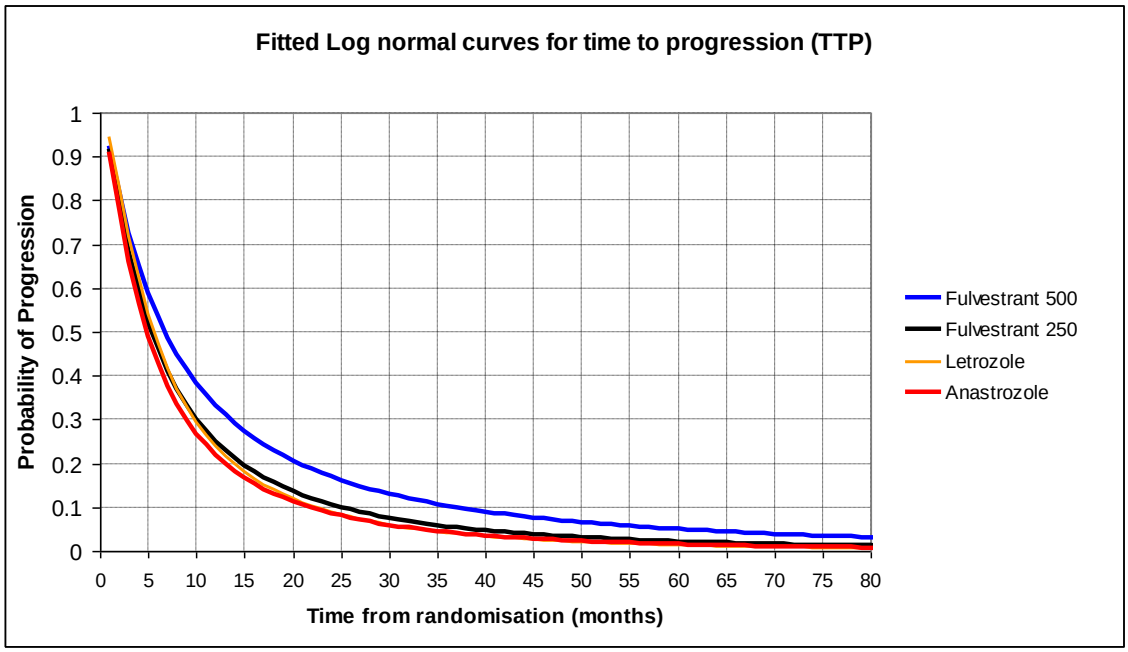
In the case of TTP, the lognormal distribution was identified as the best-fitting distribution (see section 6.3.7). As such, the baseline treatment, fulvestrant 250 mg, was extrapolated using the lognormal distribution after 36-months. However, given that the assumption of constant hazard over time is not theoretically possible with the log normal distribution. As such, the relative treatment effects of alternative treatments were applied to the baseline treatment (fulvestrant 250 mg) using the relative pooled shape and scale parameters of the log normal distribution (see section 5.7). See Appendix 17 for the Kaplan Meier data used for the TTP network meta-analysis. Figure 30 illustrates the TTP curves resulting from the network meta-analysis. See tables 8 and 9 in section 6.3.6 for the scale and shape parameters for the log normal distribution resulting from the network meta-analysis, which were used in the model to derive the probability of patients being in different health states in each cycle.

In general, minor adverse events (Grade 1 or 2) associated with hormonal treatments, such as hot flushes, arthritis and myalgia, are considered to have minor disutility implications. While injection site pain or reactions was one of the most frequently reported treatment-related adverse events in CONFIRM trial for fulvestrant 500 mg and fulvestrant 250 mg, no cases of grade 3 or higher were reported (CONFIRM clinical study report). These minor grade 1 and 2 adverse events have been excluded from the model given there is minimal cost and minor disutility implications associated with them.

It was planned to include grade 3 or 4 adverse events (as defined by the common terminology criteria for adverse events [CTCAE]) in the economic model due to the significant impact of these events may have in terms of cost and patient HRQL. Ideally, the proportion of patients experiencing adverse

events would have been analysed across the trials using a network meta-analysis to assess the risk of experiencing an adverse event relative to the incidence of adverse events in the common comparator, which could then be used to estimate the proportion of patients experiencing a grade 3 or 4 adverse event during the pre-progression stage of the economic model. However, this was not feasible because adverse events were reported inconsistently across the trials used for the post-AO network in the base case and the post-AI or post-AO network used in the secondary analysis (see Section 5.7 and 5.9). Subsequently, the alternative adverse events reported were assessed, including the serious adverse events, adverse events due to withdrawals, and finally the most common adverse events

Figure 30 Overall TTP as estimated with fixed effects lognormal network meta-analysis model



The subsequent analysis found that serious adverse events (Table B46) and adverse events due to withdrawals were reported in most of the studies, while common adverse events were reported in some of the trials. The adverse events due to withdrawals were excluded as the associated NHS costs was unclear, while common adverse events were excluded as it was assumed that most events would be grade 1 and 2 and therefore not relevant. It was decided to include serious adverse events within the model as there was sufficient data available on the number of serious adverse events to conduct a network meta-analysis. The serious adverse event data used in the model was based on any serious adverse events reported, as this was available for all the relevant RCTs used to derive the TTP and OS estimates in the base-case analysis. It is recognised that this is not ideal, as it includes both treatment-related and treatment-independent adverse events; however, this was the only data available for all comparators used in the base-case. See

section 6.3.6 for table B35, which summarises the values used for serious adverse events in the model.

Table B46: Summary of the availability of serious adverse event data within studies used in the base-case analysis for the network meta-analysis

No. trials	References of trials	Fulvestrant 500 mg	Fulvestrant 250 mg	Fulvestrant 250 mg Loading dose	Anastrozole 1mg	MA 160mg	Letrozole 0.5mg	Letrozole 2.5 mg
1	CONFIRM	☑	☑					
2	FINDER I	☑	☑	☑				
3	FINDER II	☑	☑	☑				
4	Howell_2002		☑		☑			
5	Osborne_2002		☑		☑			
6	Buzdar 1996/1998				☑	☑		
7	Buzdar_2001					☑	☑	☑

☑ serious adverse event data is available

6.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Due to the model structure and the method used to incorporate the clinical data into the model, no transition probabilities were calculated. In the model, the distribution of patients over the health states over time was imputed using an extrapolation of the trial data using the Log normal and Weibull distributions for TTP and OS, respectively. The hazard ratio for OS, which was based on the CONFIRM trial, was constant over time. However, the assumption of constant hazard over time is not theoretically possible with the log normal distribution used for the TTP.

6.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

This is not applicable as the distribution of patients over the health states over time was imputed using an extrapolation of the trial data using the Log normal and Weibull distributions for TTP and OS, respectively. See section 6.3.7 for further details regarding the extrapolation.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No

6.3.5 If clinical experts assessed the applicability of values available or estimated any values[4]:

No clinical experts were used to estimate any of the clinical parameter values used in the model.

Summary of selected values

6.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Section 6.3.1 describes how the clinical data was implemented into the model. For OS and TTP, the Weibull and the log-normal distributions, respectively, were used. Table B47 presents the hazard ratios, including the credibility intervals (2.5th and 97.5th percentile) for those treatments incorporated into the base case analysis in the model.

Table B47 Summary of variables applied in the economic model

Treatment	Hazard ratio	2.5th percentile	97.5th percentile
Fulvestrant 500 mg	0.84	0.69	1.03
Anastrozole 1 mg	1.02	0.88	1.19
Letrozole 2.5 mg	1.20	0.83	1.74

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Tables B48 and B49 presents the scale and shape parameters for the log normal distribution for the baseline comparator and the treatment alternatives based on the network meta-analysis results, which were used in the model to derive the probability of patients being in different health states in each cycle.

Table B48 Network meta-analysis TTP results (base-case): Fulvestrant 250 mg (baseline comparator)

Treatment	Scale			Log shape		
	Scale	2.5th percentile	97.5th percentile	Median of posterior distribution	2.5th percentile	97.5th percentile
Fulvestrant 250	1.676	1.600	1.750	-0.185	-0.344	-0.062

Table B49 Network meta-analysis TTP results (base-case): Difference in log normal parameters for treatment alternatives versus fulvestrant 250 mg

Treatment	Difference in scale			Difference in log shape		
	Scale	2.5th percentile	97.5th percentile	Scale	2.5th percentile	97.5th percentile
Fulvestrant 500 mg	0.229	0.167	0.293	-0.102	-0.185	-0.020
Anastrozole 1 mg	-0.094	-0.189	-0.004	0.029	-0.109	0.173
Letrozole 2.5 mg	0.045	-0.140	0.231	0.108	-0.139	0.348

Table B50 presents the proportion of patients with serious adverse events based on a network meta-analysis using a fixed-effects model conducted using the same RCTs as for the network meta-analysis for OS and TTP (see Table B46). See section 6.3.1 for further information regarding the inclusion of adverse events in the model. See appendix 18 for further details regarding the network meta-analysis conducted for serious adverse events.

Table B50 Network meta-analysis results for proportion of patients experiencing serious adverse events (base-case)

Treatment	Proportion of serious adverse events	2.5% credible interval	97.5% credible interval
Fulvestrant 250 mg	9.1%	6.4%	12.1%
Fulvestrant 500 mg	10.2%	6.5%	15.0%
Anastrozole	6.4%	4.1%	9.7%
Letrozole	8.8%	3.6%	20.2%

6.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan-Meier plots.

There are two key clinical endpoints, TTP and OS, used in the model to derive the proportion of patients residing in each health states through each cycle. Within clinical trials, time-to-event data like TTP and OS are often reported as hazard ratios ratio, which have been derived from the Cox proportional hazards model. While this is a statistically valid summary statistic, it does not provide a summary of the average survival or progression-free survival for each treatment arm, which is needed for cost-effectiveness analysis. Therefore, it is necessary to use a parametric model to estimate average survival and progression-free survival for ABC patients for the baseline and comparator treatments.

Furthermore, it was necessary to extrapolate the OS data as at the latest data cut off point in CONFIRM was based on 50% of events. Patients continue to be followed up in the CONFIRM trial and the next update is expected when 75% of events have occurred – this is anticipated between H1 2011 to H2 2012. Based on the primary data cut-off analysis of fulvestrant 500 mg versus fulvestrant 250 mg in the CONFIRM trial, the hazard ratio was 0.84, 95% CI 0.69 to 1.03. Given that the current OS data is censored in CONFIRM, the OS data has been extrapolated beyond the trial results to capture the costs and benefits for the expected duration of the patients' lifetime.

Using patient-level CONFIRM dataset, the three most commonly used parametric distributions in NICE technology appraisals (Guyot and Ouwens, 2009) that include Weibull, log logistic and log normal, for TTP and OS were evaluated for fit.

The best-fitting distribution was selected based on the fit of the curve during the trial period as well as the appropriateness of the extrapolation beyond the trial period. To assess the fit during the trial period, the curves generated were compared to the Kaplan Meier curves from the CONFIRM study. Furthermore, the Akaike's Information Criterion (AIC) was compared across the different distributions. The AIC represents a goodness of fit statistics that can be used to compare the viability of different parametric models (AIC = -2LL + 2(c + a)) (Burnham et al, 2002)[59]. When comparing two parametric models fitted to the same dataset, the model with the lowest AIC is the best fit. It should be noted that the AIC only reflects the goodness of fit where data from the CONFIRM study is present. Therefore, the AIC does not establish the most appropriate extrapolation of each distribution, which can only be evaluated by visual

inspection of the distributions versus the Kaplan Meier curves. Furthermore, the validity of the Cox proportional hazard assumption was tested for the Weibull and log logistic distributions by comparing the shape parameters of the curves.

The Weibull distribution provided the best fit for the OS data in the CONFIRM study (Figure 31). The AIC values summarised in Table B51 below demonstrate that the Weibull distribution has the lowest AIC value for both fulvestrant 250 mg and 500 mg, further supporting the selection of the Weibull distribution over the log logistic and log normal. In appendix 14 (section 9.14), further figures for the fit of the log-normal and the log-logistic are presented.

Figure 31: Overall survival (OS) from CONFIRM study using Weibull distribution

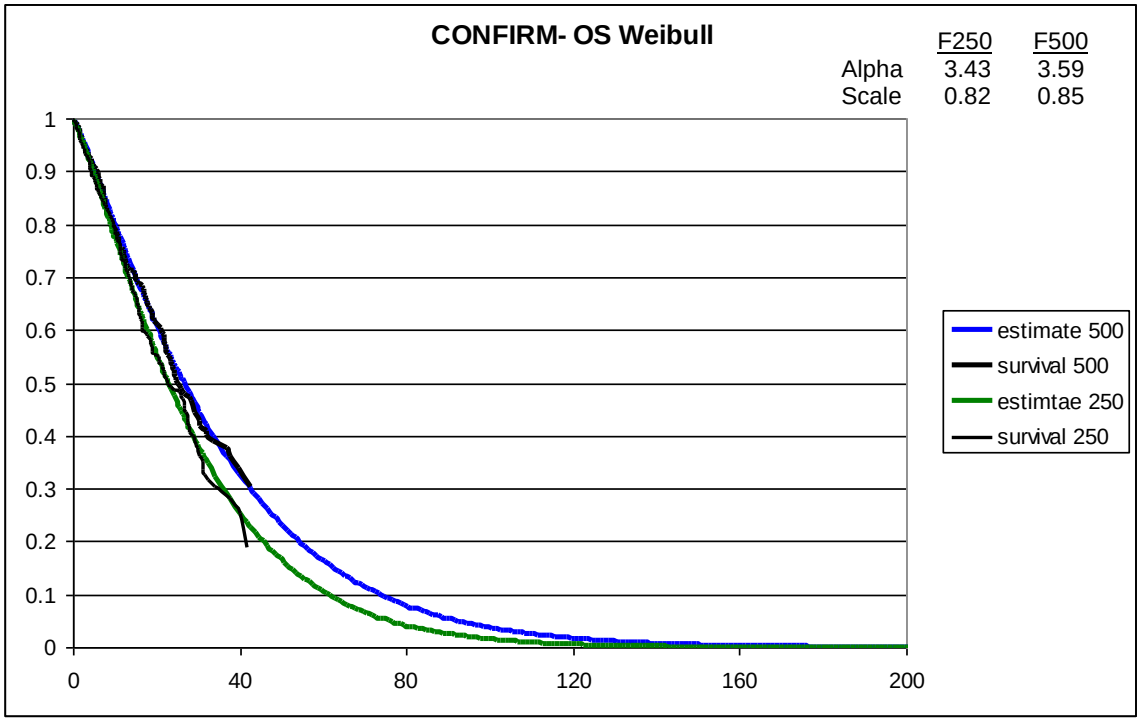


Table B51: AIC, Goodness of fit for overall survival (OS), based on the CONFIRM study

OS	**Fulvestrant 250 mg**		**Fulvestrant 500 mg**	
	Model Log likelihood	**AIC**	***Model Log likelihood***	**AIC**
Weibull	-910.00	1820.0	-814.70	1629.4
Log logistic	-912.70	1825.4	-814.90	1629.8
Log normal	-917.70	1835.4	-817.60	1635.2

The TTP analysis indicated that the log normal distribution provides the best fit to the TTP data in the CONFIRM trial (Figure 32). The AIC values summarised in Table B52 below demonstrate that the log normal distribution has the lowest AIC value for both fulvestrant 250 mg and 500 mg, further

supporting the selection of the log normal distribution over the Weibull and log logistic. In the appendix 14 (section 9.14), further figures for the fit of the Weibull and the log logistic are presented.

Figure 32: Time-to-progression (TTP) from CONFIRM study using log normal distribution

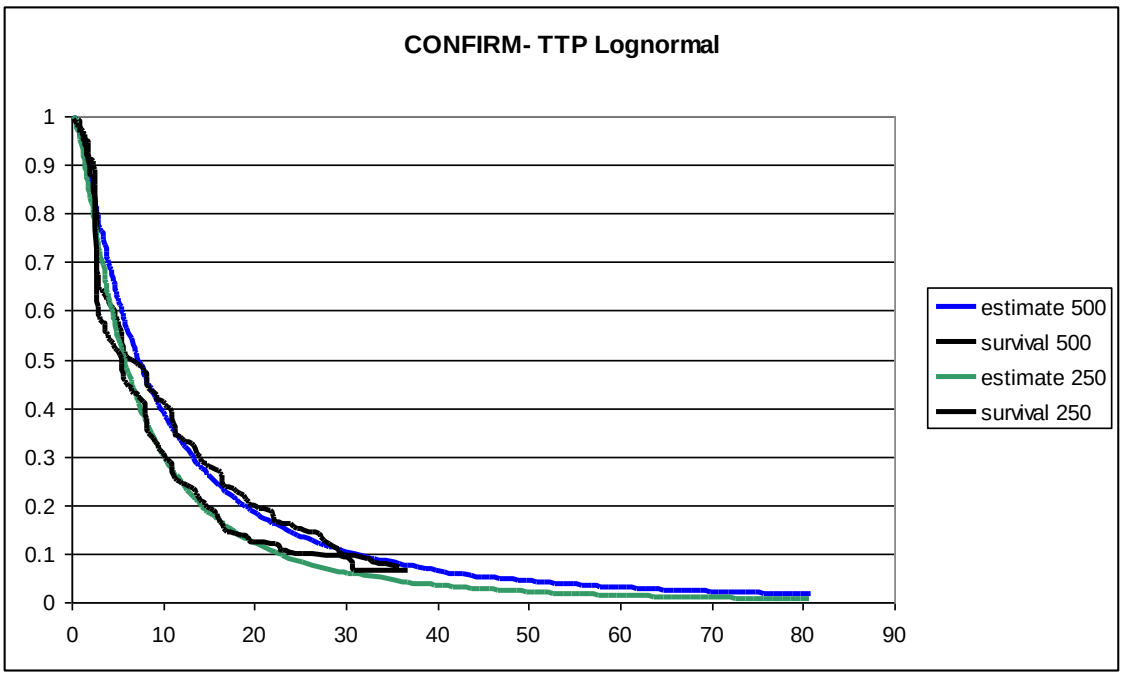


Table B52: AIC, Goodness of fit for Time-to-progression (TTP), based on the CONFIRM study

TTP	Fulvestrant 250 mg		Fulvestrant 500 mg	
	Model Log likelihood	**AIC**	***Model Log likelihood***	**AIC**
Weibull	-1041.80	2083.6	-1036.7	2073.4
Log logistic	-1013.4	2026.8	-1017.7	2035.4
Log normal	-1011.9	2023.8	-1012.6	2025.2

6.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

The key model assumptions that were used in the cost effectiveness analysis are presented in Table B53.

Table B53. Summary of key model assumptions

Assumption	Description
Discount rate	3.5% for costs and benefits (NICE reference case)
Monthly cost fulvestrant 500 mg	£522.41 (NHS List price)
Hormonal drug costs (2nd line endocrine)	Apply to patients in the pre-progression health state, which is based on TTP.
Cost of death	Excluded from model as all patients eventually die given lifetime horizon
Serious adverse events	Assumed to apply to pre-progression health state associated with second line hormonal treatment All other adverse events related to hormonal therapy assumed to be grade 1 and 2. These are excluded as no expected to be associated with significant cost or disutility
TTP	As no head-to-head RCTs of fulvestrant 500 mg versus the aromatase inhibitors exist, an estimated TTP based on indirect comparison of clinical trials in network meta-analysis assumed to follow a log normal distribution
OS	As no head-to-head RCTs of fulvestrant 500 mg versus the aromatase inhibitors exist, an estimated based on indirect comparison of clinical trials in the network meta-analysis assumed to follow a Weibull distribution with a constant hazard ratio
Resource use pre-	As no published UK resource-use data of cost-of-illness studies identified in the literature review, the resource

Assumption	Description
progression	data was based on expert opinion in the UK
Cost during post-progression	Assumed to be the same cost per month for all treatments (therefore differences across treatments are only based on different amounts of time spent in post-progression health state), based on feedback from clinical experts
Treatments during post-progression	Assumed the treatment pathway involved one of the following four treatment pathways: A) Third line hormonal therapy + supportive palliative care B) Chemotherapy + Supportive palliative care C) Third line hormonal therapy + Chemotherapy + Supportive palliative care D) Supportive palliative care
Treatment skipping (post-progression health state)	It was assumed that all patients received supportive palliative care. It was assumed that only a proportion of the patients received additional active treatments based on expert opinion.
Resource use post-progression	For third line hormonal therapy, the resource use was assumed to be the same as during second line hormonal therapy For chemotherapy and palliative care the resource use was included in the total average cost per patient incorporated from the chemotherapy model For supportive and palliative care it was assumed that no active treatment were received and that resources were related to “Package B” as proposed by the chemotherapy model
Utilities	No studies were found in the literature that provided utility values for the 2nd line treatment of ABC that would meet the NICE reference case. Utility estimates were based on published utility values by Lloyd 2006 using standard gamble in UK general population (0.72 for progressive disease; 0.44 for stable utility).

6.4 Measurement and valuation of health effects

Patient experience

6.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

There are a number of aspects that affect an ABC patient's HRQL and can be categorised into those that are disease-related and those that are treatment-related.

In terms of the disease-related aspects for ABC, these are considered to be related to:

- the degree of metastases, e.g. locally advanced or metastatic
- whether the disease is stable or progressing

The impact that the disease has on the HRQL of a patient is both physical and psychological. Among the common physical symptoms reported are pain and fatigue, which can impair the daily activities of the patient. Psychological concerns may arise from the potentially poor prognosis of ABC and the reduced HRQL. As a consequence of the condition, a key focus is on palliation of symptoms and improving HRQL.

The treatment that an ABC received can also impact on the quality of the life of the patient. If, for example, a patient is responding to treatment or has stable disease, their HRQL has been shown to improve (Earle et al, 2000; Lloyd et al, 2006) [60, 61]. Treatments can also cause disutility, particularly from treatment-related adverse events (Earle et al, 2000; Lloyd et al, 2006)[60,61] While the class of hormonal treatments are relatively well-tolerated with rare cases of grade III or IV adverse events, chemotherapy treatments are often associated with more serious and frequent side effects that may result in hair loss, nausea or vomiting.

6.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

There are a number of factors that have been identified that change the HRQL of a patient with ABC, which can include disease status (i.e. stable disease, treatment response or disease progression) as well as the stage of the disease (for example locally advanced or metastatic).

One of the distinguishing aspects of the disease that leads to a change of HRQL over time is disease progression. For example, a utility study published by Lloyd reported a disutility of -0.272 upon disease progression compared to a baseline utility for a health state for stable disease with no toxicity of 0.72.

As progression continues in breast cancer and patient reaches the end stage of the disease and requires palliative care, the HRQL further deteriorates until the patient dies. A utility value of 0.13 has been reported for a terminal metastatic patient in their last month alive (Hutton et al, 1996)[46].

Over the course of the disease, further changes to the patient's HRQL may be caused as a result of treatment. Studies have demonstrated that the HRQL of patients responding to treatment increases, while treatment-related adverse events can also cause disutility (Earle et al, 2000; Lloyd et al, 2006) [60, 61]

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

Health-related quality of life data was collected in a subgroup of patients within the CONFIRM study, with data collected in 72 patients in each of the arms of the study at baseline (see Table B54 below). The HRQL instrument used within the CONFIRM trial was the disease-specific instrument, Functional Assessment of Cancer Therapy – Breast cancer (FACT-B) questionnaire, which consists of 36 items. The HRQL data was collected in the sub-group of patients within the CONFIRM trial that lived in English and Spanish-speaking countries, since the FACT-B questionnaire was readily available in these languages.

Table B54 Summary of compliance rate - Overall FACT-B, Population = Full Analysis Set: patients with baseline FACT-B

Randomised Treatment	Protocolled Visit	Received	Expected [a]	Evaluable [b]	Compliance Rate (%) [c]	Evaluability Rate (%) [d]
Fulvestrant 500mg	Baseline	72	72	72	100	100
	3	66	72	64	89	97
	4	59	71	58	82	98
	5	46	63	46	73	100
	6	37	52	36	69	97
	7	38	44	37	84	97
	8	34	41	33	80	97
	Trt. Disc.	34	39	34	87	100
Fulvestrant 250mg	Baseline	72	72	72	100	100
	3	60	72	57	79	95
	4	57	68	56	82	98
	5	38	63	36	57	95
	6	32	42	31	74	97
	7	29	37	28	76	97
	8	24	33	22	67	92
	Trt. Disc.	36	43	35	81	97
Total	Baseline	144	144	144	100	100
	3	126	144	121	84	96
	4	116	139	114	82	98
	5	84	126	82	65	98
	6	69	94	67	71	97
	7	67	81	65	80	97
	8	58	74	55	74	95
	Trt. Disc.	70	82	69	84	99

[a] Expected forms = One at baseline, one at treatment discontinuation (if before 24 weeks), and one for each time interval a patient entered.
[b] Evaluable forms = Forms where all domains/subscales can be determined.
[c] Compliance rate = The number of evaluable forms divided by the number of expected forms.
[d] Evaluability rate = The number of evaluable forms divided by the number of received forms.

The HRQL data was collected at each visit during the trial. The means values, with the standard deviations are presented in Table B55.

Table B55 Summary of FACT-B score over the course of the study, Population = Full Analysis Set: patients with baseline FACT-B

Randomised Treatment		Protocolled Visit Baseline	3	4	5	6	7	8	Trt. Disc
Fulvestrant 500mg	N[a]	72	64	58	46	36	37	33	34
	Mean	96.5	96.0	93.3	94.5	97.6	98.3	98.2	86.2
	SD	16.13	18.03	18.09	18.61	20.34	18.01	23.62	17.27
	Median	97.2	97.9	94.8	93.4	99.6	102.0	101.0	85.9
	Minimum	53	55	53	65	57	62	59	50
	Maximum	130	139	138	137	137	134	141	116
Fulvestrant 250mg	N[a]	72	57	56	36	31	28	22	35
	Mean	95.0	96.7	93.0	88.2	94.7	93.0	92.8	84.5
	SD	20.73	20.06	22.05	18.71	20.04	20.67	22.64	23.17
	Median	94.9	97.0	89.0	84.2	94.3	87.9	86.8	87.0
	Minimum	42	50	52	62	66	60	64	36
	Maximum	137	142	138	137	141	133	137	127
Total	N[a]	144	121	114	82	67	65	55	69
	Mean	95.8	96.4	93.2	91.7	96.3	96.0	96.0	85.3
	SD	18.53	18.94	20.05	18.81	20.10	19.23	23.17	20.35
	Median	95.6	97.0	91.3	89.6	97.0	95.0	92.0	86.8
	Minimum	42	50	52	62	57	60	59	36
	Maximum	137	142	138	137	141	134	141	127

Baseline is defined as the last assessment prior to start of treatment.
SD Standard deviation.
[a] Number of patients with data available.

The change in FACT-B HRQL scores were evaluated, at most time points, there was a small decrement in HRQL mean scores at each visit compared to the baseline (Table B56).

Table B56 Summary of FACT-B score over the course of the study - change from baseline, Population = Full Analysis Set: patients with baseline FACT-B

Randomised Treatment		Protocolled Visit 3	4	5	6	7	8	Trt. Disc
Fulvestrant 500mg	N[a]	64	58	46	36	37	33	34
	Mean	-0.7	-2.1	-1.6	-0.2	-0.4	-0.5	-8.4
	SD	12.08	11.83	10.79	13.66	11.99	15.62	13.54
	Median	-0.5	-2.2	-0.6	-0.4	-1.0	-1.1	-7.5
	Minimum	-24	-29	-33	-24	-31	-28	-33
	Maximum	25	29	24	29	24	31	27
Fulvestrant 250mg	N[a]	57	56	36	31	28	22	35
	Mean	1.9	-2.3	-2.9	2.7	-2.7	-3.2	-9.4
	SD	11.67	14.89	15.75	16.40	17.72	18.53	18.31
	Median	4.3	-1.9	-2.0	3.0	-3.0	-3.5	-5.1
	Minimum	-29	-45	-39	-36	-44	-52	-46
	Maximum	25	25	23	40	40	38	24
Total	N[a]	121	114	82	67	65	55	69
	Mean	0.5	-2.2	-2.2	1.1	-1.4	-1.6	-8.9
	SD	11.91	13.36	13.12	14.94	14.65	16.73	16.03
	Median	1.3	-2.0	-1.4	0.3	-1.5	-1.1	-6.0
	Minimum	-29	-45	-39	-36	-44	-52	-46
	Maximum	25	29	24	40	40	38	27

Baseline is defined as the last assessment prior to start of treatment.
SD Standard deviation.
[a] Number of patients with data available.

The analysis of the longitudinal, repeated measures data collected for FACT-B was carried out using a linear mixed model. The estimated differences in the FACT-B scores for fulvestrant 500 mg versus fulvestrant 250 mg was not significant (estimated difference in FACT-B; 1.37, 95% CI -0.65 to 3.40) (see Table B57).

Table B57 Analysis (longitudinal) of FACT-B Population = Full Analysis Set: patients with baseline FACT-B

Longitudinal analysis model adjusted for baseline covariates	Estimated differences in FACT-B	Lower 95% CI	Upper 95% CI	p-value
Fulvestrant 500mg vs. Fulvestrant 250mg	1.37	-0.65	3.40	0.1838

The HRQL data due to toxicity or progressive disease was not collected in the CONFIRM trial, and therefore relevant published utility weights have been used for the post-progression health state in the model. It was considered whether the HRQL life data collected in the CONFIRM trial was the most appropriate source to use to derive the utility value for the pre-progression health state. After consideration, it was concluded based on a number of factors that it was not and that the preferred option was to use published utility values for both the pre-progression and post-progression health states. Firstly, for the reference case NICE prefers the use of the generic HRQL instrument, EQ-5D. However within the CONFIRM trial, the disease-specific HRQL instrument, FACT-B, was used. Furthermore, given that the HRQL data was collected in a small sub-group in a the trial and the comparability issues of the utility values that would be derived by mapping this data to the EQ-5D questionnaire, the preferred option was to use published utility values in the model.

Mapping

6.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

Given that the decision was taken that the HRQL data in the CONFIRM trial was not an appropriate source of data to use, no mapping from the FACT-B questionnaire to EQ-5D was undertaken.

HRQL studies

6.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 9.12, appendix 12.

A systematic literature review of utility studies in advanced or metastatic breast cancer was conducted as part of the systematic review for cost-effectiveness publications (see section 6.1). The following bibliographic databases were searched for relevant cost-effectiveness study publications using the search strategy and the inclusion and exclusion criteria outlined in section 9.12, appendix 12:

- MEDLINE
- EMBASE
- MEDLINE--in process
- EconLIT
- National Health Service Economic Evaluation Database (NHSEED)
- Health Economic Evaluation Database (HEED)

In additional to the review of published utility studies, the additional two steps were undertaken to identify any additional publications:

- the 21 relevant cost-effectiveness study publications (see section 6.1) were reviewed
- Reference lists from past HTA submissions for NICE and SMC were searched

The inclusion and exclusion criteria was based on identifying utility studies or systematic reviews of utility values in any country, although there was preference for studies in-line with NICE's reference case (i.e. preferences values elicited from a UK-based population using a choice-based method, time-trade-off).

6.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

Based on the review summarised in section 6.4.5, 10 potentially relevant sources of utility values were identified (see table below for a summary of the utility values) (Table B58). These included one systematic review published by Earle et al. in 2000 which reviewed cost-utility studies for cancer[60]. As part of the review, it identified the most number of relevant studies in breast cancer and presented utilities specifically pertaining to breast cancer.

From the review conducted, four sources of utility values were identified for hormonal therapies. Among these, none directly elicited preferences from the general public in the UK – one was based on interviewing cancer patients (country not stated) (Glasziou, 1998)[62], two were based on clinician interviews in the UK (Cameron, 2008)[40] and Belgium (Lux *et al.*, 2009)[50] and one was based on a mixture of women and health care professionals in Canada (Dranitsaris et al., 2000). Among these four studies, one study used time trade-off to elicit values (Dranitsaris et al., 2000)[63], two used the visual analogue scale (VAS) (Cameron, 2008; Lux *et al.*, 2009)[40, 50] while one used Q-TWiST (Quality-Adjusted Time Without Symptoms of disease and Toxicity of treatment) method of quality adjustment.

A further five sources for utility values were identified for chemotherapy agents. Two of the five sources, Lloyd *et al.*, 2006 and the utility values used in the, were based on eliciting preferences from 100 people in the UK general public using standard gamble. The utility values used in the gemcitabine submission were not available with the manufacturer's submission. Of the remaining sources, two were based on oncology nurses in the UK (Hutton, Brown *et al.*, 1996 and Brown *et al.*, 2001)[39,46] and one was based on methods-of-moments estimations (Briggs *et al.*, 2000)[64]

Table B58: Summary of utility studies

		Reference	Elicitation Technique	Description	Source country	Population	Health state	Utility range	95% CI, *if available*	Used in:
Economic Evaluations	**Systematic Review**	Earle et al., 2000[60]	Literature (VAS, TTO, SG)	Systematic review provided range of utilities from 40 identified CUAs, breast cancer represented the largest share of CUAs reviewed with 32.5% of articles pertaining to breast cancer.	No restrictions (English language)	Breast cancer patients	Terminal MBC (last month)	0.16-0.54	_	2 studies by Karnon et al., 2003[47,48]
							Febrile neutropenia +/- sepsis requiring hospitalization	0.20-0.47	_	
							CT-induced gastrointestinal toxicity requiring hospitalization	0.48	_	
							Progressive MBC, depending on toxicity from treatment	0.41-0.69	_	
							Febrile neutropenia without hospitalization for MBC on a II-line taxane	0.66	_	
							Stable MBC, depending on toxicity from treatment	0.50-0.80	_	
							Partial response to II-line taxane for MBC, depending on toxicity	0.53-0.81	_	

							Supportive care with palliative CT for MBC	0.82	_	
							Stable MBC, not on therapy	0.58-0.86	_	
							Supportive care with palliative HT for MBC	0.92	_	
							Adjuvant CT for BC, depending on regimen and toxicity	0.94-0.99	_	
							Adjuvant radiotherapy for BC	0.97	_	
							MBC in complete remission and off therapy	0.99	_	
							Diagnostic work-up for BC; false-positive breast screen followed by a benign biopsy	0.99	_	
							Adjuvant tamoxifen for 2 to 5 years	0.98-1.00	_	
mic Evaluat	**nal Therap**	Glasziou, 1998[62]	Q-TWiST	Q-TWiST method of quality adjustment	n/a	Cancer patients	Time with any toxicity*	0.5	*utility weight graded by severity: mild=0.7; moderate=0.5; severe=0.3	Simons *et al.,* 2003[54]

								Public volunteers/ Health care workers	**Public volunteers/ Health care workers**	
		Dranitsaris *et al.*, 2000[63]	Time Trade-off	Quality-adjusted progression-free periods were measured as 'healthy months equivalent' for the time spent in each outcome of the decision model	Ontario, Canada	Hormonal therapy for ABC (I and II line) 25 Canadian women and 25 female health professionals (oncology pharmacists and nurses) selected at random	no response to letrozole and progression during FAC	0.45 / 0.53	(0.37-0.55)/ (0.45-0.92)	Dranitsaris *et al.,* 2000 and 2003.[42,42,63]
							no response to letrozole but response to FAC	0.67 / 0.57	(0.55-0.79)/ (0.49-0.65)	
							response to letrozole	0.80 / 0.78	(0.49-0.73)/ (0.71-0.84)	
							no response to anastrozole and progression during FAC	0.45 / 0.53	(0.37-0.55)/ (0.45-0.92)	
							no response to anastrozole but response to FAC	0.67 / 0.57	(0.55-0.79)/ (0.49-0.65)	
							response to anastrozole	0.80 / 0.72	(0.70-0.92)/ (0.66-0.78)	
							no response to MA and progression during FAC	0.45 / 0.40	(0.35-0.55) / (0.30-0.48)	
							no response to MA but response to FAC	0.64 / 0.53	(0.52-0.76) / (0.44-0.61)	
							response to MA	0.80 / 0.67	(0.69-0.91) / (0.58-0.76)	

Economic Evaluations	**Hormonal Therapy**						**With Fulvestrant/ Without**	**With Fulvestrant/ Without**	
		Cameron et al., 2008[40]	1-100 VAS	Clinician interviews	UK	Hormonal therapy for ABC (II line post AO) 7 clinicians (oncologists) interviewed	Treatment line 1 (NSAI)	0.81/0.81	_	Cameron *et al.*, 2008[40] Lux *et al.*, 2009[50]
							Treatment line 2 (AI: fulvestrant or exemestane)	0.73/0.73	_	
							Treatment line 3	0.53/0.42	_	
							Treatment line 4	0.42/0.42	_	
							Treatment line 5	0.35/ -	_	
							Best supportive care	0.19/0.19	_	
							Death	0	_	
							With Fulvestrant/ Without	**With Fulvestrant/ Without**	
		Lux et al., 2009[50]	1-100 VAS	Clinician interviews as part of a HE analysis for fulvestrant in the Belgian health care system.	Belgium	Hormonal therapy for ABC (II line post AO) Panel of 5 Belgian clinicians	Treatment line 1 (NSAI)	0.89/0.89	_	Lux *et al.*, 2009[50]
							Treatment line 2 (AI: fulvestrant or exemestane)	0.82/0.82	_	
							Treatment line 3	0.63/0.53	_	
							Treatment line 4	0.42/0.42	_	
							Treatment line 5	0.36/ -	_	
							Best supportive care	0.13/0.13	_	
							Death	0	_	

Economic Evaluations	**Chemotherapy**	Briggs *et al.,* 2000[64]	Methods-of-moments estimations	Beta distributions	n/a	Parameter values for the illustrative Markov model of disease progression	Quality-of-life weight for 1 cycle in the asymptomatic disease state	0.95	0.90-1.00	Cooper *et al.*, 2003[41]
							Quality-of-life weight for 1 cycle in the progressive disease state	0.75	0.60-0.90	
		Hutton, Brown *et al.*, 1996[46]	Standard gamble	Method adopted based on approach by Furlong *et al*. 1990 and others. ABC hypothetical health states	UK	30 oncology nurses selected from 2 specialist cancer centres *(other samples taken from 4 other countries not reported)*	Partial response	0.84	_	Hutton, Brown *et al.*, 1996[46]
							Partial response and severe peripheral oedema	0.78	_	
							Stable disease	0.62	_	
							Before second-line therapy begins	0.56	_	
							Partial response and severe peripheral neuropathy	0.62	_	
							Progressive disease	0.33	_	
							Sepsis	0.16	_	
							Terminal disease	0.13	_	
		Brown *et al.*, 2001[39]	Standard gamble	Method adopted based on approach by Furlong *et al.* 1990 and others. ABC health states defined without reference to a particular CT	UK	30 oncology nurses selected from specialist cancer centres *(and 150 nurses across Western Europe)*	Start of second-line therapy	0.64	±(0.15)	Brown *et al.*, 2001[39]; Benedict *et al.*, 2009[38]
							Partial complete response	0.84	±(0.12)	
							Stable disease	0.62	±(0.22)	
							Progressive disease	0.33	±(0.24)	
							Terminal disease	0.13	±(0.12)	
							Peripheral neuropathy with partial/complete response	0.62	±(0.16)	
							Severe oedema with partial/complete response	0.78	±(0.15)	
							Severe skin condition with partial/complete response	0.56		
							Febrile neutropenia and hospitalised	0.24	±(0.12)	

							Infection without hospitalisation	0.48		
							Death	0		
HTA submissions	**Chemotherapy**	Lloyd *et al.*, 2006[61]	Standard gamble	Designed to elicit societal preferences for different MBC disease health states combined with different grade 3/4 toxicities and hair loss. Health states made no explicit reference to cancer, were gender neutral, and described a 3-week period.	UK	100 members of the general public recruited from Greater London (fairly representative group of England and Wales)	Stable on treatment, no toxicity (base state)	0.715	_	Lapatinib ERG report, 2007[65]; Gemcitabine ERG report, 2006[66]; Benedict *et al*, 2009[38].
							Responding disease, no toxicity.	0.790 (+0.075)	_	
							Progressive disease, no toxicity.	0.443 (-0.272)	_	
							Febrile neutropenia	(-0.150)	_	
							Diarrhoea and vomiting	(-0.103)	_	
							Hand-foot syndrome	(-0.116)	_	
							Stomatitis	(-0.151)	_	
							Fatigue	(-0.115)	_	
							Hair loss	(-0.114)	_	
		Gemcitabine ERG report, 2006[66]	VAS and standard gamble	Survey	UK	100 members of the general public	"Academic or commercial information removed"	"Academic or commercial information removed"	"Academic or commercial information removed"	Gemcitabine ERG report, 2006[66]

6.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

The differences could not be evaluated, as the utility values collected in the trial were not mapped to EQ-5D.

Adverse events

6.4.8 Please describe how adverse events have an impact on HRQL.

Treatment-related adverse events can have an impact on HRQL, but this is largely dependent on the severity as well as the longevity of the adverse events. However, hormonal therapies are considered as well tolerated, with minimal severe side effects (see section 5.9). This is a contrast to some chemotherapy agents that have been reported to have a greater frequency of grade III or higher adverse events.

The severity of adverse events can be captured using the common terminology for adverse events (CTCAE), with adverse events graded on a scale from Grade 1 (mild adverse event) to Grade 5 (death-related to adverse event). In general, minor adverse events (Grade 1 or 2) associated with hormonal treatments, such as hot flushes, arthritis and myalgia, are considered to have minor disutility implications. While injection site pain or reactions was one of the most frequently reported treatment-related adverse events in CONFIRM trial for fulvestrant 500 mg and fulvestrant 250 mg, no cases of grade 3 or higher were reported (CONFIRM clinical study report). As a consequence of the minimal cost and minor disutility implications associated with these minor adverse events, these have been excluded from the cost-effectiveness modelling.

As part of the cost-effectiveness model, the costs associated with serious adverse events were incorporated in the absence of Grade III or Grade IV adverse event data across the comparators. The disutility associated with these events was not modelled due to the short duration associated with the hospitalisation (5 days), and it was therefore concluded these would have minimal impact on overall QALYs accrued in the model.

While the hormonal therapies are associated with some long-term side effects, such as bone loss, fractures and increased cardiovascular risk, given the prognosis of ABC patients, these were excluded on the model. Furthermore, many metastatic breast cancer patients may have visceral metastases and thus will be receiving bisphosphonate therapy, which is a common therapy for bone loss.

Quality-of-life data used in cost-effectiveness analysis

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The HRQL data due to toxicity or progressive disease was not collected in the CONFIRM trial, and therefore relevant published utility weights have been used for the post-progression health state in the model. It was considered whether the HRQL life data collected in the CONFIRM trial was the most appropriate source to use to derive the utility value for the pre-progression health state. After consideration, it was concluded based on a number of factors that it was not and that the preferred option was to use published utility values for both the pre-progression and post-progression health states. Firstly, for the reference case NICE prefers the use of the generic HRQL instrument, EQ-5D. However within the CONFIRM trial, the disease-specific HRQL instrument, FACT-B, was used. Furthermore, given that the HRQL data was collected in a small sub-group in a the trial and the comparability issues of the utility values that would be derived by mapping this data to the EQ-5D questionnaire, the preferred option was to use published utility values in the model.

Based on the sources of utility data identified in section 6.4.6, none of these were consistent with all characteristics outlined in the NICE reference case – i.e. utilities were elicited from the general public in the UK using a choice-based method (the time trade-off method). However, two sources (Lloyd et al. 2006)[61] and utility values used in the gemcitabine NICE STA submission in 2006[67] were considered very similar to the NICE reference case, with utilities elicited from the general public in the UK using an alternative choice-based method, standard gamble. However, it was not possible to use the utility figures from the gemcitabine submission as these were academic or commercial information removed from the publicly available submission. While it is recognised that the Lloyd et al. study has a degree of uncertainty given that the preferences are elicited from a relatively small sample of the general public in the UK and uses standard gamble, this is considered the best available utility data for this cost-utility analysis.

Within the Lloyd *et al.* 2006 study[61], UK societal preferences were elicited for the base state of metastatic breast cancer with stable disease and no toxicity and utility gains and decrements associated with treatment response, progression and grade 3/4 adverse events. The health states were developed from a literature review and through interviews with clinical experts. Lloyd et al used a logit model describing the coefficients according to tumour status, age of the respondent and the presence of adverse events. Table B59 summarises the utility values used for the three health states in the model. As explained in section 6.3.8, the disutility associated with minor adverse events and long-terms adverse events have been excluded from the model.

Table B59 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Standard error	Reference in submission	Justification
Pre-progression	0.72	0.014	Lloyd *et al.*, 2006	Most appropriate utility values available, in relation to NICE reference case
Post-progression	0.44	0.016	Lloyd *et al.*, 2006	Most appropriate utility values available, in relation to NICE reference case
Death	0	n/a	n/a	Convention

As Table B59 shows, the patient is considered to have a higher HRQL in the pre-progression health state compared to after disease progression. A patient is expected to have a utility of 0.72 in the pre-progression health state and after disease progression this decreases by 0.272 to 0.44. Both the values for the pre-progression and post-progression health state utility was derived from Lloyd 2006. The utility value used for death was zero, as per convention.

6.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

Not applicable.

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

6.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

The pre-progression health state in the model reflects the HRQL of the patient while they are receiving second-line hormonal therapy. For the purposes of the model, this is assumed to be constant irrespective of the length of time spent in this health state. However, evidence suggests that response to treatment is associated with an improvement of HRQL. For example, in Lloyd *et al*. 2006[61], treatment response was associated with an increase of 0.075 in utility compared to the baseline state (stable disease with no toxicity). It was considered clinically inappropriate to include objective response as a separate health state in the cost-utility model as this clinical endpoint is not routinely assessed in the UK. Therefore, in the model, a patient is considered to have the same HRQL whether they are stable or responding to treatment.

Within the post-progression health state, this represents a weighted average of the time and the HRQL a patient experiences after disease progression on their second-line hormonal therapy. Therefore, it has been considered appropriate to assign an average utility value that is constant, irrespective of the length of time spent in the state, which is represented by stable disease with disease progression and no toxicity.

6.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

A small number of the relevant cost-effectiveness studies identified in the systematic review conducted (see Section 6.1) modelled the pre-progression health state as two health states – one representing pre-progression (stable disease) and pre-progression (objective response). Evidence suggests that response to treatment is associated with an improvement of HRQL. For example, in Lloyd *et al*. 2006[61], treatment response was associated with an increase of 0.075 in utility compared to the baseline state (stable disease with no toxicity). However, as previously explained in section 6.2 and 6.4.11, it was considered inappropriate to include objective response as a separate health state in the cost-utility model as this clinical endpoint is not routinely assessed in the UK. Therefore, in the model, a patient is considered to have the same HRQL whether they are stable or responding to treatment. No further potentially relevant health effects were identified in the literature or clinical trial and excluded from the analysis.

6.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

All patients within the cost-utility model begin in the pre-progression health state. It has not been assumed that the baseline HRQL is different from the pre-progression health state.

6.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

The HRQL is assumed to be constant over time for each health state.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

6.5 Resource identification, measurement and valuation

NHS costs

6.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

The NHS schedule for reference cost for 2009-2010 and the NHS Indicative tariff for 2010-2011 were examined to identify the relevant codes for the administration of hormonal therapies and management of patients with ABC[68]. For the current tariff, fulvestrant 500 mg has been included within tariff as a hormonal antagonist. However, it was recognised that the current tariff would not sufficiently reimburse hospital trusts given the monthly cost of the treatment and the associated administration costs in the outpatient setting. For the purposes of this cost-effectiveness analysis, the administration costs associated with the hormonal therapies has been costed separately to the tariff to better reflect the true costs to the NHS. Furthermore, it is expected that fulvestrant may be excluded from the tariff in the future.

Routine patient monitoring costs for oncology patients were identified and relevant costs that were used in the modelling can be found in sections 6.5.5 and 6.5.6.

6.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

Given no NHS reference costs directly related to the administration costs or hormonal therapies could be found, it has been necessary to use general codes in the NHS reference costs and NHS indicative tariff related to oncologist visit and outpatient visits with nurses to estimate the cost of administration for hormonal therapies. In cases where unit costs were not identified in these sources, unit costs were sourced from the PSSRU Unit costs of health care and social care (2010)[69] or from previous cost-effectiveness studies where values were reported. Where necessary, these costs were inflated to 2009/10 values using the PSSRU Hospital and Community Health Services pay and price index. Further details of this are provided in section 6.5.5 and 6.5.6.

Resource identification, measurement and valuation studies

6.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and

consider published and unpublished studies. The search strategy used should be provided as in section 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

A systematic literature review of published sources of resource data relevant to the decision problem was conducted as part of the systematic review for cost-effectiveness publications (see section 6.1). The following bibliographic databases were searched for relevant cost-effectiveness study publications using the search strategy and the inclusion and exclusion criteria outlined in section 9.12, appendix 12:

- MEDLINE
- EMBASE
- MEDLINE--in process
- EconLIT
- National Health Service Economic Evaluation Database (NHSEED)
- Health Economic Evaluation Database (HEED)

In addition to the review of published resource data, the additional two steps were undertaken to identify any additional potentially relevant sources:

- the resource data in the cost-effectiveness studies of hormonal therapies in the UK identified in section 6.1 were reviewed
- past HTA submissions and clinical guidelines for NICE and SMC were searched.

The literature search in the database identified one cost-of-illness in women with stage IV breast cancer in the UK[70].No further cost-of-illness studies were identified in the UK. The objective of the Remak and Brazil study was to estimate the lifetime cost of treatment for newly diagnosed patients with MBC. A summary of the paper can be found in table B60. However, the paper did not provide a breakdown of resource use by each treatment option or line of therapy; therefore, it was considered to contain insufficient information to use in the model.

Table B60: Summary of cost of illness study on ABC interventions in the UK

Study	Objectives	Methodology	Clinical data source	Outcomes	Costs (data source)	Results
"Cost of managing women presenting with stage IV breast cancer in the United Kingdom" [70]	To estimate lifetime cost of treatment for patients in the UK presenting with stage IV breast cancer	Incidence approach	Four English cancer registries and the Scottish Cancer registry, as well as the Royal Marsden Hospital database	Lifetime cost of metastatic (stage IV) breast cancer treatment per patient (and average monthly costs per patient) and total population costs	Direct healthcare resources/ costs (Medical staff salaries, overheads as well as equipment costs were included in the calculations.) Unit costs: £GBP 2000 (British National Formulary and the MEDTAP Database of International Unit Costs)	Treatment for MBC was estimated to cost £12 502 (95% CI; £9008–£16 701) over the lifetime of each patient; translating this individual cost to the population level, it was calculated that treating all patients in England that present with stage IV breast cancer in 1 year costs approx. £22 million, and treating all patients throughout the UK costs approx. £26 million

Of the 21 cost-effectiveness studies identified in section 6.1, there were five relevant cost-effectiveness publications for hormonal therapies in the UK. Table B61 below summarises the resources use and costing of subsequent therapies.

Table B61: Resource use and costing of subsequent lines of therapy in UK-based hormonal therapy models

Reference	Subsequent lines of therapy	Assumptions	Source of resource use	Costing details
		For resource utilisation		
Drummond *et al.,* 1999[44]	Investigated 4 additional therapies in 55 patients from three study sites: chemotherapy (CT), endocrine therapy (HT), radiotherapy, and other	Data collected did not allow for calculations so lifetime costs were derived from literature	Richards *et al.*, "ABC use of resources and cost implications", 1993	Updated to 1998 values using hospital and community health services pay and price inflation index
Nuijten *et al.,* 1999[52]	Defined the following mutually exclusive health states: 3rd-line HT (with AI/progestin), chemotherapy (CT) 1, chemotherapy (CT) 2, observational care, end-stage palliative care, death	Treatment patterns after 2nd-line HT were assumed to be equal in both treatment arms Max. of 6 months CT duration No 4th-line HT or combination therapies	Units of healthcare utilisation were derived from expert opinion (panel of clinicians, telephone interview with specialist oncology nurse)	Official price lists from 1996
Karnon and Jones, 2003[48]	Alternative HT (max. of three lines in total), alternative chemotherapies (max. of two lines), observational care, end-stage palliative care, death	Same as Nuijten *et al.,* 1999.	Nuijten *et al.,* 1999	UK NHS national schedule for reference costs and from the British National Formulary (BNF)
Karnon *et al.,* 2003[47]	No data informing differential treatment pathways between the alternative therapies from the end of HT identified	Prognosis independent of 1st- and 2nd -line HT	Nuijten *et al.,* 1999	NHS Trust, consultation and hospital costs, BNF
Cameron *et al.,* 2008[40]	3rd-line HT (exemestane), CT 1 (docetaxel), CT 2 (capecitabine), best supportive care, death	Treatment skipping was possible	Derived from clinician survey	PSSRU costs for 2005, BNF

Among the five studies, three studies (Nuijten et al., 1999[52]; Karnon and Jones, 2003[47]; Karnon et al., 2003[48]) were based on resource data from the same study, Nuijten et al. (1999)[52]. The resource data used in the Nuijten et al. study were derived from expert opinion (panel of clinicians, telephone interview with specialist oncology nurse). The Drummond et al. cost-effectiveness study published in 1999[44] used a cost-of-illness study published in 1993, however, this was excluded an appropriate source as it was conducted over 15 years ago and is unlikely to reflect current clinical practice. The most recent cost-effectiveness study, published by Cameron et al[40], used data from a clinical survey in the UK. The data used for this publication was obtained, as an author on the publication is an AstraZeneca employee. While the Cameron *et al*. clinician survey contained some useful data, there were still some data gaps for the information needed. Section 6.5.4 describes the expert opinion sought to address these data gaps.

6.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

No relevant source of resource data in the UK was identified (section 6.5.3). However, an economic evaluation conducted by Nuijten *et al*. (2000)[53] evaluating the cost-effectiveness of letrozole as a second-line hormone therapy for the treatment of ABC in postmenopausal women in Canada, used treatment-independent resource use for routine care collected from eight experts via interviews. This source was also previously used in the UK cost-effectiveness study by Karnon *et al*. (2003) [48]evaluating the cost-effectiveness of hormonal treatments in ABC in the UK (Table B61). While the patient population were similar to that of the decision problem, it was recognised that this Canadian data may not be clinically relevant to the England. As such, the data was presented to clinical experts in England to validate the values and where they were deemed invalid by the clinical experts, they were asked to provide appropriate estimates (section 6.5.4).

Several clinicians that were known by AstraZeneca to regularly treat patients with breast cancer were invited to participate in the clinician survey. Two clinicians in England agreed to participate in the survey and a face-to-face interview was arranged. A questionnaire outlining the questions and the data that needed to be validated was used as part of the interview.

A copy of the questionnaire used has been included in the Appendix 9.15, which includes the questions that were asked.

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[6] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

The cost for each hormonal treatment relevant to the decision problem and the treatment-related resource use for drug administration are described in Table B62. There are no treatment-related monitoring costs associated with fulvestrant 500 mg (see section 1.13) or its comparators (fulvestrant 250 mg, anastrozole, letrozole and exemestane). More detailed information regarding the drug costs for all relevant hormonal therapies either used second-line or third-line and the treatment-related administration costs are provided below Table B62.

Table B62 Unit costs associated with the technology in the economic model per cycle (excluding first month*)

Items	Fulvestrant 500 mg	Ref. in submission	Fulvestrant 250 mg	Ref. in submission	Anastrozole	Ref. in submission	Exemestane	Ref. in submission	Letrozole	Ref. in submission
Technology cost	£522.41	MIMS March 2011	£348.27	MIMS March 2011	£74.48	MIMS March 2011	£90.03	MIMS August 2010	£92.18	MIMS August 2010
Administration cost	£79.79	NHS Reference Cost 2009-2010[68]; PSSRU, 2010[69]	£79.79	NHS Reference Cost 2009-2010[68]; PSSRU, 2010[69]	£22.00	Unit costs of health care and social care, PSSRU 2010[69]	£22.00	Unit costs of health care and social care, PSSRU 2010[69]	£22.00	Unit costs of health care and social care, PSSRU 2010[69]
Total	**£601.19**	**-**	**£427.06**	**-**	**£96.48**	**-**	**£114.18**	**-**	**£112.03**	**-**

*First month cost for fulvestrant 500mg includes loading dose and treatment initiation costs

1. Hormonal therapy costs

The unit costs for the fulvestrant and other hormonal therapy that may be used as a second or third-line hormonal treatment for patients with advanced breast cancer are presented in Table B51, as these are relevant to the pre-progression and post-progression health state (see section 6.2.4). Please note that the price per month for fulvestrant 500 mg in the first month includes an additional loading dose administered two weeks after the initial dose, and therefore the cost of fulvestrant 500 mg Is £1,044.81 in the first month (£522.41*2=£1,044.81). The administration for fulvestrant 500 mg was based on the current SPC, which states the current "recommended dose is 500 mg at intervals of one month, with an additional 500 mg dose given two weeks after the initial dose". In the economic model the cost of fulvestrant 500 mg is applied twice in the first month to represent the initial dose and loading dose, and then once in every subsequent month as per the SPC. Given that the original license for fulvestrant 250 mg was once per month, without a loading dose, the cost of fulvestrant 250 mg has been applied once per month in the economic model.

Table B63 Drug costs for hormonal therapy

Treatment	Dose description	Vial/pack	Price per vial/pack	Price per month*
Fulvestrant 250 mg	1x5ml intramuscular injections at intervals of 1 month	50 mg/mL, net price 5-mL (250 mg)	£348.27	**£348.27**
Fulvestrant 500 mg*	2x5ml intramuscular injections at intervals of 1 month, with additional dose two weeks after initial dose	2x50 mg/mL, net price 5-mL (250 mg)	£522.41	**£522.41**
Anastrozole 1 mg	1 mg daily	28 tablet-pack	£68.56	**£74.48**
Letrozole 2.5 mg	2.5 mg daily	28 tablet-pack	£84.86	**£92.18**
Megestrol acetate 160mg	160mg in single or divided doses daily	30 tablet-pack	£19.52	**£19.79**
Exemestane 25mg	25mg daily	30 tablet-pack	£88.80	**£90.03**
Medroxyprogesterone acetate 400 mg	400 mg twice daily	100 tab-pack (400mg)	£58.67	**£118.97**

NB. Cycle length in model represents 30.4 days per month (365 days / 12 months = 30.42 days)

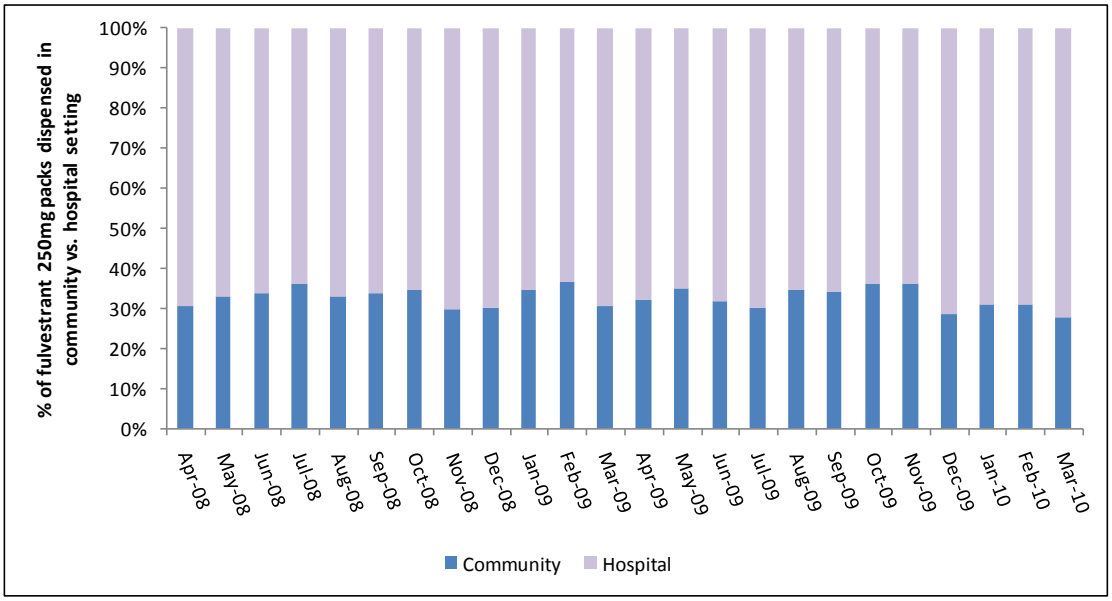
**The price per month for fulvestrant 500 represents every month after the first month. In the first month fulvestrant 500 is administered twice; Source: MIMS, March 2011*

2. Treatment-related resource use for drug administration

Based on expert opinion in the UK (see section 6.5.4), it has been assumed that to initiate a second-line hormonal treatment, whether it is fulvestrant or an aromatase inhibitor, an ABC patient has an initial consultation with an oncologist to make an assessment and determine the appropriate treatment for the patient. It was assumed that if the patient was initiated on fulvestrant 250 mg or 500 mg, they would be administered this after the initial oncologist visit by a nurse. If the patient was initiated on an aromatase inhibitor (i.e. anastrozole, exemestane or letrozole), the oncologist would provide a prescription during this initial visit. In the model, a cost of £179 has been used per initial visit with an oncologist. This is based on the 'Consultant Led: First Attendance Non-Admitted Face to Face' (Medical Oncology Code 370) cost in the NHS reference cost (NHS Trust, 2009-2010)[68].

Subsequent administrations of fulvestrant 250 mg and 500 mg may be delivered by a nurse as a 15 minute appointment either in the outpatient or primary care setting. Prior to the marketing authorisation of fulvestrant 500 mg as a treatment option for ABC, data from IMS Health has shown that approximately a third of fulvestrant 250 mg packs (32.3%) issued in the 12 month period between April 2009 to March 2010 were used in the community setting with the remaining two-thirds used in the hospital setting[71]. Furthermore, the level of use of fulvestrant 250 mg has been a consistent level over the 24 month period from April 2008 to March 2010 (figure 33). It is assumed that the location where the packs are purchased reflects the location where fulvestrant is administered – i.e. that approximately one-third of use is in the primary care setting and two-thirds is in the outpatient setting. Based on this data, it has been assumed that 32.3% of fulvestrant 250 mg and 500 mg is administered in the primary care setting for the base-case. It has been assumed that this is the minimum level of fulvestrant that will be administered in the primary care setting in the NHS in the future.

Figure 33: Proportion of fulvestrant 250 mg packs dispensed in the community versus hospital setting, April 2008 to March 2010



For those subsequent administrations of fulvestrant 250 mg and 500 mg that are delivered in the primary care setting by a nurse, the cost of a 15 minute appointment with a nurse specialist (£23) in the community from the Unit Costs of Health and Social Care (PSSRU, 20010) has been used[69].

For those subsequent administrations of fulvestrant 250 mg and 500 mg that are delivered in the outpatient appointment by a nurse, the tariff for hormonal antagonists was not believed to sufficiently reflect the administration costs associated with fulvestrant. Consequently, a cost of £105 for a follow-up outpatient appointment with a nurse from NHS Reference Costs (National Reference costs, NHS Trusts, 2009-2010)[68] was used in the model to reflect the administration costs associated with the subsequent doses of fulvestrant 500 mg and 250 mg. This was based on a 'Non-consultant led, follow-up attendance, non-admitted, face to face' (medical oncology 370) cost.

Based on expert opinion, it was determined that repeat prescriptions for anastrozole, exemestane and letrozole are provided by GPs on a monthly basis as these are oral medications. As such, within the model, the cost of refill prescription each month (after the first month) was based on a telephone consultation with general practitioner lasting 7.1 minutes (£22)[69].

Table B64 presents the treatment-related costs associated with each drug based on the resource utilisation required to initiate treatment and for treatment administration for the first month and then the subsequent months. The treatment-related administration costs fulvestrant 500 mg in the first month is £377, which includes an initial visit with the oncologist for the initial dose (£193), the administration of fulvestrant by a nurse (£105), plus the

average cost of administrating the loading dose two weeks later where 32.3% are administered in the primary care setting and 67.7% are administered in the secondary care outpatient setting (£79).

Table B64 Treatment-related administration costs for second-line or third-line hormonal therapy, assuming 32.3% of fulvestrant 500 mg and 250 mg administered in primary care setting (base case)

Treatment	Total for first month	Total for subsequent months
Fulvestrant 500 mg	£377[1,2,3]	£79[2,3]
Fulvestrant 250 mg	£298[1]	£79[2,3]
Anastrozole	£193[1]	£22[4]
Exemestane	£193[1]	£22[4]
Letrozole	£193[1]	£22[4]

[1]*source: NHS Reference Cost 2009-2010 (NHS Trusts Consultant Led: First Attendance Non-Admitted Face to Face, Medical Oncology Code 370)*[68]

[2]*source: NHS Reference Cost 2009-2010 (NHS Trusts Non-Consultant Led: Follow up Attendance Non-Admitted Face to Face,Medical oncology Code 370)*[68]

[4]*source:Unit costs of health care and social care, PSSRU 2010 (Per 15 minutes visit Community Nurse Specialist)*[69]

[3]*source:Unit costs of health care and social care, PSSRU 2010 (Per GP telephone consultation lasting 7.1 minutes)*[69]

Health-state costs

Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 6.2.4.

The costs included in the pre-progression and post-progression health states are described in the following sections.

Cost included in pre-progression health state

The duration of second line hormonal treatment was assumed to be the same as the amount of time spent in the pre-progression health state given that the average duration of treatment was not consistently reported in the clinical trials (see section 6.3.4 for further details).

Health care resource utilisation associated with the pre-progression health state (i.e. second line hormonal therapy) was divided into four categories:

1. hormonal therapy costs;
2. treatment-related resource use for drug administration;
3. treatment-independent resource use for routine care (such as monitoring disease progression);
4. and, resource use associated with for serious adverse events due to second-line hormonal therapy costs.

The costs associated with the hormonal therapy costs and treatment-related resource use for drug administration are described in section 6.5.5, while further detail about the adverse event cost is described in section 6.5.7.

Treatment-independent resource use for routine care

No source was identified that provided a source of resource data related to treatment-independent routine care, i.e. patient monitoring, of ABC patients on second-line hormonal therapy in the UK (section 6.5.3). However, an economic evaluation conducted by Nuijten *et al*. (2000)[53] evaluating the cost-effectiveness of letrozole as a second-line hormone therapy for the treatment of ABC in postmenopausal women in Canada, used treatment-independent resource use for routine care collected from eight experts via interviews. This source was also previously used in the cost-effectiveness study by Karnon *et al*. (2003)[47] evaluating the cost-effectiveness of hormonal treatments in ABC in the UK. While the patient population was similar to that of the decision problem, it was recognised that this Canadian data may not be clinically relevant to the England. As such, the data was presented to clinical experts in England to validate the values and where they were deemed invalid by the clinical experts, they were asked to provide appropriate estimates (section 6.5.4).

Table B65 presents the proportion of patients who are assumed to receive the specific health care service per month Please note that the original publication and the estimates collected from the clinical experts in the UK provided estimates per three-month period, which was updated to one month periods for the current model (assuming the resource use was equally distributed per month). The length of stay in hospital was estimated to be 8 days in general medicine and 6 days in the oncology ward. Please note that clinical experts in England identified that in addition to the different resources included by Nuijten et al., a nurse visit is also expected once per month. This has been included in the current economic model. In order to reflect uncertainty around these parameters, the low and high values were estimated by changing the point estimates by 20% in the probabilistic sensitivity analysis (see **Section 6.6**).

Table B65. Treatment-independent resource use used in the economic model

Health care service	% patients per month
Oncology visit	**33%**
General Practitioner visit	**10%**
Radiographer	**4%**
Biochemistry test	**33%**
Blood test	**30%**
Bone scintigraphy	**8%**
CT Scan	**20%**
Chest x-ray	**3%**
Bone x-ray	**3%**
Hospitalisation (general medicine)*	**1%**
Hospitalisation (Oncology)**	**1%**
Nurse, day ward	**99%**

*Source: Data from Nuijten 2000[53] originally estimated by Canadian experts validated by clinical experts in England; *Length of stay=8 days; **Length of stay=6 days*

Where available the unit costs were based on the National Health Service (NHS) reference costs from 2009-2010 or the Personal Social Services Research Unit (PSSRU) from 2010. In cases where unit costs were not identified in these sources the unit costs reported by Karnon et al. 2003[48] were inflated to 2009/10 using the PSSRU Hospital and Community Health Services pay and price index.

Table B66 Unit costs for the resource health care utilisation for the UK.

Resource unit costs	Cost per unit	Unit	Source
Initial oncology visit	**£192.67**	per visit	NHS Reference Cost 2009-2010 (NHS Trusts Consultant Led: First Attendance Non-Admitted Face to Face Medical Oncology Code 370)[68];
Oncology visit	**£128.69**	per visit	NHS Reference Cost 2009-2010 (NHS Trusts Consultant Led: Follow up Attendance Non-Admitted Face to Face Medical oncology Code 370)[68];
General Practitioner visit	**£36.00**	per 11.7 minute visit	PSSRU Unit costs of health care and social care 2010[69]
Radiographer	**£28.00**	per 1 hour of time	PSSRU Unit costs of health care and social care 2010
Number of biochemistry	**£1.29**	per test	NHS Reference Cost 2009-2010 (NHS Trusts

Resource unit costs	Cost per unit	Unit	Source
tests (i.e. ALT, AST, ACT)			Biochemistry Code DAP841)[68];
Blood tests	**£3.06**	per test	NHS Reference cost 2009-2010 (NHS Trusts Haematology Code DAP823)[68];
Skeletal surveys or bone scans or bone scintigraphy	**£99.33**	per test	Costed by Karnon 2003 using 2000 values[47]; Costs were inflated to 2009/10 using PSSRU Hospital and Community Health Services pay and price index[69]
Chest x-ray	**£20.15**	per test	Costed by Karnon 2003 using 2000 values[47]; Costs were inflated to 2009/10 using PSSRU Hospital and Community Health Services pay and price index[69]
Bone x-ray	**£35.99**	per test	Costed by Karnon 2003 using 2000 values[47]; Costs were inflated to 2009/10 using PSSRU Hospital and Community Health Services pay and price index
Hospitalisation (General medicine)	**£321.02**	per visit	Costed by Karnon 2003 using 2000 values[47]; Costs were inflated to 2009/10 using PSSRU Hospital and Community Health Services pay and price index[69]
Hospitalisation (Oncology)	**£480.81**	per day	Costed by Karnon 2003 using 2000 values;[47] Costs were inflated to 2009/10 using PSSRU Hospital and Community Health Services pay and price index Community Health Services)[69]
Clinical Nurse Specialist (Community)	**£22.78**	per 15 minute visit	PSSRU Unit costs of health care and social care 2010[69]
CT Scan	**£145.83**	per scan	NHS Reference Cost 2009-2010 (NHS Trusts Diagnostic imaging: Outpatient- Computerised Tomography Scan, 2 areas with contrast Code RA12Z)[68];

Based on the information shown in table B65 and B66, Table B67 presents the proportion of patients who are assumed to receive the specific health care service per month and the associated costs for routine care.

Table B67 Summary of treatment-independent resource use and costs

Health care service	% patients per month[1]	Cost per month[2]
Oncology visit	**33.3%**	33.3% x £128.69 = £42.90
General Practitioner visit	**10.0%**	10.0% x £36.00 = £3.60
Radiographer	**4.2%**	4.2% x £28.00 = £1.17
Biochemistry test	**33.3%**	33.3% x £1.29 = £0.43
Blood test	**29.7%**	29.7% x £3.06 = £0.91
Bone scintigraphy	**8.3%**	8.3% x £99.33 = £8.28

Health care service	% patients per month[1]	Cost per month[2]
CT Scan	**20.0%**	20% x £145.83 = £29.17
Chest x-ray	**3.3%**	3.3% x £20.15 = £0.67
Bone x-ray	**3.3%**	3.3% x £35.99 = £1.20
Hospitalisation (general medicine)*	**0.7%**	0.7% x £321.02 = £17.12
Hospitalisation (Oncology)**	**1.3%**	1.3% x £480.81 = £38.46
Nurse, day ward	**99.99%**	99.99% x £105.00 = £105.46
Total cost per month per patient for treatment-independent resource use during pre-progression		**£249.36**

[1]*Source: Data from Nuijten 2000[53] originally estimated by Canadian experts validated by UK experts; *Length of stay=8 days; **Length of stay=6 days;* [2] *see table B66 for references*

Costs included in post-progression health state

As described in section 6.2 the post-progression health state represents a series of subsequent therapies that a patient may receive after disease progression while on second-line hormonal therapy (i.e. while in the pre-progression health state). These subsequent therapies can be categorized into the following groups:

1. Third-line hormonal therapy
2. Chemotherapy, which is based on the patients receiving up to three lines of therapy
    a. First-line chemotherapy
    b. Second-line chemotherapy
    c. Third-line chemotherapy
3. Supportive Palliative Care

As explained in section 6.2.3, treatment skipping rules has been applied to these sequential lines of line of therapies, to reflect clinical practice in England. As such four potential subsequent treatment pathways included in the economic model, including the following options (Figure 34):
A) Third-line hormonal therapy + Supportive palliative care
B) Chemotherapy + Supportive palliative care
C) Third-line hormonal therapy + Chemotherapy + Supportive palliative care
D) Supportive palliative care

The overall average cost per month post-progression was calculated as £1,084, which was applied to each treatment arm for the proportion of patients in the post-progression health state per cycle. This cost per month was based on a weighted average for the four different potential treatment sequences during post-progression as outlined in Table B68. Below the table, further information about how the estimates for the proportion of patients that receive treatment sequences, the post-progression treatment durations and the

resource utilisation and cost of third-line hormonal therapy were derived are explained.

Figure 34 Overview of treatment pathways during post-progression

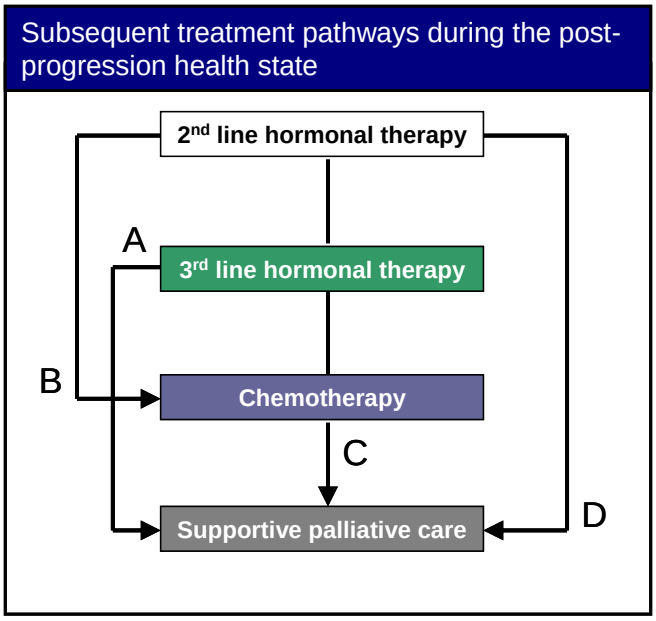


Table B68 Average costs, durations, and proportions of patients per treatment sequence

Post-progression sequences	% patients receiving sequence	Average total time (months)	Average total cost per treatment sequence
A) Third line hormonal therapy + supportive palliative care	7%	7.8 (=2.8 + 5.0)	£5,622 (=£1,580 + £4,042)
B) Chemotherapy + Supportive palliative care	30%	15.8	£18,449
C) Third line hormonal therapy + Chemotherapy + Supportive palliative care	51%	18.6 (=2.8 + 15.8)	£20,029 (=£1,580 +18,449)
D) Supportive palliative care	12%	5.0	£4,042
Total (weighted averages)	**100%**	**15.13**	**£16,628**
Average cost post-progression per month			**£1,084**

- **Proportion patients who receive treatment sequences post-progression**

Treatment skipping rules have been applied to the sequential lines of therapies received in the post-progression health state, to reflect clinical practice in England. A previously published cost-effectiveness study by Cameron *et al*. in 2008[40] used treatment skipping estimates based on a UK clinician survey. This data was used in the model after clinical experts interview validated the data published by Cameron *et al*. (section 6.3.4) and is presented in Table B56 above.

- **Post-progression treatment durations**

In order to estimate an average cost post-progression, it was necessary to estimate the duration for each of the four treatment sequences outlined in Table B68. The estimates used in the base case for the model are shown in the third column in table B68.

For sequence 'A' (third line hormonal therapy + supportive palliative care), an average duration of third line hormonal therapy was estimated to be 2.8 months. This was based on the transition probabilities presented in the economic model by Nuijen et al. 1999[52] and further validated by the clinical experts in the UK. An estimated survival time for patients receiving supportive palliative care only of five months was obtained from the cost-utility model NICE developed as part of the advanced breast cancer guidelines[1]. Therefore, during sequence 'A', patients were assumed to have 2.8 months of hormonal therapy in addition to 5.0 months of supportive palliative care, resulting in a total duration of 7.8 months.

The duration of sequence 'B' (Chemotherapy + Supportive palliative care) was estimated as 15.8 months, which was also sourced from the cost-utility model published in the advanced breast cancer guidelines (NICE CG81, 2009)[1]. This estimate was based on undiscounted overall survival.

The average duration of sequence 'C' (Third line hormonal therapy + Chemotherapy + Supportive palliative care) was estimated to be 18.6 months, which was derived by combining the duration for third-line hormonal therapy (2.8 months) and the chemotherapy and supportive palliative care durations from the NICE cost-utility model (15.8 months).

In sequence 'D' where patients received supportive palliative care only, costs were in line with the duration of 5.0 months for supportive palliative care that was estimated in the NICE cost-utility analysis (as described in sequence 'A').

- **Sequence A - Third-line hormonal therapy resource utilisation and costs**

To estimate the average cost per month associated with the post-progression health state, the costs associated with third-line hormonal therapy was required. This was estimated by evaluating the hormonal treatments that were commonly used as a third-line therapy in the England and the associated drug and administration costs.

No data from clinical trials or observational studies in the UK were found that could be used to indicate the type of hormonal therapy that is most commonly received during third line hormonal therapy. Although the NICE guidelines indicate that the recommended hormonal therapy should depend on type of endocrine therapies received by patients previously, an average of all hormonal therapy options was used for the cost of third-line hormonal therapy in order to use a constant cost post-progression per month for all treatment arms and also to avoid using a lower cost of third-line hormonal therapy for fulvestrant arms (since these patients are less likely to receive fulvestrant as third line). Therefore, an average cost of receiving the following hormonal therapies, fulvestrant 250 mg, fulvestrant 500 mg, anastrozole, letrozole, megestrol acetate or exemestane (assuming an equal chance of patients receiving these treatments), for 2.8 months was used in the economic model (£581). The associated resource utilisation for treatment administration (£301) as well as the treatment-independent resource for disease monitoring (£698) for 2.8 months was also included as an average across the aforementioned treatment options based on the same data used as resource utilisation for second line hormonal therapy. Overall, third line hormonal therapy was associated with a total cost of £1,580 for 2.8 months or £564 per month, which was used to estimate the overall average cost per month for the post-progression health state.

- **Sequence B - Chemotherapy therapy and supportive palliative resource utilisation and costs**

The estimate of the average total costs associated with sequence ‘’B (Chemotherapy + supportive palliative care), was based on the undiscounted costs from the cost-utility analysis performed by NICE as part of the advanced breast cancer guidelines (2009)[1], which compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens for patients with ABC who have previously received anthracycline treatment. The cost-utility analysis in the NICE Advanced Breast Cancer guidelines analysed the cost-effectiveness of 17 potential strategies, including up to three lines of chemotherapy. Clinical experts interviewed as part of the resource use data collection, noted that a small percentage of patients in this decision problem would be chemotherapy naive. To reflect this in the chemotherapy costs, an additional option for doxorubicin was included, which clinical experts identified as the most relevant chemotherapy agent used in England. The incremental costs for doxorubicin vs. docetaxel were obtained from the economic evaluation published by Cooper 2003[41] in order to estimate the total average costs for doxorubin. Overall, the average total cost for chemotherapy including supportive palliative care used in the model was £18,449 (see appendix 9.16 for further details).

- **Sequence D - Supportive palliative care resource utilisation and costs**

Table B69 presents the resource use and costs associated with supportive palliative care based on the “Package B” from the chemotherapy economic

model in the NICE advanced breast cancer guidelines. These resources represent an average level of supportive and palliative care a patient receiving no active treatment (no third line hormonal therapy or chemotherapy) might be expected to receive until the last two weeks before death. The total cost of supportive palliative care used in the economic model was £4,042 (£808.33* 5.0 months).

The costs associated with the final two weeks of life have not been included in the model, as a lifetime horizon has been used in the model and all patients in the cohort will eventually die.

Table B69 Resource use and costs associated with Supportive Palliative Care

Health care service	Resource use per month	Resource cost per month per type of resource
Community nurse home visits	4	£128.33
Clinical nurse specialist: 1 hour	4	£352.00
GP contact: 1 home visit	2	£240.00
Therapist: 1 hour	2	£88.00
Total cost per month for supportive palliative care		£808.33

Adverse-event costs

6.5.6 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 6.2.2.

As explained in section 6.3, it was not feasible to analyze the proportion of patients with grade 3 or 4 adverse events because this was not consistently reported across trials. Furthermore, grade 1 and 2 adverse events associated with hormonal therapies were excluded from the model given there is minimal cost and minor disutility implications associated with them. It was then concluded that serious adverse events could be included in the model, as there was sufficient data consistently reports across the RCTs used in the network meta-analysis for TTP and OS for the base case to conduct a network meta-analysis for serious adverse events (section 6.3 and Appendix 18).

In the model it was assumed that each serious adverse event was associated with hospitalization, which is in-line with previous published cost-effectiveness

studies (Nuijen et al., 1999)[52]. The clinical experts estimated that the length of stay in hospital associated with a serious adverse event ranged from 4-6 days. The model used an average of 5 days in hospital, at a cost of £321.02 per day (Table B66). Table B70 presents the proportion of patients with a serious adverse event per treatment and the associated costs.

Table B70 Proportion of patients with a serious adverse event (based on network meta-analysis) and related costs per treatment (base-case)

Treatment	Proportion of patients with a serious adverse event	Cost of serious adverse events per treatment
Fulvestrant 250 mg	9.1%	£145.94
Fulvestrant 500 mg	10.2%	£164.20
Anastrozole	6.4%	£103.03
Letrozole	8.8%	£141.73

Miscellaneous costs

6.5.7 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

None.

6.6 Sensitivity analysis

6.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

As described in section 6.3.1 and 6.3.7, the clinical data for TTP and OS were incorporated into the model as a distribution, using the best-fitting distribution for TTP and OS. Section 6.3.7 describes the approach used to select the best-fitting distribution, which demonstrated that the Weibull was the best fitting curve for overall survival and the log normal for time-to-progression.

Given the potential uncertainty of the fit of these distributions to the observed TTP and OS results seen in the CONFIRM study[20], the time horizon of the model was restricted to 36 months to be able to compare it to the modelled average TTP and OS results for fulvestrant 500 mg and fulvestrant 250 mg. This time horizon was selected based on the follow-up period in the CONFIRM study and represents the time point where the number of patients

at risk was less than five. Table B71 below summarises the average TTP from the model and from the CONFIRM study.

Table B71 Summary of average TTP from cost effectiveness model and from the CONFIRM study

	Average TTP (months)	Time horizon: 36 month follow-up period		
		Fulvestrant 250 mg	**Fulvestrant 500 mg**	**Absolute difference**
Average TTP (months)	Kaplan Meier from CONFIRM	9.0	11.3	2.3
	Network meta-analysis (lognormal) with half-cycle correction (base-case)	9.2	11.4	2.5
Average OS (months)	Kaplan Meier from CONFIRM study	22.5	23.9	1.4
	Network meta-analysis (Weibull) with half-cycle correction for post-Anti-oestrogen scenario	22.3	23.9	1.6

As evident, the modelled and observed values for both TTP and OS are very similar up to the 36 month time period, supporting the good fit of the model. It is recognised that there is uncertainty regarding the extrapolation of the curve beyond the trial, but no observational data was found to validate the extrapolation. No further structural sensitivity analyses of the survival analysis were available at the time of the submission to assess the uncertainty further.

6.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A one-way sensitivity analysis was undertaken on key inputs to the model. Table B72 summarises the low and high values used for the clinical parameters, i.e. TTP and OS, in the model. The low to high range of values used were sourced from the 95% credible intervals calculated in the network

meta-analysis (see section 6.7.6). The one-way sensitivity analysis for those clinical values incorporated into the model using two parameters, shape and log-scale, was undertaken by varying both values at once and assessing the impact on model outputs.

Table B72 Ranges used for the one-way sensitivity analysis using parameter groups

Parameter group	Parameter	Mean	Range		Source
			Low	High	
Fulvestrant 250 mg OS	Shape	3.43	3.31	3.55	95% credible interval (network meta-analysis)
	Log scale	-0.20	-0.32	-0.08	95% credible interval (network meta-analysis)
Relative OS, fulvestrant 500 mg	Log hazard ratio	-0.17	0.03	-0.37	95% credible interval (network meta-analysis)
Relative OS, anastrozole	Log hazard ratio	0.02	0.17	0.13	95% credible interval (network meta-analysis)
Relative OS, letrozole	Log hazard ratio	0.18	0.56	-0.19	95% credible interval (network meta-analysis)
Fulvestrant 250 mg TTP	Scale	1.68	1.60	1.75	95% credible interval (network meta-analysis)
	Log shape	-0.18	-0.06	-0.34	95% credible interval (network meta-analysis)
Relative TTP, fulvestrant 500 mg	Scale	0.23	0.17	0.29	95% credible interval (network meta-analysis)
	Log shape	-0.10	-0.19	-0.02	95% credible interval (network meta-analysis)
Relative TTP, anastrozole	Scale	-0.09	-0.19	0.00	95% credible interval (network meta-analysis)
	Log shape	0.03	-0.11	0.17	95% credible interval (network meta-analysis)
Relative TTP, letrozole	Scale	0.05	-0.14	0.23	95% credible interval (network meta-analysis)
	Log shape	0.11	-0.14	0.35	95% credible interval (network meta-analysis)

Further inputs for utilities, resource utilisation and costs were also subjected to one-way sensitivity analysis. These are summarised in table B73.

Table B73. Ranges used for the one-way sensitivity analysis using parameter groups

Parameter group	Parameter	Mean	Low	High	Source
Utility pre-progression		0.72	0.50	0.84	Range from review (Low from Brown 2001[39]; High from Hutton 1996[46])
Disutility during post-progression		0.27	0.53	0.03	Range from review (Low from Cameron 2008=0.19[40]; High from Brown 2001 =0.69[39])
Resource utilisation post-progression	Oncology visit	33.3%	25.0%	41.7%	Varied +/- 20%
	General Practitioner visit	10.0%	7.5%	12.5%	
	Radiographer	4.2%	3.1%	5.2%	
	Biochemistry test	33.3%	25.0%	41.7%	
	Blood test	29.7%	22.3%	37.1%	
	Bone scintigraphy	8.3%	6.3%	10.4%	
	CT Scan	20.0%	15.0%	25.0%	
	Chest x-ray	3.3%	2.5%	4.2%	
	Bone x-ray	3.3%	2.5%	4.2%	
	Hospitalisation (general medicine)*	0.7%	0.5%	0.8%	
	Hospitalisation (Oncology)**	1.3%	1.0%	1.7%	
	Clinical nurse specialist	99.9%	75.0%	100.0%	
% fulvestrant administered in primary care setting by nurse		32.3%	27.6%	36.6%	AstraZeneca Data on file[71]
Cost per month post-progression		£1,084	£867	£1,301	Varied +/- 20%

The upper and the lower values used in the one-way sensitivity analysis of utility values were derived from the upper and lower utility values identified from the economic literature review for the pre- and post-progression health states (see section 6.4.5 and 6.4.5). The variation in the percentage of patients that are administered subsequent doses of fulvestrant 250 mg or 500 mg in the primary care setting was based on analysing the lowest and the highest percentage of packs that were used in primary care over the 24 month period between April 2008 and March 2010. The one-way sensitivity analysis

for the underlying inputs used for resource utilisation for post-progression, was undertaken by varying all listed values with their respective ranges at once and assessing the impact on model outputs.

6.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 6.3.6, including the derivation and value of 'priors'. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

Probabilistic sensitivity analysis (PSA) was undertaken in the cost-utility model to assess the uncertainty in the models outputs. Uncertainty around the shape and the log-shape parameters used for the TTP and OS functions was analysed using a normal distribution using the range derived from the 95% credibility limits of the network meta-analysis. The same range was used for the one-way deterministic analysis (section 6.6.2). It was found, however, that the curve parameters for the TTP and OS functions were correlated. A correlation factor was calculated using the following steps:

1. the correlation matrix for the difference parameters was estimated using WinBugs software

2. the variance matrix was calculated from the correlation matrix

3. the Cholesky decomposition matrix was calculated

The product of above was multiplied by a value sampled from a normal distribution. The correlation factor calculated for the low and high values were used in the PSA.

The distributions for the remaining parameters used for the PSA are outlined in Table B74. Resource utilisation data was varied for those parameters where clinical experts provided a range. The upper and the lower values used in the PSA for utility values were derived from alternative source to that used in the deterministic sensitivity analysis (section 6.6.2). The pre-progression utility value is based on the 95% confidence interval reported in the Lloyd et al. study[61] (Lloyd et al., 2006; see section 6.4), while the disutility associated with moving from the pre-progression to post-progression is based on the standard difference between the utility values.

Table B74. PSA variables, distributions and their source

Parameters		Base case	Low	High	Distribution	Source
Percentage of patients with serious adverse event during pre-progression state	Fulvestrant 250 mg	9.1%	6.4%	12.1%	beta	95% credible interval (network meta-analysis)
	Fulvestrant 500 mg	10.2%	6.5%	15.0%	Beta	95% credible interval (network meta-analysis)
	Anastrozole	6.4%	4.1%	9.7%	Beta	95% credible interval (network meta-analysis)
	Letrozole	8.8%	3.6%	20.2%	Beta	95% credible interval (network meta-analysis)
Resource utilisation post-progression	Oncology visit	33.3%	26.7%	40.0%	Beta	+/-20%
	GP visit	10.0%	8.0%	12.0%	Beta	+/-20%
	Radiographer	4.2%	3.3%	5.0%	Beta	+/-20%
	Biochemistry test	33.3%	26.7%	40.0%	Beta	+/-20%
	Blood test	29.7%	23.7%	35.6%	Beta	+/-20%
	Bone scintigraphy	8.3%	6.7%	10.0%	Beta	+/-20%
	CT Scan	20.0%	16.0%	24.0%	Beta	+/-20%
	Chest x-ray	3.3%	2.7%	4.0%	Beta	+/-20%
	Bone x-ray	3.3%	2.7%	4.0%	Beta	+/-20%
	Hospitalisation (general medicine)	0.7%	0.5%	0.8%	Beta	+/-20%
	Hospitalisation (Oncology)	1.3%	1.1%	1.6%	Beta	+/-20%
	Clinical nurse specialist	99.9%	79.9%	99.9%	Beta	+/-20%
Pre-progression utility		0.72	0.69	0.74	Beta	Lloyd *et al*. 2006 [61]
Post-progression disutility		0.27	0.23	0.31	Beta	Lloyd *et al*. 2006[61]
% fulvestrant administered in primary care setting by nurse		32.3%	27.6%	36.6%	Beta	AstraZeneca Data on file[71]
Hospital length of stay (days)		5	4	6	Uniform	Expert opinion
Cost post-progression		£1,084	£867	£1,301	Gamma	+/-20% of mean

6.7 Results

Clinical outcomes from the model

6.7.1 For the outcomes highlighted in the decision problem (see section 4), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

As a network meta-analysis was conducted for the two key clinical outcomes, TTP and OS, table B75-78 summarises the results from the model for these endpoints, in comparison with the results from the network meta-analysis for the primary analysis. The modelled and the observed results from the network meta-analysis results show that the mean TTP (months) is the same for fulvestrant 500 mg, fulvestrant 250 mg, anastrozole and letrozole. The average OS from the Weibull curve used for the reference treatment, fulvestrant 250 mg, was 29.0 months. The model results for the average OS for fulvestrant 250 mg is the same. The survival curves used in the model for fulvestrant 500 mg, anastrozole and letrozole were derived by applying the hazard ratios derived from the network meta-analysis to the survival curve for fulvestrant 250 mg. As a consequence, the overall survival results from the model for these interventions have not been compared to the network meta-analysis results.

Table B75 Summary of model results compared with clinical data for fulvestrant 500 mg

Outcome	Network meta-analysis results	Model result
Mean TTP (months)	15.0	15.0
Mean OS (months)	n/a	33.4

Table B76 Summary of model results compared with clinical data for fulvestrant 250 mg

Outcome	Network meta-analysis results	Model result
Mean TTP (months)	10.8	10.8
Mean OS (months)	29.0	29.0

Table B77 Summary of model results compared with clinical data for anastrozole

Outcome	Network meta-analysis results	Model result
TTP (months)	9.5	9.5
OS (months)	n/a	28.5

Table B78 Summary of model results compared with clinical data for letrozole

Outcome	Network meta-analysis results	Model result
TTP (months)	9.9	9.9
OS (months)	n/a	24.9

6.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The four tables B79-82 summarise the proportion of the cohort that transitions through the health states over the lifetime horizon of the model for fulvestrant 500 mg and for each comparator.

Table B79. Markov trace for fulvestrant 500 mg (base-case analysis)

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
1	96%	3%	1%	76	3%	5%	92%
2	87%	11%	2%	77	3%	5%	92%
3	77%	19%	4%	78	3%	4%	92%
4	69%	25%	6%	79	3%	4%	93%

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
5	62%	30%	8%	80	3%	4%	93%
6	56%	34%	10%	81	3%	4%	93%
7	51%	37%	12%	82	3%	3%	94%
8	47%	39%	14%	83	3%	3%	94%
9	43%	41%	16%	84	3%	3%	94%
10	40%	42%	18%	85	3%	3%	94%
11	37%	43%	20%	86	3%	3%	95%
12	34%	43%	22%	87	3%	3%	95%
13	32%	44%	24%	88	3%	2%	95%
14	30%	44%	26%	89	3%	2%	95%
15	28%	44%	28%	90	3%	2%	95%
16	27%	43%	30%	91	3%	2%	96%
17	25%	43%	32%	92	3%	2%	96%
18	24%	42%	34%	93	2%	2%	96%
19	22%	42%	36%	94	2%	2%	96%
20	21%	41%	38%	95	2%	1%	96%
21	20%	40%	40%	96	2%	1%	96%
22	19%	39%	42%	97	2%	1%	97%
23	18%	38%	43%	98	2%	1%	97%
24	17%	38%	45%	99	2%	1%	97%
25	17%	37%	47%	100	2%	1%	97%
26	16%	36%	48%	101	2%	1%	97%
27	15%	35%	50%	102	2%	1%	97%
28	15%	34%	52%	103	2%	1%	97%
29	14%	33%	53%	104	2%	1%	97%
30	13%	32%	55%	105	2%	0%	98%
31	13%	31%	56%	106	2%	0%	98%
32	12%	30%	58%	107	2%	0%	98%
33	12%	29%	59%	108	2%	0%	98%
34	11%	28%	60%	109	2%	0%	98%
35	11%	27%	62%	110	2%	0%	98%
36	11%	26%	63%	111	2%	0%	98%
37	10%	26%	64%	112	2%	0%	98%
38	10%	25%	65%	113	2%	0%	98%
39	10%	24%	67%	114	2%	0%	98%
40	9%	23%	68%	115	2%	0%	98%
41	9%	22%	69%	116	2%	0%	98%
42	9%	22%	70%	117	1%	0%	99%
43	8%	21%	71%	118	1%	0%	99%
44	8%	20%	72%	119	1%	0%	99%

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
45	8%	19%	73%	120	1%	0%	99%
46	8%	19%	74%	121	1%	0%	99%
47	7%	18%	75%	122	1%	0%	99%
48	7%	17%	76%	123	1%	0%	99%
49	7%	16%	77%	124	1%	0%	99%
50	7%	16%	77%	125	1%	0%	99%
51	7%	15%	78%	126	1%	0%	99%
52	6%	15%	79%	127	1%	0%	99%
53	6%	14%	80%	128	1%	0%	99%
54	6%	13%	81%	129	1%	0%	99%
55	6%	13%	81%	130	1%	0%	99%
56	6%	12%	82%	131	1%	0%	99%
57	6%	12%	83%	132	1%	0%	99%
58	5%	11%	83%	133	1%	0%	99%
59	5%	11%	84%	134	1%	0%	99%
60	5%	10%	85%	135	1%	0%	99%
61	5%	10%	85%	136	1%	0%	99%
62	5%	10%	86%	137	1%	0%	99%
63	5%	9%	86%	138	1%	0%	99%
64	5%	9%	87%	139	1%	0%	99%
65	4%	8%	87%	140	1%	0%	99%
66	4%	8%	88%	141	0%	0%	100%
67	4%	8%	88%	142	0%	0%	100%
68	4%	7%	89%	143	0%	0%	100%
69	4%	7%	89%	144	0%	0%	100%
70	4%	7%	90%	145	0%	0%	100%
71	4%	6%	90%	146	0%	0%	100%
72	4%	6%	90%	147	0%	0%	100%
73	4%	6%	91%	148	0%	0%	100%
74	4%	5%	91%	149	0%	0%	100%
75	4%	5%	91%	150	0%	0%	100%

Table B80 Markov trace for fulvestrant 250 mg (base-case analysis)

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
1	96%	3%	1%	76	1%	4%	95%
2	86%	12%	2%	77	1%	4%	95%
3	74%	22%	5%	78	1%	3%	95%
4	64%	29%	7%	79	1%	3%	96%
5	56%	35%	9%	80	1%	3%	96%
6	49%	39%	11%	81	1%	3%	96%
7	44%	43%	14%	82	1%	3%	96%
8	39%	45%	16%	83	1%	3%	96%
9	35%	46%	19%	84	1%	2%	97%
10	32%	47%	21%	85	1%	2%	97%
11	29%	48%	23%	86	1%	2%	97%
12	26%	48%	26%	87	1%	2%	97%
13	24%	48%	28%	88	1%	2%	97%
14	22%	48%	30%	89	1%	2%	97%
15	20%	47%	33%	90	1%	2%	97%
16	19%	46%	35%	91	1%	2%	98%
17	17%	45%	37%	92	1%	1%	98%
18	16%	45%	39%	93	1%	1%	98%
19	15%	44%	41%	94	1%	1%	98%
20	14%	43%	43%	95	1%	1%	98%
21	13%	41%	45%	96	1%	1%	98%
22	12%	40%	47%	97	1%	1%	98%
23	12%	39%	49%	98	1%	1%	98%
24	11%	38%	51%	99	1%	1%	98%
25	10%	37%	53%	100	1%	1%	98%
26	10%	36%	55%	101	1%	1%	99%
27	9%	35%	56%	102	1%	1%	99%
28	9%	33%	58%	103	1%	1%	99%
29	8%	32%	59%	104	1%	1%	99%
30	8%	31%	61%	105	1%	1%	99%
31	7%	30%	63%	106	1%	0%	99%
32	7%	29%	64%	107	1%	0%	99%
33	7%	28%	65%	108	1%	0%	99%
34	6%	27%	67%	109	1%	0%	99%
35	6%	26%	68%	110	1%	0%	99%
36	6%	25%	69%	111	1%	0%	99%
37	6%	24%	71%	112	1%	0%	99%
38	5%	23%	72%	113	1%	0%	99%

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
39	5%	22%	73%	114	1%	0%	99%
40	5%	21%	74%	115	1%	0%	99%
41	5%	20%	75%	116	1%	0%	99%
42	4%	20%	76%	117	1%	0%	99%
43	4%	19%	77%	118	1%	0%	99%
44	4%	18%	78%	119	0%	0%	99%
45	4%	17%	79%	120	0%	0%	99%
46	4%	16%	80%	121	0%	0%	99%
47	4%	16%	81%	122	0%	0%	100%
48	3%	15%	81%	123	0%	0%	100%
49	3%	14%	82%	124	0%	0%	100%
50	3%	14%	83%	125	0%	0%	100%
51	3%	13%	84%	126	0%	0%	100%
52	3%	13%	84%	127	0%	0%	100%
53	3%	12%	85%	128	0%	0%	100%
54	3%	11%	86%	129	0%	0%	100%
55	3%	11%	86%	130	0%	0%	100%
56	3%	10%	87%	131	0%	0%	100%
57	2%	10%	88%	132	0%	0%	100%
58	2%	9%	88%	133	0%	0%	100%
59	2%	9%	89%	134	0%	0%	100%
60	2%	9%	89%	135	0%	0%	100%
61	2%	8%	90%	136	0%	0%	100%
62	2%	8%	90%	137	0%	0%	100%
63	2%	7%	91%	138	0%	0%	100%
64	2%	7%	91%	139	0%	0%	100%
65	2%	7%	91%	140	0%	0%	100%
66	2%	6%	92%	141	0%	0%	100%
67	2%	6%	92%	142	0%	0%	100%
68	2%	6%	92%	143	0%	0%	100%
69	2%	5%	93%	144	0%	0%	100%
70	2%	5%	93%	145	0%	0%	100%
71	2%	5%	93%	146	0%	0%	100%
72	2%	5%	94%	147	0%	0%	100%
73	2%	4%	94%	148	0%	0%	100%
74	1%	4%	94%	149	0%	0%	100%
75	1%	4%	95%	150	0%	0%	100%

Table B81. Markov trace for anastrozole (base-case analysis)

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
1	96%	4%	1%	76	1%	4%	95%
2	84%	13%	3%	77	1%	4%	95%
3	72%	24%	5%	78	1%	3%	96%
4	61%	32%	7%	79	1%	3%	96%
5	53%	38%	9%	80	1%	3%	96%
6	46%	42%	12%	81	1%	3%	96%
7	40%	46%	14%	82	1%	3%	96%
8	36%	48%	17%	83	1%	3%	97%
9	32%	49%	19%	84	1%	3%	97%
10	28%	50%	21%	85	1%	2%	97%
11	26%	51%	24%	86	1%	2%	97%
12	23%	51%	26%	87	1%	2%	97%
13	21%	50%	29%	88	1%	2%	97%
14	19%	50%	31%	89	1%	2%	97%
15	18%	49%	33%	90	1%	2%	98%
16	16%	48%	35%	91	1%	2%	98%
17	15%	48%	38%	92	1%	2%	98%
18	14%	47%	40%	93	1%	1%	98%
19	13%	45%	42%	94	1%	1%	98%
20	12%	44%	44%	95	1%	1%	98%
21	11%	43%	46%	96	1%	1%	98%
22	10%	42%	48%	97	1%	1%	98%
23	9%	41%	50%	98	1%	1%	98%
24	9%	39%	52%	99	1%	1%	98%
25	8%	38%	54%	100	0%	1%	99%
26	8%	37%	55%	101	0%	1%	99%
27	7%	36%	57%	102	0%	1%	99%
28	7%	34%	59%	103	0%	1%	99%
29	7%	33%	60%	104	0%	1%	99%
30	6%	32%	62%	105	0%	1%	99%
31	6%	31%	63%	106	0%	1%	99%
32	5%	30%	65%	107	0%	1%	99%
33	5%	29%	66%	108	0%	1%	99%
34	5%	28%	67%	109	0%	1%	99%
35	5%	27%	69%	110	0%	0%	99%
36	4%	26%	70%	111	0%	0%	99%
37	4%	25%	71%	112	0%	0%	99%
38	4%	24%	72%	113	0%	0%	99%

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
39	4%	23%	74%	114	0%	0%	99%
40	4%	22%	75%	115	0%	0%	99%
41	3%	21%	76%	116	0%	0%	99%
42	3%	20%	77%	117	0%	0%	99%
43	3%	19%	78%	118	0%	0%	99%
44	3%	18%	79%	119	0%	0%	99%
45	3%	18%	80%	120	0%	0%	100%
46	3%	17%	80%	121	0%	0%	100%
47	3%	16%	81%	122	0%	0%	100%
48	3%	15%	82%	123	0%	0%	100%
49	2%	15%	83%	124	0%	0%	100%
50	2%	14%	84%	125	0%	0%	100%
51	2%	13%	84%	126	0%	0%	100%
52	2%	13%	85%	127	0%	0%	100%
53	2%	12%	86%	128	0%	0%	100%
54	2%	12%	86%	129	0%	0%	100%
55	2%	11%	87%	130	0%	0%	100%
56	2%	11%	88%	131	0%	0%	100%
57	2%	10%	88%	132	0%	0%	100%
58	2%	10%	89%	133	0%	0%	100%
59	2%	9%	89%	134	0%	0%	100%
60	2%	9%	90%	135	0%	0%	100%
61	2%	8%	90%	136	0%	0%	100%
62	1%	8%	91%	137	0%	0%	100%
63	1%	8%	91%	138	0%	0%	100%
64	1%	7%	91%	139	0%	0%	100%
65	1%	7%	92%	140	0%	0%	100%
66	1%	7%	92%	141	0%	0%	100%
67	1%	6%	93%	142	0%	0%	100%
68	1%	6%	93%	143	0%	0%	100%
69	1%	6%	93%	144	0%	0%	100%
70	1%	5%	94%	145	0%	0%	100%
71	1%	5%	94%	146	0%	0%	100%
72	1%	5%	94%	147	0%	0%	100%
73	1%	5%	94%	148	0%	0%	100%
74	1%	4%	95%	149	0%	0%	100%
75	1%	4%	95%	150	0%	0%	100%

Table B82. Markov trace for letrozole (base-case analysis)

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
1	97%	2%	1%	76	1%	2%	97%
2	89%	8%	3%	77	1%	2%	97%
3	77%	17%	5%	78	1%	2%	97%
4	67%	25%	8%	79	1%	2%	98%
5	58%	31%	11%	80	1%	2%	98%
6	51%	36%	14%	81	1%	1%	98%
7	45%	39%	16%	82	1%	1%	98%
8	39%	41%	19%	83	1%	1%	98%
9	35%	43%	22%	84	1%	1%	98%
10	31%	44%	25%	85	1%	1%	98%
11	28%	45%	27%	86	1%	1%	98%
12	25%	45%	30%	87	1%	1%	99%
13	23%	44%	33%	88	1%	1%	99%
14	21%	44%	35%	89	1%	1%	99%
15	19%	43%	38%	90	1%	1%	99%
16	17%	42%	40%	91	0%	1%	99%
17	16%	41%	43%	92	0%	1%	99%
18	15%	40%	45%	93	0%	1%	99%
19	13%	39%	47%	94	0%	1%	99%
20	12%	38%	50%	95	0%	0%	99%
21	11%	37%	52%	96	0%	0%	99%
22	11%	36%	54%	97	0%	0%	99%
23	10%	34%	56%	98	0%	0%	99%
24	9%	33%	58%	99	0%	0%	99%
25	9%	32%	59%	100	0%	0%	99%
26	8%	31%	61%	101	0%	0%	99%
27	7%	30%	63%	102	0%	0%	99%
28	7%	28%	65%	103	0%	0%	99%
29	7%	27%	66%	104	0%	0%	99%
30	6%	26%	68%	105	0%	0%	100%
31	6%	25%	69%	106	0%	0%	100%
32	5%	24%	71%	107	0%	0%	100%
33	5%	23%	72%	108	0%	0%	100%
34	5%	22%	73%	109	0%	0%	100%
35	5%	21%	75%	110	0%	0%	100%
36	4%	20%	76%	111	0%	0%	100%
37	4%	19%	77%	112	0%	0%	100%
38	4%	18%	78%	113	0%	0%	100%

Cycle	Health state			Cycle	Health state		
	Pre-progression (TTP)	Post-progression	Dead		Pre-progression (TTP)	Post-progression	Dead
39	4%	17%	79%	114	0%	0%	100%
40	4%	16%	80%	115	0%	0%	100%
41	3%	16%	81%	116	0%	0%	100%
42	3%	15%	82%	117	0%	0%	100%
43	3%	14%	83%	118	0%	0%	100%
44	3%	13%	84%	119	0%	0%	100%
45	3%	13%	85%	120	0%	0%	100%
46	3%	12%	85%	121	0%	0%	100%
47	2%	11%	86%	122	0%	0%	100%
48	2%	11%	87%	123	0%	0%	100%
49	2%	10%	87%	124	0%	0%	100%
50	2%	10%	88%	125	0%	0%	100%
51	2%	9%	89%	126	0%	0%	100%
52	2%	9%	89%	127	0%	0%	100%
53	2%	8%	90%	128	0%	0%	100%
54	2%	8%	90%	129	0%	0%	100%
55	2%	7%	91%	130	0%	0%	100%
56	2%	7%	91%	131	0%	0%	100%
57	2%	7%	92%	132	0%	0%	100%
58	2%	6%	92%	133	0%	0%	100%
59	1%	6%	93%	134	0%	0%	100%
60	1%	6%	93%	135	0%	0%	100%
61	1%	5%	93%	136	0%	0%	100%
62	1%	5%	94%	137	0%	0%	100%
63	1%	5%	94%	138	0%	0%	100%
64	1%	4%	94%	139	0%	0%	100%
65	1%	4%	95%	140	0%	0%	100%
66	1%	4%	95%	141	0%	0%	100%
67	1%	4%	95%	142	0%	0%	100%
68	1%	3%	96%	143	0%	0%	100%
69	1%	3%	96%	144	0%	0%	100%
70	1%	3%	96%	145	0%	0%	100%
71	1%	3%	96%	146	0%	0%	100%
72	1%	3%	96%	147	0%	0%	100%
73	1%	2%	97%	148	0%	0%	100%
74	1%	2%	97%	149	0%	0%	100%
75	1%	2%	97%	150	0%	0%	100%

6.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

To calculate the associated QALYs for each intervention through each health state and cycle, the proportion of patients in the pre-progression and post-progression health states in each cycle (as shown in the Markov traces in section 6.7.2) are multiplied by the one twelfth (to reflect cycle length of one month) of the utility associated with the respective health state. Cumulative QALYs are accrued through each subsequent cycle of the model for each intervention.

6.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Table B83 below shows the life years and QALYs accrued for each clinical outcome for each comparators, alongside the associated costs.

Table B83 Model outputs by clinical outcomes (discounted)

Treatment	Outcome	LY	QALY	Cost (£)
Fulvestrant 500 mg	Pre-progression	1.189	0.851	£12,418
	Post progression	1.435	1.773	£18,657
Fulvestrant 250 mg	Pre-progression	0.867	0.620	£6,978
	Post progression	1.432	1.679	£18,625
Anastrozole	Pre-progression	0.769	0.550	£3,024
	Post progression	1.495	1.714	£19,443
Letrozole	Pre-progression	0.806	0.577	£3,370
	Post progression	1.189	1.419	£15,466
LY, life years; QALY, quality-adjusted life year				

6.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Tables B84 to B86 summarise the disaggregated incremental QALYs for fulvestrant 500 mg versus each of the comparators by each health state used in the model (excluding death).

Table B84 Summary of QALY gain by health state, fulvestrant 500 mg vs. fulvestrant 250 mg (base case)

Health state	QALY intervention (fulvestrant 500 mg)	QALY comparator (fulvestrant 250 mg)	Absolute increment	% absolute increment
Pre-progression health state	0.851	0.620	0.230	99.5%
Post-progression health state	0.637	0.636	0.001	0.5%
Total	1.487	1.256	0.232	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B85 Summary of QALY gain by health state, fulvestrant 500 mg vs. anastrozole (base case)

Health state	QALY intervention (fulvestrant 500 mg)	QALY intervention (anastrozole)	Absolute increment	% absolute increment
Pre-progression health state	0.851	0.550	0.300	109.8%
Post-progression health state	0.637	0.663	-0.027	-9.8%
Total	1.487	1.214	0.274	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B86 Summary of QALY gain by health state, fulvestrant 500 mg versus letrozole (base case)

Health state	QALY intervention (fulvestrant 500 mg)	QALY intervention (letrozole)	Absolute increment	% absolute increment
Pre-progression health state	0.851	0.577	0.274	71.5%
Post-progression health state	0.637	0.528	0.109	28.5%
Total	1.487	1.105	0.383	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Tables B87 to B89 summarise the costs for fulvestrant 500 mg versus each of the comparators by each health state used in the model (excluding death).

Table B87 Summary of costs by health state, fulvestrant 500 mg versus fulvestrant 250 mg (base case)

Health state	Cost intervention (fulvestrant 500 mg)	Cost intervention (fulvestrant 250 mg)	Absolute increment	% absolute increment
Pre-progression health state	£12,418	£6,978	£5,440	99.4%
Post-progression health state	£18,657	£18,625	£32	0.6%
Total	£31,075	£25,603	£5,432	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B88 Summary of costs by health state, fulvestrant 500 mg vs. anastrozole (base case)

Health state	Cost intervention (fulvestrant 500 mg)	Cost intervention (anastrozole)	Absolute increment	% absolute increment
Pre-progression health state	£12,418	£3,024	£9,394	109.1%
Post-progression health state	£18,657	£19,443	-£786	-9.1%
Total	£31,075	£22,467	£8,608	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Table B89 Summary of costs by health state, fulvestrant 500 mg vs. letrozole (base case)

Health state	Cost intervention (fulvestrant 500 mg)	Cost intervention (letrozole)	Absolute increment	% absolute increment
Pre-progression health state	£12,418	£3,370	£9,048	73.9%
Post-progression health state	£18,657	£15,466	£3,191	26.1%
Total	£31,075	£18,836	£12,239	100%

QALY, quality-adjusted life year

Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee

Tables B90 to B92 summarise the disaggregated costs for fulvestrant 500 mg versus each of the comparators for pre-progression and the total post-progression health state used in the model. Given that no costs are associated with the health state for death, no cost data are presented.

Table B90 Summary of predicted resource use by category of cost, fulvestrant 500 mg vs. fulvestrant 250 mg (base case)

Health state	Item	Cost intervention (fulvestrant 500 mg)	Cost comparator (fulvestrant 250 mg)	Absolute increment	% absolute increment
Pre-progression health state	Hormonal therapy drug cost (2nd line)	£7,956	£3,623	£4,333	79.2%
	Treatment-related resource use costs	£1,411	£1,104	£307	5.6%
	Treatment-independent costs	£2,887	£2,105	£782	14.3%
	Adverse events	£164	£146	£18	0.3%
Post-progression health state	Total	£18,657	£18,625	£32	0.6%
Total		£31,075	£25,603	£5,472	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table B91 Summary of predicted resource use by category of cost, fulvestrant 500 mg vs. anastrozole (base case)

Health state	Item	Cost intervention (fulvestrant 500 mg)	Cost intervention (anastrozole)	Absolute increment	% absolute increment
Pre-progression health state	Hormonal therapy drug cost (2nd line)	£7,956	£687	£7,269	84.4%
	Treatment-related resource use costs	£1,411	£366	£1,045	12.1%
	Treatment-independent costs	£2,887	£1,867	£1,020	11.8%
	Adverse events	£164	£103	£61	0.7%
Post-progression health state	Total	£18,657	£19,443	-£786	-9.1%
Total		£31,075	£22,467	£8,608	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Table B92 Summary of predicted resource use by category of cost, fulvestrant 500 mg vs. letrozole (base case)

Health state	Item	Cost intervention (fulvestrant 500 mg)	Cost intervention (letrozole)	Absolute increment	% absolute increment
Pre-progression health state	Hormonal therapy drug cost (2nd line)	£7,956	£892	£7,064	57.7%
	Treatment-related resource use costs	£1,411	£379	£1,032	8.4%
	Treatment-independent costs	£2,887	£1,958	£929	7.6%
	Adverse events	£164	£142	£22	0.2%
Post-progression health state	Total	£18,657	£15,466	£3,191	26.1%
Total		£31,075	£18,836	£12,239	100%
Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee					

Base-case analysis

6.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

Table B93 summarises the base-case results. In ranking ascending order of total costs, letrozole was associated with £18,836, followed by anastrozole (£22,467), fulvestrant 250 mg (£25,603) and fulvestrant 500 mg (£31,075). Letrozole was used as the reference case as it was associated with the lowest cost. Fulvestrant 500 mg was associated with the highest total QALY of 1.487, followed by fulvestrant 250 mg (1.256 QALYs), anastrozole (1.214 QALYs) and letrozole (1.105 QALYs).

Table B93 Base-case results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Letrozole	£18,836	1.996	1.105	-	-	-	-	-
Anastrozole	£22,467	2.264	1.214	£3,631	0.269	0.109	£33,286	ED
Fulvestrant 250 mg	£25,603	2.299	1.256	£3,136	0.035	0.042	£44,763	ED
Fulvestrant 500 mg	£31,075	2.624	1.487	£5,472	0.325	0.232	£31,982	£31,982
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; ED, extended dominance								

Based on an incremental analysis ranking of technologies, the base-case results demonstrate that there is extended dominance for anastrozole and fulvestrant 250 mg. The ICER of fulvestrant 500 mg versus letrozole is £31,982 per QALY, with incremental costs of £12,239 and incremental QALYs of 0.383 associated with fulvestrant 500 mg in comparison with letrozole (Table B93).

Sensitivity analyses

6.7.7 Please present results of deterministic sensitivity analysis.

Consider the use of tornado diagrams.

The tornado diagrams below illustrate the impact of varying the key inputs from their low and high values, as outlined in section 6.6.2, on the ICER for fulvestrant 500 mg versus each of the comparators (i.e. anastrozole, letrozole and fulvestrant 250 mg).

The model output was found to be sensitive to a number of the key model parameters (see figure 35, 36 and 37). The main key drivers of the cost-effectiveness results that were identified in the one-way sensitivity analysis were:

- Fulvestrant 500 mg versus letrozole
    - TTP for letrozole: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £21,894/QALY to £55,166/QALY;
    - Utility for pre-progression: ± 95% confidence interval from Lloyd et al. (2006) from base case, gave an ICER range of £26,553/QALY to £49,473/QALY;
    - Utility for post-progression: ± 95% confidence interval from Lloyd et al. (2006) from base case, gave an ICER range of £27,691/QALY to £38,331/QALY;

- OS for letrozole: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £30,700/QALY to £40,781/QALY
- TTP for fulvestrant 500 mg: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £27,406/QALY to £37,453/QALY.

- Fulvestrant 500 mg versus anastrozole:
  - TTP for anastrozole: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £22,184/QALY to £48,050/QALY;
  - Utility for pre-progression: ± 95% confidence interval from Lloyd et al. (2006) from base case, gave an ICER range of £27,036/QALY to £43,881/QALY;
  - TTP for fulvestrant 500 mg: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £25,386/QALY to £39,416/QALY.
- Fulvestrant 500 mg versus fulvestrant 250 mg:
  - TTP for fulvestrant 500 mg: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £17,880/QALY to £31,625/QALY;
  - Utility for pre-progression: ± 95% confidence interval from Lloyd et al. (2006) from base case, gave an ICER range of £20,122/QALY to £33,862/QALY;
  - OS for fulvestrant 500 mg: ± 95% credibility interval for scale and log shape from the base-case gave an ICER range of £12,281/QALY to £25,913/QALY.

Figure 35 Tornado Diagram of base-case analysis of fulvestrant 500 mg versus letrozole

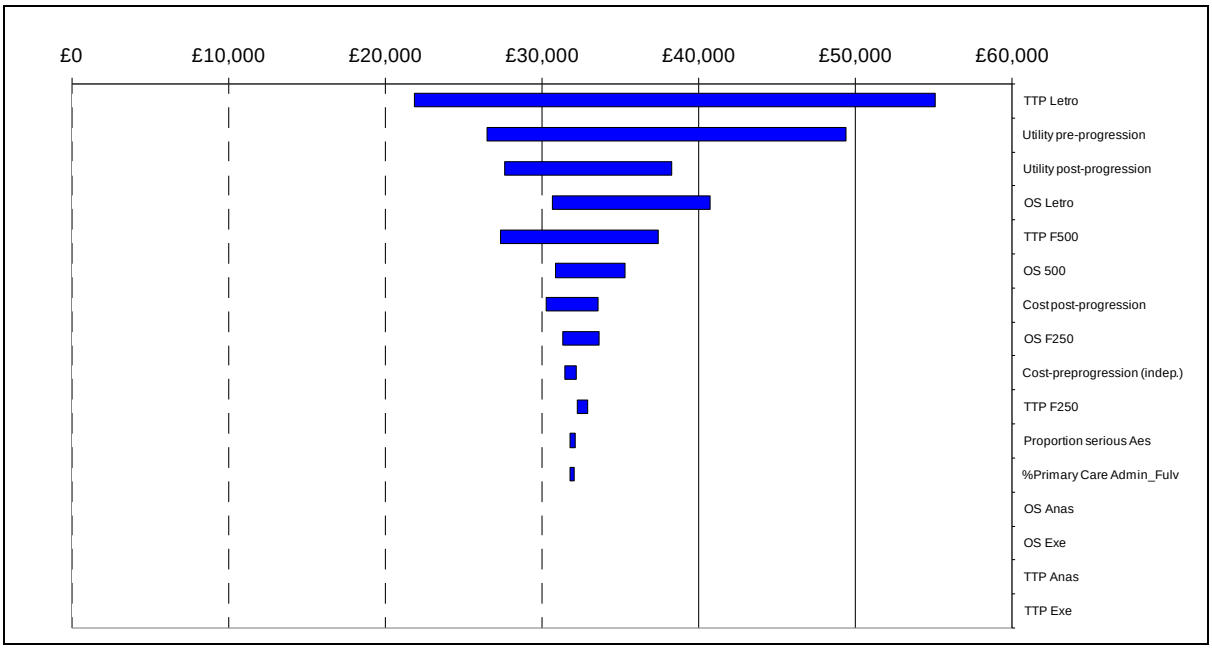


Figure 36. Tornado Diagram of base-case analysis of fulvestrant 500 mg versus anastrozole

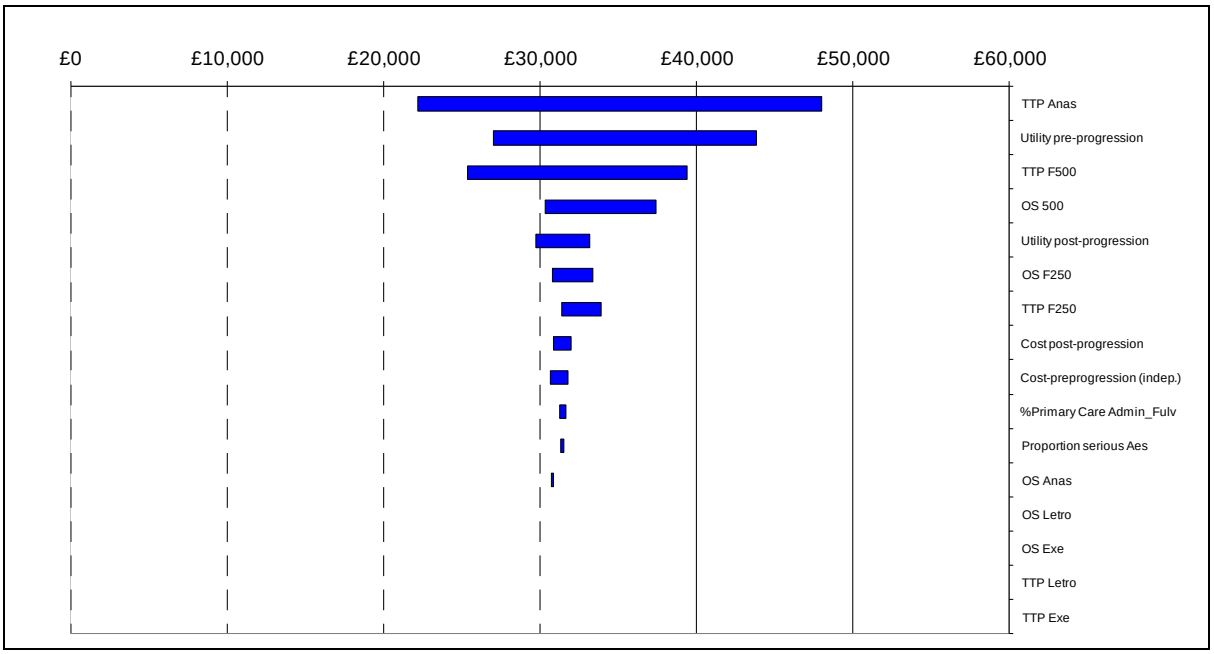
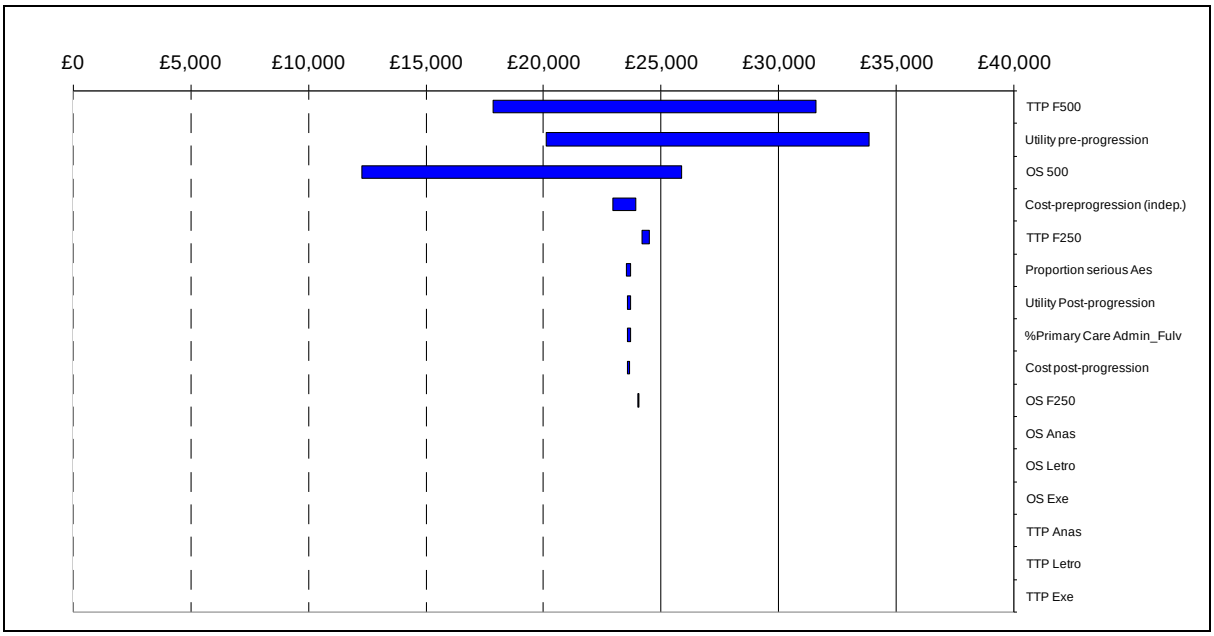


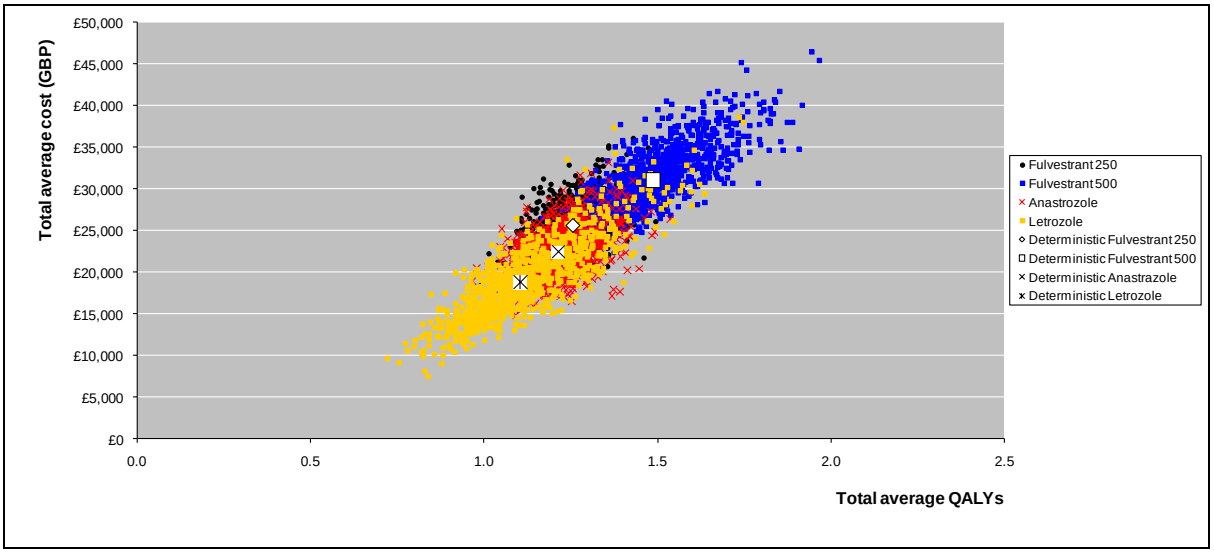
Figure 37. Tornado Diagram of base-case analysis of fulvestrant 500 mg versus fulvestrant 250 mg



6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

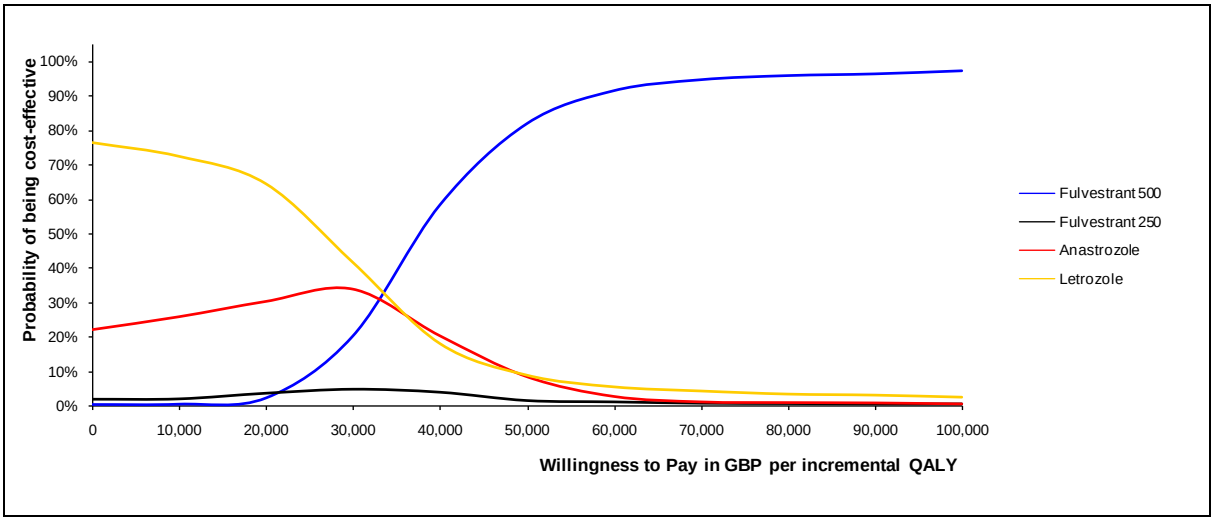
As there is more than one competing intervention being considered in the decision problem, the total average QALYs and total average costs for fulvestrant 500 mg, fulvestrant 250 mg, anastrozole and letrozole from the PSA results have been presented on the cost-effectiveness plane.

Figure 38 Scatter plot of total average QALYs and total average cost for fulvestrant 500 mg, fulvestrant 250 mg, anastrozole and letrozole for the base-case patient population



At a willingness to pay threshold (WTP) of £20,000 per QALY, there is a 2% probability of fulvestrant 500 mg being a cost-effective versus fulvestrant 250 mg, anastrozole or letrozole. This increases to 20% at a WTP threshold of £30,000 per QALY. At a WTP of £30,000 per QALY, anastrozole has a 34% probability of being cost-effective, while letrozole has a probability of 41% and fulvestrant 250 mg has a probability of 5%.

Figure 39: cost-effectiveness acceptability curve for fulvestrant 500 mg, fulvestrant 250 mg, anastrozole and letrozole for the base-case patient population



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Six scenario analyses have been conducted to assess the impact of key assumptions made in the base case analysis to assess their impact on the results from the cost-utility analysis. These are summarised in the following table and discussed in more details (including the ICERs) below:

Scenario	Description
A	Expand patient population to post anti-oestrogen or aromatase inhibitor to enable the inclusion of exemestane within the network meta-analysis
B	Cost of administration of fulvestrant 500 mg and 250 mg using alternative proportions of administration in the primary care setting
C	Cost of post-progression using alternative mix of chemotherapies
D	Cost of post-progression eliminating treatment skipping
E	Discounting costs and benefits at 0% and 6%
F	Altering time horizon

- **Scenario A: Post-AO/AI patient population**

The base-case analysis presented in this submission is based on the licensed patient population for fulvestrant 500 mg, which is post anti-oestrogen therapy. However, no clinical data was available for one of the comparators, exemestane, outlined in the decision problem in the patient group and line of therapy. As a result, this scenario analysis, looking at a broader patient population after anti-oestrogen or aromatase inhibitor therapy where appropriate clinical data for exemestane exists, has been undertaken. A network meta-analysis using the same methodology as outlined in section 5.7, was used to generate the relative efficacy of fulvestrant 500 mg compared with fulvestrant 250 mg and the aromatase inhibitors, anastrozole, exemestane and letrozole for TTP, OS and serious adverse events. See Appendix 16, 17 and 18 for further details of the network meta-analysis conducted. The OS and TTP results from these analysed are presented in table B94, B95, B96 and B97.

Table B94. Network meta-analysis TTP results (post-anti-oestrogen or aromatase inhibitor therapy): Fulvestrant 250 mg (baseline comparator)

Treatment	Scale			Log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250 mg	1.677	1.606	1.747	-0.187	-0.327	-0.076

Table B95. Network meta-analysis TTP results (post-anti-oestrogen or aromatase inhibitor therapy): Difference in log normal parameters for treatment alternatives versus fulvestrant 250 mg

Treatment	Difference in scale			Difference in log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 500 mg	0.228	0.166	0.293	-0.102	-0.183	-0.021
Anastrozole 1 mg	-0.092	-0.178	-0.002	0.027	-0.103	0.161
Letrozole 2.5 mg	0.094	-0.051	0.250	0.028	-0.165	0.233
Exemestane	0.156	0.015	0.304	0.116	-0.103	0.341

Table B96. Network meta-analysis OS results (post-anti-oestrogen or aromatase inhibitor therapy): Hazard Ratios relative to fulvestrant 250 mg

Treatment	Hazard Ratio	2.5th percentile	97.5th percentile
Fulvestrant 500 mg	0.84	0.69	1.03
Anastrozole 1 mg	1.02	0.88	1.19
Letrozole 2.5 mg	1.14	0.81	1.60
Exemestane	1.12	0.78	1.60

Table B97 Network meta-analysis results using random-effects model for the proportion of patients experiencing serious adverse events (post-anti-oestrogen or aromatase inhibitor therapy)

Treatment	Proportion of serious adverse events	2.5% credible interval	97.5% credible interval
Fulvestrant 250 mg	9.5%	6.8%	12.6%
Fulvestrant 500 mg	9.9%	3.7%	20.6%
Anastrozole	6.8%	2.4%	16.9%
Letrozole	5.0%	0.6%	27.9%
Exemestane	24.0%	4.8%	66.2%

The cost-utility analysis was replicated using the efficacy outputs from this network meta-analysis in those ABC patients that had received prior anti-oestrogen or aromatase inhibitor therapy, with all other assumptions remaining the same as the base case. Table B97 summarises the outputs of this analysis.

Table B98 Scenario A results

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Letrozole	£18,832	2.078	1.171	-	-	-	-	Reference
Exemestane	£19,804	2.114	1.180	£972	0.036	0.009	£105,272	ED
Anastrozole	£22,422	2.264	1.215	£2,618	0.151	0.035	£80,726	ED
Fulvestrant 250 mg	£25,593	2.299	1.257	£3,171	0.035	0.041	£79,025	ED
Fulvestrant 500 mg	£31,045	2.623	1.488	£5,452	0.324	0.231	£38,566	£38,566
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years; ED, extended dominance								

- **Scenario B: Cost of administration of fulvestrant 500 mg and 250 mg using alternative proportions of administration in the primary care setting**

Based on historical trends in sales, it was assumed that 32.3% of fulvestrant 250mg and 500mg doses would be administered by a nurse in the primary care setting, with the remaining in the hospital setting, in the base case. However, it is recognised that this assumption is associated with uncertainty and therefore a scenario analysis varying this proportion between zero to one hundred percent, in increments of twenty-five percentage points has been undertaken. Table B98 shows the results from the cost-utility model by varying the proportion of patients that are administered fulvestrant 250 mg and 500 mg in the primary care setting from 0% to 100% in increments of 25%. In all of

these scenarios, both anastrozole and fulvestrant 250 mg are excluded as comparators due to extended dominance. The ICER for fulvestrant 500 mg versus letrozole in these scenarios ranges from £29,881 (100%) to £32,981 per QALY (at 0%).

Table B99. Scenario B results

Proportion of patients administered subsequent fulvestrant 250 mg and 500 mg in primary care setting	Intervention	Total Costs	Total QALYs	ICER
0%	Letrozole	£18,846	1.105	Reference
	Anastrozole	£22,479	1.214	ED
	Fulvestrant 250 mg	£25,891	1.256	ED
	Fulvestrant 500 mg	£31,467	1.487	£32,981
25%	Letrozole	£18,838	1.105	Reference
	Anastrozole	£22,470	1.214	ED
	Fulvestrant 250 mg	£25,667	1.256	ED
	Fulvestrant 500 mg	£31,163	1.487	£32,206
50%	Letrozole	£18,831	1.105	Reference
	Anastrozole	£22,460	1.214	ED
	Fulvestrant 250 mg	£25,444	1.256	ED
	Fulvestrant 500 mg	£30,859	1.487	£31,431
75%	Letrozole	£18,824	1.105	Reference
	Anastrozole	£22,451	1.214	ED
	Fulvestrant 250 mg	£25,220	1.256	ED
	Fulvestrant 500 mg	£30,555	1.487	£30,656
100%	Letrozole	£18,816	1.105	Reference
	Anastrozole	£22,442	1.214	ED
	Fulvestrant 250 mg	£24,997	1.256	ED
	Fulvestrant 500 mg	£30,251	1.487	£29,881

ED, Extended dominance

- **Scenario C: Cost of post-progression using alternative mix of chemotherapies**

Section 6.5.5 described the approach used to estimate the cost of post-progression per month, given no published source was available. The costs associated with the potential chemotherapy that a patient may receive further in the treatment pathway after the pre-progression health state in the model was based on identifying the most commonly used chemotherapy first-, second- and third-line using expert opinion. Based on the advanced breast

guideline published by NICE in 2009, there were three regimens that were identified as the most cost-effective:

Table B100: Cost of progression using alternate mix of chemotherapies

First line	Second line	Third line	Total expected time (months)	Total Expected Costs (£)	Proportion of patients
Docetaxel	Capecitabine	Vinorelbine	**21.3**	**£23,055**	**33%**
Docetaxel	Capecitabine	No Chemotherapy	**16.7**	**£18,118**	**33%**
Docetaxel	Vinorelbine	Capecitabine	**21.3**	**£23,027**	**33%**

In this scenario analysis, the cohort was assigned an equal chance of receiving any of these three regimens (i.e. 33.3% patients receives each regimen). The ICER for fulvestrant 500 mg versus anastrozole gave an ICER of £31,623 per QALY.

Table B101. Scenario C results

Intervention	Total Costs	Total QALYs	ICER
Letrozole	£17,969	1.105	Reference
Anastrozole	£21,377	1.214	£31,242
Fulvestrant 250 mg	£24,559	1.256	ED
Fulvestrant 500 mg	£30,029	1.487	£31,623

- **Scenario D: Cost of post-progression eliminating treatment skipping**

Eliminating treatment skipping from the post-progression treatment pathway, results in an ICER of £31,944 per QALY for fulvestrant 500 mg versus letrozole, which are very similar to the base case results. Based on an incremental analysis ranking of technologies, the results demonstrate that there is extended dominance for anastrozole and fulvestrant 250 mg.

Table B102 Scenario D results

Intervention	Total Costs	Total QALYs	ICER
Letrozole	£18,767	1.105	Reference
Anastrozole	£22,380	1.214	ED
Fulvestrant 250 mg	£25,519	1.256	ED
Fulvestrant 500 mg	£30,991	1.487	£31,944

- **Scenario E: Discounting costs and benefits at 0% and 6%**

Changing the discount rate for costs and benefits from 3.5% in the base case to 0% and 6% has minimal impact on the model outputs (Table B103). When applying a 0% discount rate, the ICER for fulvestrant 500 mg versus letrozole was £30,810 per QALY, while increasing the discount rate to 6% resulted in an ICER of £32,810 per QALY.

Table B103. Scenario E results

Discount rate (costs and benefits)	Intervention	Total Costs	Total QALYs	ICER
3.5 %	Letrozole	£18,836	1.105	Reference
	Anastrozole	£22,467	1.214	ED
	Fulvestrant 250 mg	£25,603	1.256	ED
	Fulvestrant 500 mg	£31,075	1.487	£31,982
0%	Letrozole	£19,729	1.147	Reference
	Anastrozole	£23,719	1.269	ED
	Fulvestrant 250 mg	£26,955	1.315	ED
	Fulvestrant 500 mg	£32,927	1.575	£30,811
6%	Letrozole	£18,268	1.078	Reference
	Anastrozole	£21,679	1.179	ED
	Fulvestrant 250 mg	£24,753	1.218	ED
	Fulvestrant 500 mg	£29,926	1.433	£32,810

- **Scenario F: Altering time horizon**

The time horizon of the model was adjusted to 3 years (in-line with the follow-up period of the CONFIRM trial), 5, 10 years. The results from the lifetime time horizon in the model are presented alongside these results in Table B104.

Table B104 Scenario F results

Time Horizon (years)	Intervention	Total Costs	Total QALYs	ICER
3	Letrozole	£15,483	0.951	Reference
	Anastrozole	£17,435	0.996	£43,025
	Fulvestrant 250 mg	£20,179	1.022	ED
	Fulvestrant 500 mg	£23,382	1.130	£44,418
5	Letrozole	£18,090	1.065	Reference
	Anastrozole	£21,057	1.147	£36,132
	Fulvestrant 250 mg	£24,034	1.181	ED
	Fulvestrant 500 mg	£28,430	1.351	£36,149
10	Letrozole	£18,831	1.104	Reference
	Anastrozole	£22,448	1.211	ED
	Fulvestrant 250 mg	£25,570	1.253	ED
	Fulvestrant 500 mg	£30,969	1.479	£32,301
Lifetime (base case)	Letrozole	£18,836	1.105	Reference
	Anastrozole	£22,467	1.214	ED
	Fulvestrant 250 mg	£25,603	1.256	ED
	Fulvestrant 500 mg	£31,075	1.487	£31,982

ED, Extended dominance

6.7.10 What were the main findings of each of the sensitivity analyses?

For a summary of the main findings from the scenario analysis, see section 6.7.9.

6.7.11 What are the key drivers of the cost-effectiveness results?

See section 6.7.7.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-

reference to evidence identified in the clinical, quality of life and resources sections.

The following measures were taken to check and validate the integrity of the model:

1. The agency that developed the model undertook an internal quality assurance of the model which involved checking the data inputs and referencing, choices of distributions, inclusion of uncertainty, cell calculations and the macros. Further tests were performed, which included extreme value testing and calculations by hand to ensure that the results were logical, consistent with input data, and made intuitive sense.

2. A health economist at AstraZeneca independently reviewed the model to conducted internal validity checks on the data inputs and calculations.

3. At key stages during the development of the model, a clinician involved in regularly treating patients with breast cancer in England, was consulted to provide feedback on the clinical relevance of the modelling approach.

4. An advisory panel consisting of two independent health economists from academia and two oncologists who specialise in the treatment of were commissioned to critique the structure of the model, the key assumptions and data inputs. Furthermore, they validated the outputs of the network meta-analysis and the cost-utility model.

5. To evaluate whether the model outputs were consistent with the TTP and OS efficacy results for all the comparators available in the network meta-analysis (section 6.7.5 and 6.7.6), the time horizon of the model was restricted to 36 months and the results were compared to the observed network meta-analysis results. See section 6.7.1 for the results. In summary, the modelled and the observed results from the network meta-analysis results show that the TTP is very similar for

anastrozole and letrozole. The modelled results for fulvestrant 50mg and fulvestrant 250 mg were lower than expected in comparison to the network meta-analysis results by approximately 0.7 months for fulvestrant 500 mg and 0.4 months for fulvestrant 250 mg. As the model is under-estimating these results, it is expected that the model is under-estimating the QALY gain and thus the ICER given by the model for fulvestrant 500 mg versus anastrozole and letrozole may be lower in the base case.

6.9 Subgroup analysis

6.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

No sub-group analysis was undertaken. This was in-line with the findings in section 5.3.7 in which there were no significant differences between a priori identified subgroups.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

6.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

Not applicable.

6.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 4.

Not applicable.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

The literature review undertaken to identify the relevant published cost-effectiveness evaluation analyses (see section 6.1 for further detail) did not identify any studies that have previously evaluated the cost-effectiveness of fulvestrant 500 mg as a hormonal therapy for ABC in any country. Therefore, it is not possible to compare the results from this cost-effectiveness analysis to previous cost-effectiveness studies.

A comparison of the base-case results from this cost-effectiveness analysis for anastrozole and letrozole with previously published cost-effectiveness studies relevant to this decision problem (described in section 6.1) is not possible. This is because 18 of the 19 relevant studies identified from the literature review did not have the same comparators as used in this cost-effectiveness analysis. Although the Verma *et al*. 2003 study[55] did analyses the cost-effectiveness of anastrozole versus exemestane, the clinical benefit was only reported as life years – thus a comparison of the cost per QALYs is not possible.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

In section 6.4, the expected position that fulvestrant 500 mg may be used within license shows that it may be used in two scenarios. Firstly, as 2nd line hormonal alternative to aromatase inhibitors for patients previously treated with tamoxifen. This population is reflected in the base-case cost-effectiveness analysis undertaken as part of the submission, which is consistent with population in CONFIRM. Fulvestrant may also be used after patient has had previous tamoxifen and aromatase inhibitor therapy, as described in section 6.3. A small proportion of the patients in CONFIRM are known to represent this population. However, due to the small size of this population, a sub-group analysis was not considered appropriate.

The historical use of fulvestrant 250 mg in clinical practice has been as a third or fourth line hormonal treatment option for ABC. Given that no clinical trials have been conducted in this population for fulvestrant 500 mg in this population, the cost-effectiveness of fulvestrant 500 mg in third or fourth line has not been assessed as part of this analysis. As a consequence, the cost-effectiveness analysis undertaken within this submission is not considered relevant to this patient population.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

There are four key weaknesses of the cost-effectiveness study undertaken that have been identified. Firstly, there is limited data available for the network meta-analysis undertaken in the post-anti-oestrogen ABC population. However, the uncertainty associated with this is reflected within the 95% credibility intervals for the scale and log-shape parameters for the underlying distributions used for TTP and OS. This 95% credibility interval was used in the one-way sensitivity and probabilistic sensitivity analysis and thus the impact of this on the cost-utility results has been evaluated (see section 6.7.7 and 6.7.8).

Secondly, a further limitation of the base-case cost-effectiveness analysis undertaken is that no appropriate clinical data is available to compare the clinical effectiveness of exemestane in postmenopausal women with ER+ locally advanced or metastatic breast cancer, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) therapy (see section 5.7.2.1). As such, it has not been possible to compare the cost-effectiveness of fulvestrant 500 mg against exemestane in this patient population. However, there is clinical data available for fulvestrant 500 mg and all the relevant comparators relevant to this decision problem (fulvestrant 250 mg, anastrozole, exemestane and letrozole) in postmenopausal women with ER+ metastatic or locally ABC, whose disease progresses or has relapsed while on or after endocrine (anti-oestrogen) or aromatase inhibitor therapy. As a consequence, a secondary analysis has been conducted to compare the cost-effectiveness of fulvestrant 500 mg versus exemestane in this patient population. The results from this scenario are presented in section 6.7.9 & appendix 9.17.

Thirdly, the clinical data for TTP and OS were incorporated into the model as a distribution, using the best-fitting distribution for TTP and OS (As described in section 6.3.1 and 6.3.7). It was determined that the best-fitting distribution was the Weibull for overall survival and the log normal for time-to-progression. However, it is recognised that there is a degree of uncertainty with regard to the fit of these distributions to the observed TTP and OS results seen in the CONFIRM study as well as the extrapolation. An assessment of the fit of the model to the observed results was undertaken (see section 6.6.1), which showed that the modelled and observed values are very similar – indicating a good fit of the model.

Lastly, it was planned to include grade 3 and 4 adverse events for each of the comparators into the economic model due to the significant impact that these may have in terms of cosy and patient HRQL (see section 6.3.1 for further details). However, this was not feasible because the adverse events were reported inconsistently across the RCTs included in the base-case network meta-analysis for the post anti-oestrogen population. While serious adverse events have been included in the model, it is recognised that as Grade 3 and 4 adverse events have not been modelled, this is a potential limitation of the analysis. However, it is expected that if it had been possible to include Grade 3 and 4 adverse events in the model, the impact on both costs and HQRL is expected to be minimal as the hormonal therapies are well tolerated in general and grade 3 and 4 adverse events are rare across the treatments of interest.

In contrast, one of the key strengths of the model is the time-in-state structure of the model.Using the time-in-state approach, the proportion of patients transiting to the post-progression health state within a given cycle was estimated as the difference between the proportion of patients being alive at that time point and the proportion of patient being progression-free – i.e. the difference between OS and TTP. Given that there is an unproven relationship between TTP and OS for both fulvestrant 500 mg and the lower dose (250 mg) that was previously marketed, the time-in-state approach allows both TTP and overall survival can be incorporated independently with requiring additional assumptions. If a Markov model structure had been used, for example, it would have been necessary to derive information regarding the probability of transitioning between health states. However, based on the clinical data for TTP, it is normally not possible to differentiate how patients transition to death from pre-progression or post-progression. Therefore, while the Markov typically requires an assumption that death can only occur post progression, the time-in-state approach allows the amount of time spent in each health state to be modelled explicitly, thereby avoiding this assumption.

A further strength of the analysis is that the patient flow pathway used in the model is consistent with the current advanced breast cancer clinical guidelines published by NICE. However, to ensure that the model and inputs did appropriately reflect clinical practice, expert opinion was obtained at key stages in developing the model. Finally, it is recognised by NICE that further research is recommended to investigate the most effective endocrine therapy (Advanced Breast Cancer Guidelines, CG91, 2009). Given the limited cost-effectiveness analyses that have been undertaken in this patient population, the cost-effectiveness model developed provides new evidence to compare the cost and effectiveness of the hormonal therapies in ABC patients.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

There are two further analyses that AstraZeneca recommends to enhance the robustness of the results. Firstly, it is recommended that the modelled results

are validated with observational data, when fulvestrant 500 mg has been used in the real-world for an adequate follow-up period. Given that fulvestrant 500 mg was licensed in April 2010 (see section **1.3**), it is expected that this may be possible two to three years after launch. Secondly, given that the overall survival data from the CONFIRM study represents 50% of events, once the next dataset is available after 75%, it would be recommended to undertake further analysis of relative benefits of fulvestrant 500 mg versus its comparators using an indirect comparison.

7 Section C – Implementation

Assessment of factors relevant to the NHS and other parties

7.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

The number of ABC patients that are eligible for second-line hormonal therapy figure has been estimated. The total number of women with ABC in England only has been estimated to be 10,786 in 2009[11]. The same methodology used the NICE costing template has been used to estimate the total number of women with ABC in England and Wales in 2011.

According to the latest available National Statistic data, there were 23,147,700 women in England and Wales 15 years or older in mid-2009. To estimate the population estimate for women 15 years or older in England and Wales in 2011 until 2015, a constant annual growth rate of 0.7%, which is based on the annual population growth rate between 2008 to 2009, (National Statistics, 2010)[12] has been applied to the mid-2009 estimate. Table C1 below outlines the key assumptions applied to estimate the proportion of these women with breast cancer that will have advanced stage breast cancer.

Table C1. Key assumptions applied to estimate the total number of women with advanced breast cancer in England and Wales

Description	Proportion	Source
Proportion of female population ≥15 yrs with invasive breast cancer	0.18%	NICE, Early and locally advanced breast cancer costing template and NICE clinical guidelines 80 and 81, February 2009[11]
Proportion of women with early and locally advanced invasive breast cancer	95.00%	
Proportion of women presenting with advanced breast cancer at diagnosis	5.00%	
Proportion presenting with early breast cancer that die before disease progresses	30.00%	
Proportion with early and locally advanced breast cancer progressing into advanced stage	35.00%	

Applying the 0.7% year-on-year growth, it has been estimated that the total number of women with ABC in England and Wales will be 11,603 in 2011.

The number of the patients that are considered eligible for second-line hormonal treatment in-line with fulvestrant 500 mg's license was then estimated from the total population of women with ABC in England and Wales estimated above, by applying the following assumptions:

- the proportion of women with oestrogen hormone receptor-positive breast cancer (85%) (West Midlands Cancer Intelligence Unit, 2009) [13]
- the proportion of women with hormone receptor-positive ABC for whom endocrine (hormonal) therapy is appropriate (70%) Advanced Breast Cancer NICE Clinical Guideline, 2009)[14]
- the proportion of women in whom disease progresses or relapses while on, or after, other anti-oestrogen therapy (32%) (AstraZeneca Data on file, 2010[15])

It has been assumed that these assumptions are also applicable to Wales. Based on these assumptions, it is estimated that up to 2,209 patients in England and Wales are considered eligible for fulvestrant 500 mg treatment in 2011 based on population in the marketing authorisation. Table C2 below shows the estimated population eligible for fulvestrant 500 mg as per its licensed indication over the next five years.

Table C2: Total estimated population in England and Wales eligible for fulvestrant 500 mg treatment as per its licensed indication

Year	2011	2012	2013	2014	2015
Total number of women ≥15 yrs in England and Wales with ABC	11,603	11,684	11,766	11,849	11,932
Total population eligible for fulvestrant 500 mg (as per licensed indication)	2,209	2,225	2,240	2,256	2,272

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

The current treatment options used for the budget impact analysis was based on the same comparators used for the base case cost-effectiveness analysis where OS and TTP estimates were available – i.e. fulvestrant 250 mg, anastrozole and letrozole. Given that the license for fulvestrant 250 mg was withdrawn in April 2010, it is expected that the fulvestrant 250 mg pack will no longer be available after 2012. Therefore, it has been assumed that the market share will be 0% from 2012 onwards. For the budget impact analysis, the anticipated scenario, where fulvestrant 500 mg is recommended as a treatment option for it licensed indication, is compared to the scenario where there is no fulvestrant 500 mg usage in the same patient population.

7.3 What assumption(s) were made about market share (when relevant)?

As explained previously, a significant proportion of previous fulvestrant 250 mg usage has been off-license post aromatase inhibitor as a third or fourth line hormonal therapy. As such, it is unclear what proportion of current fulvestrant 250 mg and 500 mg usage is in its licensed population as specified by the decision problem. For the purpose of the budget impact analysis, it has been assumed that up until fulvestrant 250 mg was licensed, 1.2% of eligible ABC patients eligible for second-line hormonal therapy used fulvestrant 250 mg. For the reference scenario, it is assumed that there is no usage of fulvestrant 500 mg. For fulvestrant 500 mg's other comparators where it has been possible to model TTP and OS for the cost-utility analysis, i.e. anastrozole and letrozole, the remaining eligible patients has been equally split between the remaining patients in the reference scenario.

For the anticipated scenario, the market share assumption for fulvestrant 500 mg is assumed to be 1.0% in 2011, rising to 8.5% in 2015. Given that it is anticipated that fulvestrant 250 mg will cease to be available from 2012, the market share for this treatment decreases to 0.3% in 2011 and falls to 0.0% from 2012 onwards. The same assumption regarding the remaining eligible patients being equally split between anastrozole and letrozole was applied in the anticipated scenario.

7.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

None.

7.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

The unit costs applied in the budget impact analysis are the same as those used in the cost-utility model, regarding drug costs, hormonal therapy administration costs, treatment-independent costs and for serious adverse events. Further details regarding the drug costs, hormonal therapy administration costs and treatment-independent costs can be found under section 6.5.5 in tables B63, B64 and B66, respectively. The costs associated with serious adverse events are described in section 6.5.6.

7.6 Were there any estimates of resource savings? If so, what were they?

There are no overall resource savings estimated for fulvestrant 500 mg versus the comparators (fulvestrant 250 mg, anastrozole and letrozole) in England and Wales between 2011 and 2015 (see Table C3).

While the budget impact analysis is based on the assumptions used in the base case for the cost-effectiveness analysis where 32.3% of subsequent fulvestrant 250 mg and 500 mg dose administrations take place in the primary care setting, further cost-savings can be obtained when a greater proportion of fulvestrant 250 mg and fulvestrant 500 mg are administered by a nurse in the primary care setting in comparison to the outpatient setting. For example, for the purpose of the modelling the cost of a 15 minute appointment with a nurse in the primary care setting costs £22.78 (Unit Costs of Health and Social Care, PSSRU, 20010)[69], while fulvestrant 250 mg and 500 mg that are delivered in the outpatient appointment by a nurse, are estimated to cost £105 (follow-up oncology visit, National Reference costs, NHS Trusts, 2009-2010)[68].

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated annual budget impact for the NHS in England and Wales, in the first five years following the introduction of fulvestrant 500 mg as a second-line hormonal therapy option for ABC patients is presented in table C3. Based on analysing the costs associated with the drug, administration, serious adverse events and treatment-independent costs, the net estimated annual budget impact for the NHS in England & Wales in 2011 is £116,895, rising to £1,619,909 in 2015.

Table C3 Estimated budget impact of fulvestrant 500 mg in England and Wales, 2011-15

Scenario	**Cost**	**Year**				
		2011	**2012**	**2013**	**2014**	**2015**
Anticipated : fulvestrant 500 mg adopted	Drug	£1,914,597	£2,049,870	£2,292,256	£2,686,601	£3,113,080
	Drug Administration	£864,318	£884,744	£923,979	£985,236	£1,051,336
	Treatment-independent	£5,224,226	£5,284,259	£5,355,181	£5,447,506	£5,553,619
	Serious Adverse Events	£271,607	£274,124	£277,448	£281,749	£286,097

	Total	**£8,274,747**	**£8,492,996**	**£8,848,865**	**£9,401,093**	**£10,004,132**
Reference: no fulvestrant 500 mg used	Drug	£1,819,563	£1,832,300	£1,845,126	£1,858,042	£1,871,049
	Drug Administration	£853,962	£859,939	£865,959	£872,021	£878,125
	Treatment-independent	£5,213,332	£5,249,825	£5,286,574	£5,323,580	£5,360,845
	Serious Adverse Events	£270,995	£272,892	£272,602	£273,400	£274,204
	Total	**£8,157,852**	**£8,214,957**	**£8,270,261**	**£8,327,043**	**£8,384,223**
Net Budget Impact		**£116,895**	**£278,039**	**£578,604**	**£1,074,050**	**£1,619,909**

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

None.

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9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

The Cochrane Library.

9.2.2 The date on which the search was conducted.

January 2010

9.2.3 The date span of the search.

Date span of the search not restricted.

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

1	TRME	Breast-Neoplasms#.DE.
2	Breast#.W..DE. OR breast.tw.	
3	((breast adj milk) OR (breast adj tender$)).ti,ab.	
4	2 NOT 3	
5	TRME	Neoplasms#.W..DE.
6	4 AND 5	
7	Lymphedema#.W..DE.	
8	4 AND 7	

9	((breast near neoplasm$1) OR (breast near cancer$1) OR (breast near tumour$1) OR (breast near tumor$1) OR (breast near carcinoma$1) OR (breast near adenocarcinoma$1) OR (breast near sarcoma$1) OR (breast near dcis) OR (breast near ductal) OR (breast near infiltrating) OR (breast near intraductal) OR (breast near lobular) OR (breast near medullary)).ti,ab.
10	((mammary near neoplasm$1) OR (mammary near cancer$1) OR (mammary near tumour$1) OR (mammary near tumor$1) OR (mammary near carcinoma$1) OR (mammary near adenocarcinoma$1) OR (mammary near sarcoma$1) OR (mammary near dcis) OR (mammary near ductal) OR (mammary near infiltrating) OR (mammary near intraductal) OR (mammary near lobular) OR (mammary near medullary))ti,ab.
11	1 OR 6 OR 8 OR 9 OR 10
12	(Advanc$ OR metasta$3 OR stage ADJ ‘3’ OR stage ADJ III OR stage ADJ ‘4’ OR stage ADJ IV).TI,AB.
13	11 AND 12
14	(fulvestrant OR Faslodex OR exemestane OR Aromasin OR Aromasil OR tamoxifen OR Nolvadex OR Soltamox OR Crisafeno:Diemon OR Farmifeno OR ginarsan OR rolap OR tamoxis OR taxfeno OR trimetro OR estroxyn OR Genox OR Kessar OR ebefen OR tamofen OR tamoplex OR bioxifeno OR estrocur OR Apo AJD Tamox OR Taxus OR Jenoxifen OR mandofen OR oncotam OR Nourytam OR Thamofam OR tamoxasta OR puretam OR zitazonium OR cidatam OR cytotam OR Nolgen OR Virtamox OR tecnofen OR Bilem).TI,AB.
15	(Soltamox OR Taxus OR anastrozole OR Arimedix OR Anastrole OR Anaskebir OR anatraze OR aromenal OR asiolex OR distalene OR Gondonar OR Pantestone OR lezone OR Trozolite OR letrozole OR Femara OR cendalon OR fecinole OR kerbizol OR oncolet OR trozet OR fempro OR megestrol ADJ acetate OR Megace OR megacorp OR meltonar OR varigestrol OR gynodal OR megostat or medroxyprogesterone ADJ acetate OR Provera OR MapAn OR farlutale OR livomedrox OR medrosterona OR depo ADJ provera).TI,AB.
16	(depo ADJ ralovera OR ralovera OR depocon OR medroxyhexal OR farlutal OR prodafem OR acemedrox OR acetoflux OR contracep OR cycrin OR tricilon OR apo medroxy OR gestapuran OR lutopolar OR mepastat OR clinofem OR clinovir OR MPAGyn OR MPA beta OR gestoral OR meprate OR veraplex OR manodepo OR depo ADJ subQ OR diethylstilbestrol OR Stilboestrol OR cilinavagin neomicina OR novo fosfostilben).TI,AB.
17	(tampovagan OR boestrol distibene OR trilostane OR Metopirone OR Modrenal OR desopan OR Toremifene OR Fareston OR Farestone).ti,ab.
18	14 or 15 or 16 OR 17
19	(randomized OR random OR RCT OR double ADJ blind ADJ method OR single ADJ blind ADJ method OR placebo OR randomly OR randomised OR cross ADJ over OR crossover or TRIAL).TI.
20	Randomized-Controlled-Trial.DE. OR Clinical-Trial.DE. OR Controlled-Clinical-Trial.DE. OR Double-Blind-Procedure.DE. OR Controlled-Clinical-Trial.DE. OR Random-Allocation#.DE. OR Randomized-Controlled-Trial#.DE. OR Placebos#.W..DE.
21	(metaanalys$2 OR meta ADJ analys$2).TI,AB. OR PT=META-ANALYSIS

22	case report or PT=CASE-REPORTS OR PT=LETTER OR Letter#.W..DE.
23	(19 OR 20 OR 21) NOT 22
24	23 AND 18 AND 13
25	ANIMAL=YES
26	HUMAN=YES
27	25 not 26
28	24 not 27

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

All clinical abstracts for the past two years from ASCO, the National Cancer Institute, and the San Antonio Breast Cancer Symposium were reviewed. Articles from these searches were combined with the abstracts retrieved from the literature database search.

9.2.6 The inclusion and exclusion criteria.

See Section 5.1

9.2.7 The data abstraction strategy.

The relevance of each citation identified from the databases was based on title and abstract according to the inclusion and exclusion criteria by one reviewer. For the abstracts that meet the inclusion criteria, full text reports were obtained, if available. Prior to ordering the papers, a second reviewer checked a random selection of the abstracts to ensure that all possible abstracts of interest were ordered in full article format. Once the full article was obtained it was then reviewed by a third reviewer to determine whether it met the criteria for inclusion.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: FINDER 1		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
Was the randomisation to the treatment groups truly random?	Conducted at a central randomisation centre upon determination of eligibility	✓
Was the treatment allocation concealed?	The placebo pre-filled syringe looked identical to the active pre-filled syringe and also had a volume of 5 ml.	✓
Were outcome assessors blinded to the treatment allocation?	All study personnel were unaware of the randomised treatment until all decisions on the quality of the data from all patients had been made and documented.	✓
Was the care provider blinded?	All study personnel were unaware of the randomised treatment until all decisions on the quality of the data from all patients had been made and documented.	✓
Was the patient blinded?	Double-blind study	✓
Were baseline characteristics comparable between groups?	See attached table	✓
Were the eligibility criteria specified?	See attached table	✓
Were withdrawals or exclusions accounted for?	See attached diagram	✓
Were the power calculations reported	See attached table	✓
Were the point estimates and measures of variability presented for the primary outcome measure?	CIs were provided	✓
Did the analyses include an intention-to-treat analysis?		✓
Were issues of generalisability addressed?		✓

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

One search strategy was conducted to identify all trials that included fulvestrant or any of the comparators of interest. From the outset it was believed that no direct trials comparing fulvestrant with a comparator of interest would be found and thus a single search strategy was conducted to find all trials that included fulvestrant as well as any comparators of interest.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Study ID or acronym: Buzdar_1996		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
Was the randomisation to the treatment groups truly random?		✓
Was the treatment allocation concealed?	Open label for megestrol acetate, in addition to the fact that the dosing schedule differed for MA and anastrozole	✗
Were outcome assessors blinded to the treatment allocation?	Not stated	?
Was the care provider blinded?	Open label for megestrol acetate, in addition to the fact that the dosing schedule differed for MA and anastrozole	✗
Was the patient blinded?	Open label for megestrol acetate, in addition to the fact that the dosing schedule differed for MA and anastrozole	✗
Were baseline characteristics comparable between groups?	Groups formed were well balanced with respect to demographic and pre-treatment characteristics. There appeared to be an imbalance in treatment allocation for the three groups however it was believed to be an artefact relatd to the large proportion of centres in the European trial in which the total number of patients was not divisible by six (allocated in blocks of 6 in European trial, compared with blocks of 3 in the US trial)	✓
Were the eligibility criteria specified?	As stated in inclusion criteria	✓
Were withdrawals or exclusions accounted for?	Three patients did not receive therapy and one patient who was ranomized to 1 mg received 10mg anastrozole	✓
Were the power calculations reported	Reported in table	✓
Were the point estimates and measures of variability presented for the primary outcome measure?	HR with 97.5% CIs were provided	✓
Did the analyses include an intention-to-treat analysis?	Calculations based on number randomised	✓
Were issues of generalisability addressed?	N/A	✗

Study ID or acronym: Trial 20		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
Was the randomisation to the treatment groups truly random?	The treatment given to individual patients was determined for each centre by a randomization schedule prepared by the Biostatistics Group, AstraZeneca. The randomisation schedule and associated code breaks were produced by computer software that incorporates a standard procedure for generating random numbers. A separate randomisation schedule was produced for each centre, but all the schemes were held and administered by a central randomisation	✓

Study ID or acronym: Trial 20		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
	centre at Covance	
Was the treatment allocation concealed?	Unblinded	✗
Were outcome assessors blinded to the treatment allocation?	Not stated	✗
Was the care provider blinded?	No – one treatment a oral and the other intramuscular	✗
Was the patient blinded?	No – one treatment a oral and the other intramuscular	✗
Were baseline characteristics comparable between groups?	Baseline characteristics were comparable	✓
Were the eligibility criteria specified?	Yes	✓
Were withdrawals or exclusions accounted for?	Detailed numbers provided in clinical study report	✓
Were the power calculations reported	To detect a hazard ratio, for fulvestrant treatment compared with anastrozole treatment, of greater than or equal to 1.43 or less than or equal to 0.70, at a significance level of 5% with 90% power, 490 endpoint events (disease progression or death before progression) had to occur in the trial (i.e., 490 patients had to progress or die; this was equal to a change of 60 days in the median time to progression for patients treated with fulvestrant). This trial had an estimated accrual time of 24 months, with a 6-month follow-up period, and this equated to 196 patients per treatment group being required	✓
Were the point estimates and measures of variability presented for the primary outcome measure?	Detailed analysis in the clinical study report	✓
Did the analyses include an intention-to-treat analysis?	The primary statistical analyses of the efficacy endpoints were conducted using all randomized patients on an intention-to-treat basis, and used response data as defined by the computer algorithm	✓
Were issues of generalisability addressed?		✓

Study ID or acronym: Trial 21		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
Was the randomisation to the treatment groups truly random?	The treatment given to individual patients was determined for each center by a randomization schedule prepared by the Biostatistics Group, AstraZeneca. The randomization schedule and associated code breaks were produced by computer software that incorporated a standard procedure for generating random numbers. A separate randomization schedule was produced for each center. Patients were allocated to treatment in balanced blocks by MEDEX Clinical Trial Services Incorporated	✓
Was the treatment allocation concealed?	Identical treatments and placebos, included a placebo injection	✓
Were outcome assessors blinded to the treatment allocation?	Treatment remained blinded to all conducting the trial (i.e., patients, investigators, AstraZeneca personnel) except for one statistician	✓
Was the care provider blinded?	Treatment remained blinded to all conducting the trial (i.e., patients, investigators,	✓

Study ID or acronym: Trial 21		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
	AstraZeneca personnel) except for one statistician	
Was the patient blinded?	Double blind, double dummy treatment	✓
Were baseline characteristics comparable between groups?	See demographic table	✓
Were the eligibility criteria specified?	Outlined in tables above	✓
Were withdrawals or exclusions accounted for?	Outlined in tables above	✓
Were the power calculations reported	Outlined in tables above	✓
Were the point estimates and measures of variability presented for the primary outcome measure?	Outlined in tables above	✓
Did the analyses include an intention-to-treat analysis?	The primary statistical analyses of the efficacy end points were conducted on an intention-to-treat basis, included all randomized patients, and used response data as defined by the computer algorithm. Secondary (supportive) statistical analyses were conducted on a per-protocol population (according to treatment received) and an intention-to-treat basis with a model that excluded baseline covariates.	✓
Were issues of generalisability addressed?		✓

Study ID or acronym: Lundgren_1989		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
Was the randomisation to the treatment groups truly random?	Not explicitly addressed	?
Was the treatment allocation concealed?	Not explicitly addressed	?
Were outcome assessors blinded to the treatment allocation?	Not explicitly addressed	?
Was the care provider blinded?	Not explicitly addressed	?
Was the patient blinded?	Not explicitly addressed	?
Were baseline characteristics comparable between groups?	As outlined in demographic table	✓
Were the eligibility criteria specified?	As outlined in table above	✓
Were withdrawals or exclusions accounted for?	As outlined in participant flow	✓
Were the power calculations reported	Not explicitly addressed	✓
Were the point estimates and measures of variability presented for the primary outcome measure?	CIs provided where necessary	✓
Did the analyses include an intention-to-treat analysis?	Calculations only involved evaluable patients who had been treated for > 8 weeks	✗
Were issues of generalisability addressed?		✓

Study ID or acronym: Buzdar_2001		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
Was the randomisation to the treatment groups truly random?	Randomisation was performed for each country without stratification by centre.	
Was the treatment allocation concealed?	Double blind – patients received either one tablet letrozole 0.5mg or letrozole 2.5 mg once daily in the morning and one placebo	✓

Study ID or acronym: Buzdar_2001		
Study question	**How is the question addressed in the study?**	**Grade (✓/✗)**
	capsule (matching a MA tablet) qid, or one 40mg capsule MA plus one placebo tablet (matching a letrozole tablet) once daily	
Were outcome assessors blinded to the treatment allocation?		?
Was the care provider blinded?	Double blinded	✓
Was the patient blinded?	Double blinded	✓
Were baseline characteristics comparable between groups?	As outlined in table above – treatment arms were similar with respect to demographics, disease characteristics and extent of prior treatment at the beginning of the study	✓✗
Were the eligibility criteria specified?	As outlined in table above	✓
Were withdrawals or exclusions accounted for?		✓✗
Were the power calculations reported		✓✗
Were the point estimates and measures of variability presented for the primary outcome measure?		✓✗
Did the analyses include an intention-to-treat analysis?	ITT defined as the set of randomised patients who took at least one dose of trial medication. All patients, regardless of their length of treatment were included in the ITT analysis.	✓✗
Were issues of generalisability addressed?		✓

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The following information should be provided.

9.6.1 The specific databases searched and the service provider used (for example, Dialog, Data Star, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

The Cochrane Library.

Not applicable.

9.6.2 The date on which the search was conducted.

Not applicable.

9.6.3 The date span of the search.

Not applicable.

9.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable.

9.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

9.6.6 The inclusion and exclusion criteria.

Not applicable.

9.6.7 The data abstraction strategy.

Not applicable.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Not applicable.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

The following information should be provided.

9.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline
Embase
Medline (R) In-Process
The Cochrane Library.

Not applicable.

9.8.2 The date on which the search was conducted.

Not applicable.

9.8.3 The date span of the search.

Not applicable.

9.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

Not applicable.

9.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

9.8.6 The inclusion and exclusion criteria.

Not applicable.

9.8.7 The data abstraction strategy.

Not applicable.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

9.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

N/A

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

EconLIT

NHS EED.

The following bibliographic databases were searched for relevant cost-effectiveness study publications using the search strategy listed in section 9.10, appendix 10:

- MEDLINE
- EMBASE
- MEDLINE--in process
- EconLIT
- National Health Service Economic Evaluation Database (NHSEED)
- Health Economic Evaluation Database (HEED)

9.10.2 The date on which the search was conducted.

January 2010

9.10.3 The date span of the search.

No restriction applied

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

1	TRME	Breast Neoplasms (MeSH term)
2		Breast (MeSH term)
3		((breast adj milk) OR (breast adj tender$)).ti,ab.
4		2 NOT 3
5	TRME	Neoplasms (MeSH term)
6		4 AND 5
7		Lymphedema (MeSH term)
8		4 AND 7
9		((breast near neoplasm$1) OR (breast near cancer$1) OR (breast near tumour$1) OR (breast near tumor$1) OR (breast

		near carcinoma$1) OR (breast near adenocarcinoma$1) OR (breast near sarcoma$1) OR (breast near dcis) OR (breast near ductal) OR (breast near infiltrating) OR (breast near intraductal) OR (breast near lobular) OR (breast near medullary))ti,ab.
10		((mammary near neoplasm$1) OR (mammary near cancer$1) OR (mammary near tumour$1) OR (mammary near tumor$1) OR (mammary near carcinoma$1) OR (mammary near adenocarcinoma$1) OR (mammary near sarcoma$1) OR (mammary near dcis) OR (mammary near ductal) OR (mammary near infiltrating) OR (mammary near intraductal) OR (mammary near lobular) OR (mammary near medullary))ti,ab.
11		1 OR 6 OR 8 OR 9 OR 10
12		(Advanc$ OR metasta$3 OR stage ADJ '3' OR stage ADJ III OR stage ADJ '4' OR stage ADJ IV).TI,AB.
13		11 AND 12
14		Costs-and-Cost-Analysis (MeSH term) OR Cost-Benefit-Analysis (MeSH term) OR Cost-Of-Illness (MeSH term)
15		Economics OR (cost allocation) OR (cost control) OR (cost saving$1) OR ((cost sharing) OR (deductible$1 AND coinsurance) OR (medical savings account$1) OR (health care cost$1) OR (direct service cost$1) OR (drug cost$1) OR (employer health cost$1) OR (hospital) OR (cost$1) OR (health expenditure$1) OR (capital expenditure$1) OR (value of life) OR (fee) OR (charge) OR (fiscal) OR (funding) OR (financial) OR (finance) OR (pharmacoeoconomics) OR (price$) OR (pricing) OR (expenditure$) OR (cost-utility) OR (cost ADJ utilit$3) OR (quality of life) OR QALY OR QALIES).ti,ab.
16		Models-Economic (MeSH term) OR Economics-Medical (MeSH term) OR Economics-Pharmaceutical (MeSH term)
17		(Markov OR (decision analys$2))ti,ab.
18		13 AND (14 OR 15 OR 16 OR 17)
19		Limit to LG = English

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

Study question	Grade (yes/no/not clear/N/A)	Comments
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	UK NHS
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	CEA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	Not based on single study
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	Not included
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	

17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	£GBP 2005-06
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	10 years
23. Was the discount rate stated?	Yes	3.5%
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	One-way, deterministic and PSA
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination.

"Cost Effectiveness of Treatment Options in Advanced Breast Cancer in the UK", Brown, 2001		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	National Health Service, in UK.
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Not clear	To some extent: Phase III trials.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	

13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	n/a	Not included
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	No	Unit costs were given per unit of resource use, but resource use data not provided
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	£GBP 1998
19. Were details of price adjustments for inflation or currency conversion given?	Yes	The National Health Service Hospital and Community Inflation Index was used to convert these costs to 1997/1998 prices
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	6%
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if costs or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	

33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	Comparison with other studies?

"Economic evaluation of fulvestrant as an extra step in the treatment sequence for ER-positive advanced breast cancer" Cameron, 2008.		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	Median TTP data were used by line of treatment and based on meta-analyses in case based on multiple studies; no further details of the meta-analysis provided, only referred to a publication on methodology
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	

12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	Valuation of health states provided by the clinicians
14. Were productivity changes (if included) reported separately?	Not included	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	Only details of drug frequency and dosing provided, but not related to other resources
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Currency conversion not needed; not clear if price adjustments for inflations were needed
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

"A Bayesian Approach to Markov Modelling in Cost-Effectiveness Analyses: Application to Taxane Use in Advanced Breast Cancer", Cooper, 2003		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	No	Assumed to be National Health Service, in UK
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	

11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Not clear	From literature so limited details, but selection criteria provided
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if costs or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	

31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Publication bias
36. Were generalisability issues addressed?	No	

"Cost-utility analysis of second-line hormonal therapy in advanced breast cancer: a comparison of two aromatase inhibitors to megestrol acetate", Drantsaris, G. 2000.		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Bayesian probabilities

11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	Decision analysis model
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	From the start of second-line hormonal therapy until disease progression
23. Was the discount rate stated?	Yes	Future costs and benefits were not discounted because of the short time periods involved
24. Was the choice of rate justified?	Yes	0%
25. Was an explanation given if cost or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	95% CI best and worst case, utilities from general public women vs. health care professionals

30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Not clear	CER calculated for each HT but not an incremental analysis
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	E.g.: cost of managing drug-related side effects was not included in the analysis
36. Were generalisability issues addressed?	No	

"Cost utility analysis of first-line hormonal therapy in advanced breast cancer: comparison of two aromatase inhibitors to tamoxifen", Dranitsaris, 2003		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	Determine whether the new agents are economically acceptable alternatives to tamoxifen
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost-utility analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	

9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Meta analysis of randomized trials
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost per quality-adjusted progression-free year gained
12. Were the methods used to value health states and other benefits stated?	Yes	Letrozole and anastrozole disease responses and failures
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	n/a	
16. Were quantities of resources reported separately from their unit cost?	n/a	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	No	
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	n/a	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	No	
25. Was an explanation given if costs or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	n/a	

28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	n/a	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	n/a	
36. Were generalisability issues addressed?	Yes	

"*nab*-paclitaxel weekly or every 3 weeks compared to standard docetaxel as first-line therapy in patients with metastatic breast cancer: an economic analysis of a prospective randomized trial", Dranitsaris, 2010		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Docetaxel
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	COI from trial resource use data
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		

8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	No	Direct health resource and costs only
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	£GPB 2007
19. Were details of price adjustments for inflation or currency conversion given?	Yes	CPI from UK Office of National Statistics
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	From the first cycle until the last dose of chemotherapy
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	

27. Was the approach to sensitivity analysis described?	n/a	
28. Was the choice of variables for sensitivity analysis justified?	n/a	
29. Were the ranges over which the parameters were varied stated?	n/a	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes (with limits)	"The initial study plan was to estimate the incremental cost per progression-free and life year gained with each of the nab-paclitaxel groups relative to the docetaxel arm. However, at the time of the analysis, the survival curves for all of the nab-paclitaxel arms had not as yet matured. Therefore, only the incremental cost per PFY relative to docetaxel could be calculated."
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"Cost-effectiveness implications of increased survival with anastrozole in the treatment of advanced breast cancer", Drummond, 1999.		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	Anastrozole (1 mg or 10 mg) with megestrol acetate (160 mg)

6. Was the form of economic evaluation stated?	Yes	Cost-effectiveness analysis
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Life years gained
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Duration of drug treatment and life years gained
12. Were the methods used to value health states and other benefits stated?	Yes	ICER
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Kaplan-Meier, Weilbull method, AUC method and sensitivity analysis
18. Were currency and price data recorded?	Yes	Costs were expressed in 1998 prices
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Since treatment costs are highly dependent on duration of treatment is was judged at the beginning of the analysis that AUC would give the most conservative estimate of the ICER
Analysis and interpretation of results		

22. Was the time horizon of costs and benefits stated?	Not clear	
23. Was the discount rate stated?	No	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if costs or benefits were not discounted?	Yes	Costs and benefits occurring in the future were not discounted to present values owing to the short time duration over which these were observed
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	n/a	
27. Was the approach to sensitivity analysis described?	Yes	To explore the impact on study results of uncertainties in the estimate or methods used
28. Was the choice of variables for sensitivity analysis justified?	Yes	The impact of 3 factors was explored
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

"Cost-effectiveness analysis of exemestane compared with megestrol in patients with advanced breast carcinoma", Hillner, 2001.		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Stated: yes; Justified: no	

4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	MA has been used most commonly but is only modestly effective and is associated with frequent side effects; therefore evaluate exemestane a steroidal aromatase inactivator (well tolerated and significantly delayed tumour progression)
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	No	Not stated is clearly cost-effectiveness (cost/life-year gained)
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Specified that no significant difference in global health score prior to progression between treatment arms (therefore excluded quality of life)
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	One RCT
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Economic: overall survival primary outcome; clinical: overall survival secondary
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	No	Only stated that half-day of lost wages for family or companion was included
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Drug cost based on current wholesale price, and utilization based on RCT, others costs not reported
18. Were currency and price data recorded?	Only for drugs	

19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No justification, but key parameters described	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	No	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes (although no PSA performed)	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	In terms of $50,000 threshold/ life-year
35. Were conclusions accompanied by the appropriate caveats?	Yes	Did not evaluate cost post-progression (delaying chemotherapy and thereby potentially saving costs); Survival EXE based on projection
36. Were generalisability issues addressed?	Yes	In terms of - % patients with visceral disease - other classes of drug

"A new decision model for cost-utility comparisons of chemotherapy in

recurrent metastatic breast cancer.", Hutton, 1996		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Not clear	Assumed NHS in UK
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	CUA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Pooled analysis of 3 clinical studies
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	30 UK oncology nurses
14. Were productivity changes (if included) reported separately?	n/a	
15. Was the relevance of productivity changes to the study question discussed?	No	

16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	£GBP 1994
19. Were details of price adjustments for inflation or currency conversion given?	Yes	National Health Service hospital and community health service inflation index
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	n/a	
24. Was the choice of rate justified?	n/a	
25. Was an explanation given if costs or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	n/a	
27. Was the approach to sensitivity analysis described?	No	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	n/a	No ranges applied
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"A Stochastic Economic Evaluation of Letrozole versus Tamoxifen as a First-Line Hormonal Therapy For Advanced Breast Cancer in Postmenopausal Patients", Karnon, 2003		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	CEA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	RCT
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	Mostly for 1st-line estimates from 1 RCT
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	

16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	£GBP 2000
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	6% for resources and 1.5% for life years
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"A trial-based cost-effectiveness analysis of letrozole followed by tamoxifen versus tamoxifen followed by letrozole for postmenopausal advanced breast cancer", Karnon, 2003		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	No	Based on literature, but no explanation provided
13. Were the details of the subjects from whom valuations were obtained given?	No	
14. Were productivity changes (if included) reported separately?	Not included	

15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Expert interviews
18. Were currency and price data recorded?	Yes and no	Currency provided; no price date provided
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	n/a	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	Results only presented as total costs, LYs and QALYs
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	

36. Were generalisability issues addressed?	no	

"Cost-Effectiveness Analysis of Exemestane Compared with Megestrol in Advanced Breast Cancer. A Model for Europe and Australia", Lindgren, 2002		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	Cost per LYG
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	Clinical data from one trial
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	LYG
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	

15. Was the relevance of productivity changes to the study question discussed?	Not clear	Stated that non-medical costs, such as copayment for patients, and indirect costs were excluded but no discussion of productivity
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	EUR 1999
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	Within trial and lifetime time frame
23. Was the discount rate stated?	Yes	5%
24. Was the choice of rate justified?	No	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Not clear	Assumed to be one-way
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	

35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"Cost-utility analysis for advanced breast cancer therapy in Germany: results of the fulvestrant sequencing model", Lux, 2009.		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	Median TTP data were used by line of treatment and based on meta-analyses in case based on multiple studies; no further details of the meta-analysis provided, only referred to a publication on methodology
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	Valuation of health states provided by the clinicians

14. Were productivity changes (if included) reported separately?	Not included	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	Only details of drug frequency and dosing provided, but not related to other resources
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	No	Currency conversion not needed; not clear if price adjustments for inflations were needed
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	no	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	
24. Was the choice of rate justified?	Yes	
25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Yes	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	

35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	

"Cost Utility and Budget Impact of Third-Generation Aromatase Inhibitors for Advanced Breast Cancer: A Literature-Based Model Analysis of Costs in the Italian national Health Service", Marchetti, 2004		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	CEA and CUA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	Based on more than one RCT
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Meta-analysis was performed and pooled relative risks were provided
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	LYG, and quality-adjusted LYG
12. Were the methods used to value health states and other benefits stated?	Yes	Mostly from the literature
13. Were the details of the subjects from whom valuations were obtained given?	n/a	

14. Were productivity changes (if included) reported separately?	n/a	Not included in health service perspective.
15. Was the relevance of productivity changes to the study question discussed?	n/a	
16. Were quantities of resources reported separately from their unit cost?	Yes	Table III.
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	2003 Euros
19. Were details of price adjustments for inflation or currency conversion given?	n/a	
20. Were details of any model used given?	Yes	Markov model structure provided
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	Previously published economic evaluations.
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	100 cycles of 1 month
23. Was the discount rate stated?	Yes	3% for cost and QALYs
24. Was the choice of rate justified?	Yes	International guidelines
25. Was an explanation given if costs or benefits were not discounted?	(see above)	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Not clear	95% CI (no methodology described)
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Justified choice of comparators and lines of therapy
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Table I (clinical efficacy and safety), Table II (health state utilities), Table III (economic data), Table IV (key economic and effectiveness outcomes), Table V (sensitivity analysis)

33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	Limitations were stated
36. Were generalisability issues addressed?	Not clear	Although, authors do stress the local nature of their analysis in the Italian setting

"Cost Effectiveness of Letrozole in the Treatment of Advanced Breast Cancer in Postmenopausal Women in the UK", Nuijten, 1999		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	NHS in the UK, 1996
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	CEA
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	n/a	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	To some extent
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	

12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	Not in scope of study
15. Was the relevance of productivity changes to the study question discussed?	Yes	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	£GPB 1996
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	Yes	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	Lifetime
23. Was the discount rate stated?	Yes	5% costs only
24. Was the choice of rate justified?	No	
25. Was an explanation given if costs or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	Assumed to be one-way
28. Was the choice of variables for sensitivity analysis justified?	Not clear	
29. Were the ranges over which the parameters were varied stated?	No	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	

32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"Economic Evaluation of Letrozole in the Treatment of Advanced Breast Cancer in Postmenopausal Women in Canada", Nuijten, M. 2000		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	Letrozole or megestrol acetate
6. Was the form of economic evaluation stated?	Yes	
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	A semi-Markov process model was constructed to simulate the course of advanced breast cancer in a typical patient treated either with letrozole or megestrol acetate as a second-line hormone therapy
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Clinical trials
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	(not from just 1 study)
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	Yes	Average weighted values were determined from the appropriate literature where the weighting was based on the number of patients in each clinical trial

11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	n/a	Productivity excluded
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	Resource utilization patterns were determined by assessing direct medical resources for each health State defined by the model. (no data provided)
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Resources were identified and quantified by the eight Canadian expert interviews; costs sources given
18. Were currency and price data recorded?	? (Not clear)	Drug costs given
19. Were details of price adjustments for inflation or currency conversion given?	n/a	
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	? (Not clear)	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	The maximum follow-up period of the model was based on a cut-off point where less than 1% of the patients would still be alive
23. Was the discount rate stated?	Yes	In the primary analysis costs were discounted at 5% annually while outcomes were not discounted
24. Was the choice of rate justified?	No	
25. Was an explanation given if costs or benefits were not discounted?	No	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	? (Not clear)	
28. Was the choice of variables for sensitivity analysis justified?	Yes	

29. Were the ranges over which the parameters were varied stated?	Not clear	In a second series of analyses, major cost drivers in health states (hospitalization, drugs and adverse events) were varied by ±20%
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	n/a	
31. Was an incremental analysis reported?	No	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	The present study suggests that letrozole 2.5 mg may be a suitable alternative to megestrol acetate 160 mg as second-line hormone therapy in the treatment of advanced breast cancer patients in Canada
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"Cost-Effectiveness of Anastrozole Versus Tamoxifen as First-Line Therapy for Postmenopausal women with Advanced Breast Cancer" Simons, 2003		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	Letrozole
6. Was the form of economic evaluation stated?	Yes	

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	North American trial
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Limited	No table of trial results, patient population details, etc.
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	n/a	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Incremental cost savings per patient
12. Were the methods used to value health states and other benefits stated?	Yes	
13. Were the details of the subjects from whom valuations were obtained given?	Yes	
14. Were productivity changes (if included) reported separately?	No	Not included in health system perspective
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	Yes	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	
19. Were details of price adjustments for inflation or currency conversion given?	Not clear	Mentioned
20. Were details of any model used given?	n/a	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Not clear	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	None were used
24. Was the choice of rate justified?	Yes	

25. Was an explanation given if costs or benefits were not discounted?	Yes	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	Not clear	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	No	Not economic evaluation
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	No	

"Economic evaluation of antiaromatase agents in the second-line treatment of metastatic breast cancer", Verma, 2003		
Study question	**Grade (yes/no/not clear/N/A)**	**Comments**
Study design		
1. Was the research question stated?	Yes	
2. Was the economic importance of the research question stated?	Yes	
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Public health care system
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	
5. Were the alternatives being compared clearly described?	Yes	
6. Was the form of economic evaluation stated?	Yes	CEA

7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Not clear	
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Phase III trial, published and unpublished literature, expert opinion
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	
10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No	
11. Was/were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	
12. Were the methods used to value health states and other benefits stated?	n/a	
13. Were the details of the subjects from whom valuations were obtained given?	n/a	
14. Were productivity changes (if included) reported separately?	No	
15. Was the relevance of productivity changes to the study question discussed?	No	
16. Were quantities of resources reported separately from their unit cost?	No	
17. Were the methods for the estimation of quantities and unit costs described?	Yes	
18. Were currency and price data recorded?	Yes	$Can 2000
19. Were details of price adjustments for inflation or currency conversion given?	No	
20. Were details of any model used given?	No	
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	
Analysis and interpretation of results		
22. Was the time horizon of costs and benefits stated?	Yes	
23. Was the discount rate stated?	Yes	5%
24. Was the choice of rate justified?	No	

25. Was an explanation given if costs or benefits were not discounted?	n/a	
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	
27. Was the approach to sensitivity analysis described?	Yes	
28. Was the choice of variables for sensitivity analysis justified?	Yes	
29. Were the ranges over which the parameters were varied stated?	Yes	
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	
31. Was an incremental analysis reported?	Yes	
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	
33. Was the answer to the study question given?	Yes	
34. Did conclusions follow from the data reported?	Yes	
35. Were conclusions accompanied by the appropriate caveats?	Yes	
36. Were generalisability issues addressed?	Yes	Not generalisable outside Canada

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

NHS Economic Evaluation Database (NHS EED)

EconLIT.

The search for relevant utility studies was conducted as part of the search strategy summarised in section 9.11, Appendix 11. The following bibliographic databases were searched for relevant cost-effectiveness study publications using the search strategy listed in section 9.10, appendix 10:

- MEDLINE
- EMBASE
- MEDLINE (R) In Process
- EconLIT
- National Health Service Economic Evaluation Database (NHSEED)
- Health Economic Evaluation Database (HEED)

9.12.2 The date on which the search was conducted.

January 2010

9.12.3 The date span of the search.

No restriction was applied

9.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

1	TRME	Breast Neoplasms (MeSH term)
2		Breast (MeSH term)
3		((breast adj milk) OR (breast adj tender$)).ti,ab.
4		2 NOT 3
5	TRME	Neoplasms (MeSH term)
6		4 AND 5
7		Lymphedema (MeSH term)
8		4 AND 7
9		((breast near neoplasm$1) OR (breast near cancer$1) OR (breast near tumour$1) OR (breast near tumor$1) OR (breast near carcinoma$1) OR (breast near adenocarcinoma$1) OR

		(breast near sarcoma$1) OR (breast near dcis) OR (breast near ductal) OR (breast near infiltrating) OR (breast near intraductal) OR (breast near lobular) OR (breast near medullary))ti,ab.
10		((mammary near neoplasm$1) OR (mammary near cancer$1) OR (mammary near tumour$1) OR (mammary near tumor$1) OR (mammary near carcinoma$1) OR (mammary near adenocarcinoma$1) OR (mammary near sarcoma$1) OR (mammary near dcis) OR (mammary near ductal) OR (mammary near infiltrating) OR (mammary near intraductal) OR (mammary near lobular) OR (mammary near medullary))ti,ab.
11		1 OR 6 OR 8 OR 9 OR 10
12		(Advanc$ OR metasta$3 OR stage ADJ '3' OR stage ADJ III OR stage ADJ '4' OR stage ADJ IV).TI,AB.
13		11 AND 12
14		Costs-and-Cost-Analysis (MeSH term) OR Cost-Benefit-Analysis (MeSH term) OR Cost-Of-Illness (MeSH term)
15		Economics OR (cost allocation) OR (cost control) OR (cost saving$1) OR ((cost sharing) OR (deductible$1 AND coinsurance) OR (medical savings account$1) OR (health care cost$1) OR (direct service cost$1) OR (drug cost$1) OR (employer health cost$1) OR (hospital) OR (cost$1) OR (health expenditure$1) OR (capital expenditure$1) OR (value of life) OR (fee) OR (charge) OR (fiscal) OR (funding) OR (financial) OR (finance) OR (pharmacoeoconomics) OR (price$) OR (pricing) OR (expenditure$) OR (cost-utility) OR (cost ADJ utilit$3) OR (quality of life) OR QALY OR QALIES).ti,ab.
16		Models-Economic (MeSH term) OR Economics-Medical (MeSH term) OR Economics-Pharmaceutical (MeSH term)
17		(Markov OR (decision analys$2))ti,ab.
18		13 AND (14 OR 15 OR 16 OR 17)
19		Limit to LG = English

9.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

9.12.6 The inclusion and exclusion criteria.

The following inclusion criteria were used for the systematic review:

Type of study	Utility study
Population	Adult women with advanced breast cancer, defined as including either stage III or stage IV (metastatic) breast cancer.
Geographical location	Any country
Interventions	Hormonal and/or chemotherapy in 1st or sequential lines of

	treatments for ABC.
Outcomes of interest	Utility weights

The following exclusion criteria were used for the systematic review:

Other	Early breast cancer.
Language	Non-English language.

9.12.7 The data abstraction strategy.

The relevance of each citation identified from the databases was based on title and abstract according to the inclusion and exclusion criteria by one reviewer. For the abstracts that meet the inclusion criteria, full text reports were obtained, if available and assessed against the inclusion and exclusion criteria.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The following information should be provided.

9.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

Medline

Embase

Medline (R) In-Process

NHS EED

EconLIT.

The search for relevant resource data was conducted as part of the search strategy summarised in section 9.11, Appendix 11. The following bibliographic databases were searched for relevant cost-effectiveness study publications using the search strategy listed in section 9.10, appendix 10:

- MEDLINE
- EMBASE

- MEDLINE (R) In Process
- EconLIT
- National Health Service Economic Evaluation Database (NHSEED)
- Health Economic Evaluation Database (HEED)

9.13.2 The date on which the search was conducted.

January 2010

9.13.3 The date span of the search.

No restriction was applied

9.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

1	TRME	Breast Neoplasms (MeSH term)
2		Breast (MeSH term)
3		((breast adj milk) OR (breast adj tender$)).ti,ab.
4		2 NOT 3
5	TRME	Neoplasms (MeSH term)
6		4 AND 5
7		Lymphedema (MeSH term)
8		4 AND 7
9		((breast near neoplasm$1) OR (breast near cancer$1) OR (breast near tumour$1) OR (breast near tumor$1) OR (breast near carcinoma$1) OR (breast near adenocarcinoma$1) OR (breast near sarcoma$1) OR (breast near dcis) OR (breast near ductal) OR (breast near infiltrating) OR (breast near intraductal) OR (breast near lobular) OR (breast near medullary))ti,ab.
10		((mammary near neoplasm$1) OR (mammary near cancer$1) OR (mammary near tumour$1) OR (mammary near tumor$1) OR (mammary near carcinoma$1) OR (mammary near adenocarcinoma$1) OR (mammary near sarcoma$1) OR (mammary near dcis) OR (mammary near ductal) OR (mammary near infiltrating) OR (mammary near intraductal) OR (mammary near lobular) OR (mammary near medullary))ti,ab.
11		1 OR 6 OR 8 OR 9 OR 10

12		(Advanc$ OR metasta$3 OR stage ADJ '3' OR stage ADJ III OR stage ADJ '4' OR stage ADJ IV).TI,AB.
13		11 AND 12
14		Costs-and-Cost-Analysis (MeSH term) OR Cost-Benefit-Analysis (MeSH term) OR Cost-Of-Illness (MeSH term)
15		Economics OR (cost allocation) OR (cost control) OR (cost saving$1) OR ((cost sharing) OR (deductible$1 AND coinsurance) OR (medical savings account$1) OR (health care cost$1) OR (direct service cost$1) OR (drug cost$1) OR (employer health cost$1) OR (hospital) OR (cost$1) OR (health expenditure$1) OR (capital expenditure$1) OR (value of life) OR (fee) OR (charge) OR (fiscal) OR (funding) OR (financial) OR (finance) OR (pharmacoeoconomics) OR (price$) OR (pricing) OR (expenditure$) OR (cost-utility) OR (cost ADJ utilit$3) OR (quality of life) OR QALY OR QALIES).ti,ab.
16		Models-Economic (MeSH term) OR Economics-Medical (MeSH term) OR Economics-Pharmaceutical (MeSH term)
17		(Markov OR (decision analys$2))ti,ab.
18		13 AND (14 OR 15 OR 16 OR 17)
19		Limit to LG = English

9.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable

9.13.6 The inclusion and exclusion criteria.

The following inclusion criteria were used for the systematic review:

Type of study	Resource use study
Population	Adult women with advanced breast cancer, defined as including either stage III or stage IV (metastatic) breast cancer.
Geographical location	UK
Interventions	Hormonal and/or chemotherapy in 1st or sequential lines of treatments for ABC.

The following exclusion criteria were used for the systematic review:

Other	Early breast cancer.
Language	Non-English language.

9.13.7 The data abstraction strategy.

The relevance of each citation identified from the databases was based on title and abstract according to the inclusion and exclusion criteria by one

reviewer. For the abstracts that meet the inclusion criteria, full text reports were obtained, if available and assessed against the inclusion and exclusion criteria.

1.1 Appendix 14: Survival analysis (section 6.3.7)

Figure 3 and Figure 4 below show the overall survival from the CONFIRM study using the log-logistic and the log-normal distribution, respectively.

Figure 3: Overall survival (OS) from CONFIRM study using log logistic distribution

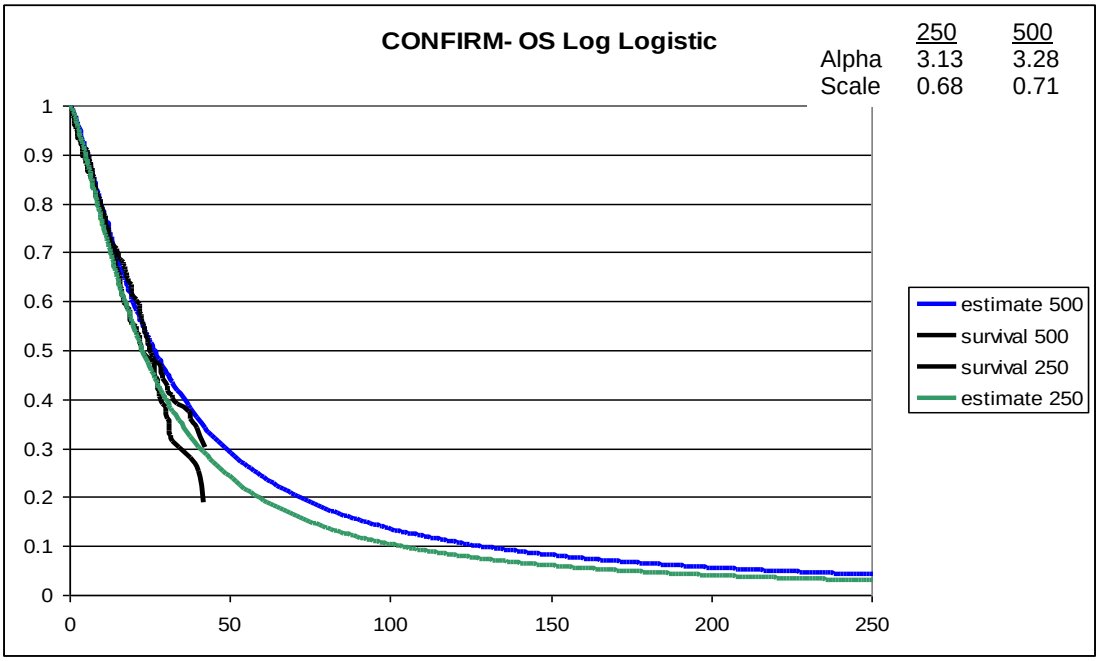


Figure 4: Overall survival (OS) from CONFIRM study using log normal distribution

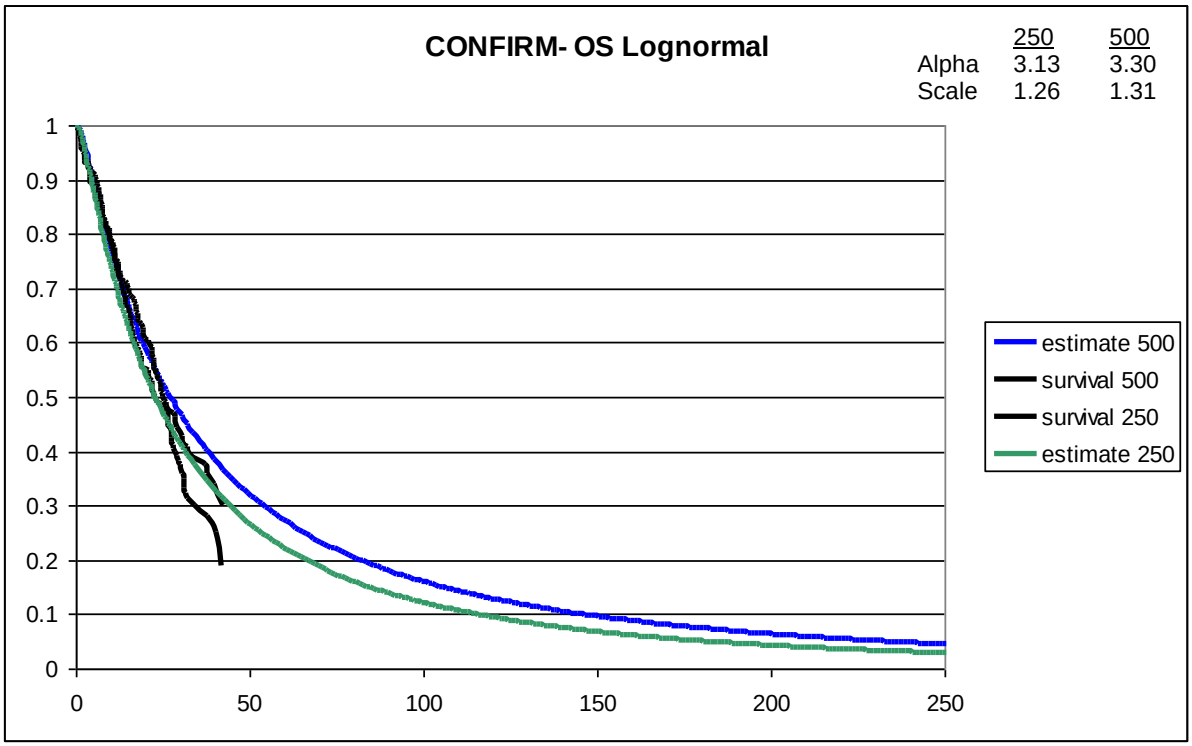


Figure 5 and Figure 6 below show the overall survival from the CONFIRM study using the log-logistic and the log-normal distribution, respectively.

Figure 5: TTP from CONFIRM study using Weibull distribution.

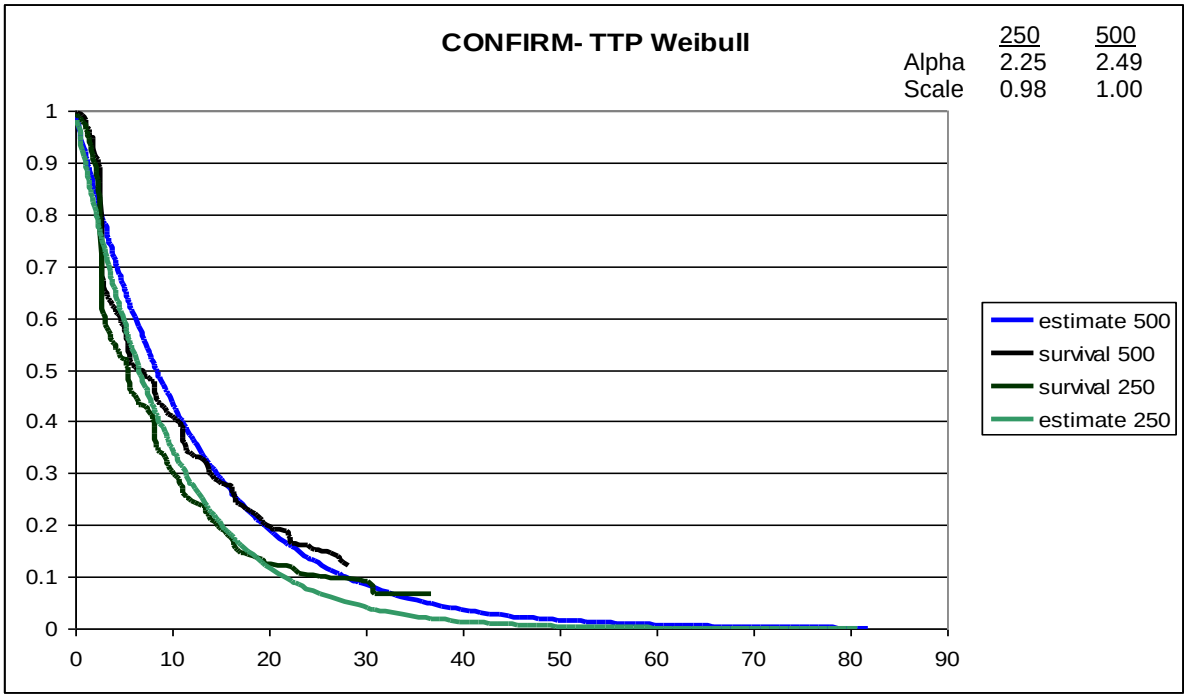
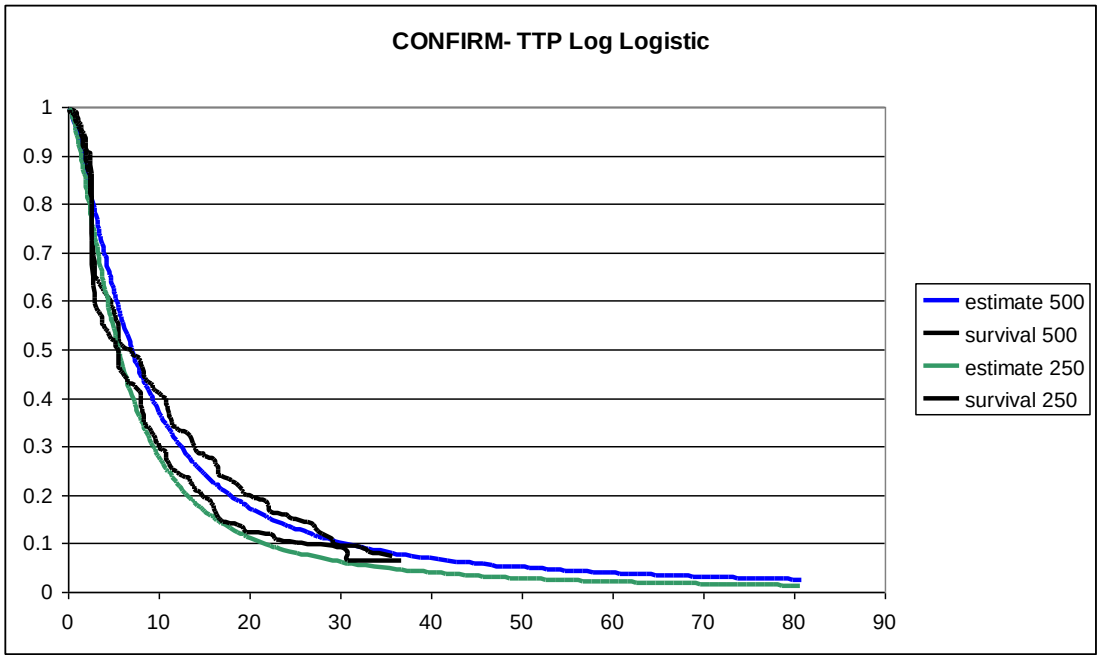


Figure 6: TTP from CONFIRM study log logistic distribution.

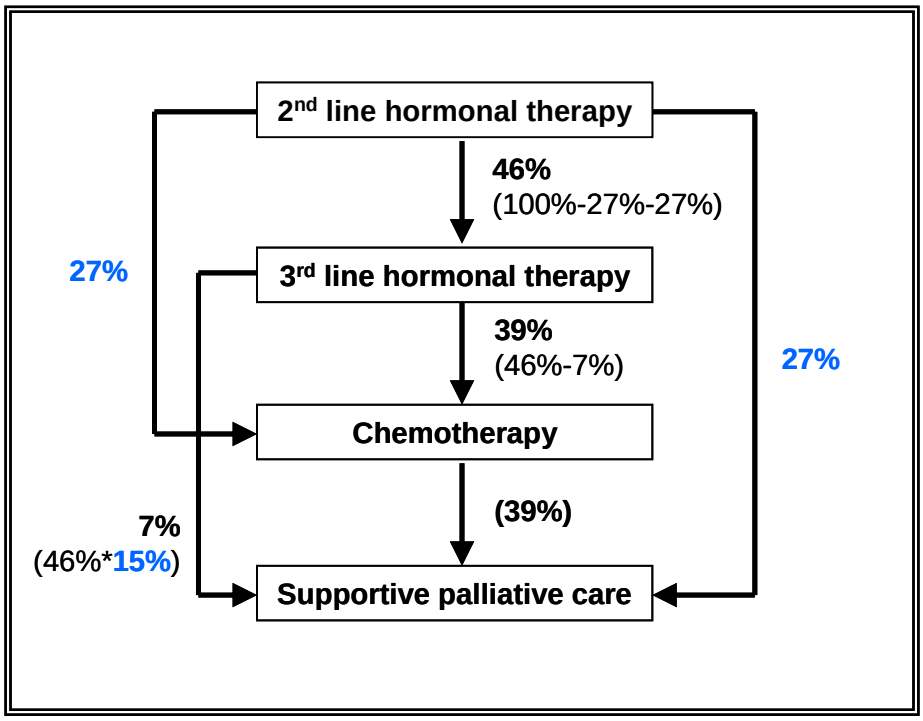


1.2 Appendix 14: Expert opinion questionnaire on treatment sequence and resource utilisation question (section 6.5.4)

10 I. Treatment skipping

In order to establish more realistic costs once the patients have progressed on 2nd line hormonal therapy, it is important to understand the proportion of patients who skip different treatment options within the current clinical practice in the UK. Treatment skipping refers to any patient who does not receive all the recommended treatments within the sequence in Figure 1. A health economic evaluation of Faslodex 250 mg published by Cameron et al. in 2008 reported treatment skipping data that were derived from a clinician survey, which are illustrated in Figure 2.

Figure 2. Faslodex 500 mg economic model treatment skipping



Source: Cameron et al. 2008. Treatment skipping data were derived from the clinician survey, as these data were not available in the literature

Q1. Can you please indicate whether you agree with the estimations? If you disagree could you please estimate the proportion of patients for each skipping pattern?

a. Do you agree that **27%** of patients who receive 2nd line hormonal therapy will skip 3rd line hormonal therapy and directly receive chemotherapy?

Agree: _____ Disagree: _____ → If disagree, proportion estimated? _____

b. Do you agree that **27%** of patients who receive 2nd line hormonal therapy will skip 3rd line hormonal therapy and chemotherapy and directly receive supportive palliative care?

Agree: _____ Disagree: _____ → If disagree, proportion estimated? _____

c. Do you agree of those patients that received 2nd line hormonal therapy and 3rd line hormonal therapy, **15%** will skip chemotherapy and directly receive supportive palliative care?

11 II. Third line hormonal therapy

There are no clear recommendations on the specific types of hormonal therapies that should be used for third line therapy in the NICE ABC guidelines. NICE recommends offering an aromatase inhibitor (either non-steroidal or steroidal) to postmenopausal women with ER-positive breast cancer and no prior history of endocrine therapy and topostmenopausal women with ER-positive breast cancer previously treated with tamoxifen. However, it is acknowledged that there is currently no evidence on the most appropriate endocrine treatment for patients who have received prior treatment with an AI. The guidelines state that there is no evidence directly comparing these agents so it is not possible to recommend any particular aromatase inhibitor.

Since there is insufficient information reported across the clinical trials to evaluate the previous endocrine therapies received by patients, an average cost of all the 2nd line hormonal therapies (excluding the hormonal therapy received during 2nd line) will be used to estimate the cost of third line therapy.

The economic model will assess the cost-effectiveness of the following hormonal therapies for second line therapy:

3. Fulvestrant 500 mg (Faslodex®)
4. Fulvestrant 250 mg (Faslodex®)
5. Anastrozole 1 mg (Arimidex®)
6. Letrozole 2.5 mg (Femara®)
7. Exemestane 25 mg (Aromasin®)

Q2. In your expert clinical opinion, is it reasonable to assume that during 3rd line hormonal therapy patients will receive an average cost associated with all of the alternative hormonal therapies, except the hormonal therapy received during 2nd line?

Agree?_____

Disagree?_____ →If disagree, please state why and suggest alternative approach:

12 III. Chemotherapy regimens

NICE recommends that for patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence:

A. first line: single-agent docetaxel
B. second line: single-agent vinorelbine or capecitabine
C. third line: single-agent capecitabine or vinorelbine (whichever not used as 2nd line treatment).

This recommendation was based on the findings of a health economic analysis performed by NICE that compared the cost-effectiveness of various sequences of single-agent and combination chemotherapy regimens for patients with advanced breast cancer who are anthracycline resistant or for whom anthracycline therapy is contraindicated.

The results of this analysis were used to rule out certain sequences of therapy that are unlikely to be cost-effective from an NHS perspective. Out of the seventeen different sequences evaluated (See Appendix 2), the three following sequences were identified as the most cost-effective options.

Q3. Based on your expert experience, can you please indicate the proportion of patients who receive the following most cost-effective chemotherapy treatment sequences?

1st line chemotherapy	**2nd line chemotherapy**	**3rd line chemotherapy**	**Proportion of patients?**
Docetaxel	Capecitabine	No chemotherapy	%
Docetaxel	Capecitabine	Vinorelbine	%
Docetaxel	Vinorelbine	Capecitabine	%

Q4. Is there another treatment sequence not mentioned above that is very commonly used in clinical practice in the UK and should be considered in the economic model? If yes, could you please circle the appropriate 1st line (a-d), 2nd line (a-c), and 3rd line (a-c) treatments below and estimate the proportion of patients you expect to receive this sequence?

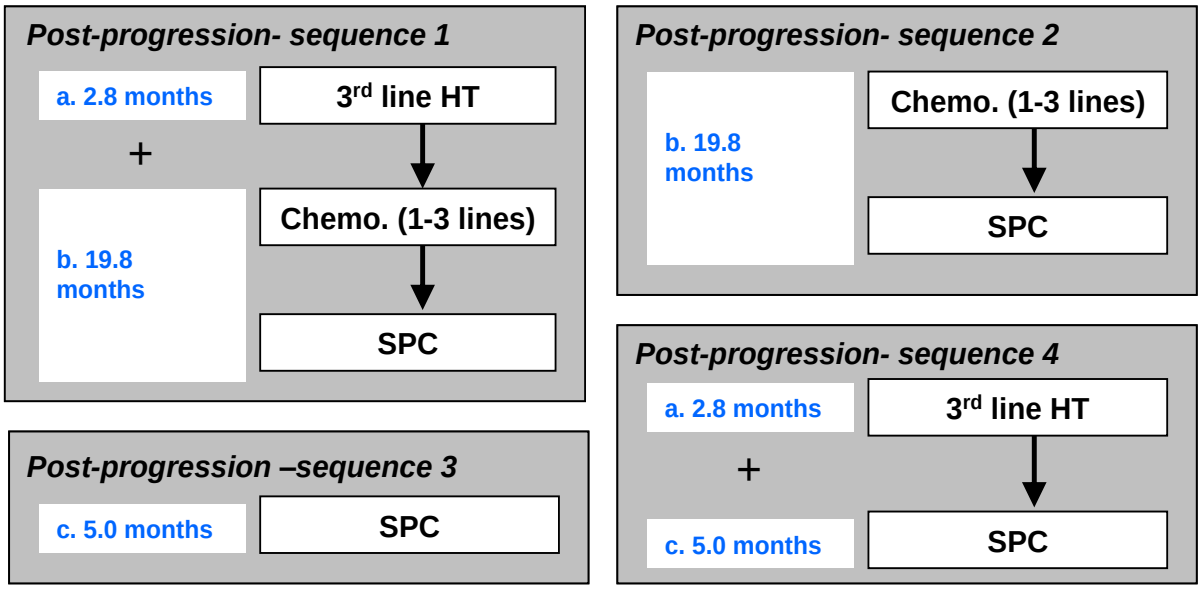
1st line chemotherapy options	**2nd line chemotherapy**	**3rd line chemotherapy**	**Proportion of patients?**
a. Capecitabine + docetaxel	a. Capecitabine	a. Capecitabine	%

b. Gemcitabine + docetaxel c. Paclitaxel d. Docetaxel	b. Vinorelbine c. Supportive palliative care only	b. Vinorelbine c. Supportive palliative care only	

13 IV. Post-progression treatment sequences

For modelling purposes, the average time to progression for each active treatment will determine the average treatment duration for patients. Figure 3 presents the treatment sequences included in the economic model and the estimated durations associated with each treatment sequence.

Figure 3. Post-progression treatment sequences and estimated average durations



Source: a. Nuijen et al 1999 and Karnon et al. 2003 [55% responding for median 7.3 months with overall survival of 16 months b. NICE ABC cost-utility model estimated overall survival times for three chemotherapy sequences including supportive palliative care; c. NICE ABC cost-utility model estimated survival for patients receiving no chemotherapy and only supportive palliative care;

Q5. Do you agree with the estimated average duration of time spent for each post-progression sequence? If not, please estimate the time in months for each sequence.

a. Do you agree with **2.8 months** for the duration of 3rd line hormonal therapy?

Agree:_____ Disagree:____ →If disagree, estimate duration? _____ months

b. Do you agree with **19.8 months** for chemotherapy including supportive palliative care?

Agree:_____ Disagree:____ →If disagree, estimate duration? _____ months

c. Do you agree with **5.0 months** for supportive palliative care alone?

Agree:_____ Disagree:____ →If disagree, estimate duration? _____ months

d. Do you agree that it is reasonable to add the durations together for each sequence?

Agree:_____ Disagree:____ →Suggest?

_____

14 V. Resource Utilisation

There is limited data available for resource use associated with each line of treatment in ABC. Therefore we are interested in validating the resources used estimated previously by UK experts.

Health care resource utilisation associated with hormonal therapy has been divided into the following categories, each of which addresses 2nd line and 3rd line hormonal therapy separately:

A. Resources related to drug administration

B. Resources related to routine care and procedure/diagnostic tests

C. Resources related to adverse event management (serious adverse events and very common adverse events with grade 1 and 2 severity)

NB: These resources are only related to patients' pre-progression health state, i.e. while patients continue to receive hormonal active treatment. The total resource utilisation is the sum of the resource for drug administration plus routine care and procedure/diagnostic tests plus adverse event management.

A. Resources related to <u>drug administration</u>

Q6. In your expert clinical opinion, are the resources related to drug administration listed below reflective of current clinical practice for **second-line hormonal therapy** in postmenopausal ER+ ABC patients in the UK? If not, please identify whether any other types of resource use should be considered for drug administration? *Please provide as much detail as possible (type of health care service required, frequency per month, and reason).*

Health care service s and reason for use	# visits	Agree or Disagree?
Consultation with oncologist to initiate 2nd line hormonal therapy (all treatments)	1 visit	Agree: ____ Disagree:____ →Frequency? _____ _____
One outpatient delivery of 2nd line hormonal therapy by injection (for Faslodex only)	1 visit per administration	Agree: ____ Disagree:____ →Frequency? _____ _____

Q7. The economic model assumes that 3rd line hormonal resource utilisation for drug administration is the same as for 2nd line hormonal therapy. In your expert clinical opinion,

is this a reasonable assumption? If not, please state why and suggest alternative resource use recommendations.

B. Resources related to routine care and procedure/diagnostic tests

Q8. Is the proportion of patients estimated to receive each of the following resources per 3 month period listed below reflective of current clinical practice in postmenopausal ER+ ABC patients in the UK for 2nd line and 3rd line hormonal therapy for routine and procedure/diagnostic tests? If not, please identify the proportion of patients that you estimate would receive each type of health care resource utilisation per 3 month period. *Please note some resources may not be relevant for consideration in the economic model and can be estimated as zero.*

Health care service visits	**2nd line hormonal therapy**		**3rd line hormonal therapy**	
	% patients/ 3 m	Agree or disagree?	% patients / 3 m	Agree or disagree?
Oncology visit	93%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	93%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
General Practitioner visit	58%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	58%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Radiographer	27%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	27%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Biochemistry test	91%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	91%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Blood test	89%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	89%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Bone scintigraphy	57%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	61%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Ultrasound	19%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	42%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Chest x-ray	44%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	34%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Bone x-ray	27%	Agree: ___ ; Disagree: ___ →if no, % patients? _____	25%	Agree: ___ ; Disagree: ___ →if no, % patients? _____
Hospitalisation (general	2% (9 days)	Agree: ___ ; Disagree: ___	3% (9.3	Agree: ___ ; Disagree: ___

medicine)		→if no, % patients? _____	days)	→if no, % patients? _____
Hospitalisation (Oncology)	4% (5 days)	Agree: ___ ; Disagree: ___ →if no, % patients? _____	10% (10 days)	Agree: ___ ; Disagree: ___ →if no, % patients? _____

Source: Expert data collected by Nuijten et al. 2000 in Canada from 8 clinical experts;

Q9. Please identify if any other important types of resource use for routine and procedure/diagnostic tests are not listed above that should be considered. Please estimate the proportion of patients that would receive the additional resource per 3 month period for patients receiving 2nd line hormonal therapy and 3rd line hormonal therapy:

Any additional resources?_____

If yes, please estimate the proportion of patients using the service per 3 month period?
2nd line HT patients: _____% / 3 months; 3rd line HT patients: _____% / 3 months

Q10. Do you think that additional oncology or GP visits would be required for orally administered 2nd line hormonal treatments beyond what is included in the routine care as described above? If yes, please estimate the type of visits required for oral administration and the frequency per month for an average patient.

C. Resources related to adverse event management

In general hormonal therapies are well tolerated; therefore there is very limited data reported in the clinical trials regarding grade 3 and 4 adverse events. Consequently, the economic model will include serious adverse events and very common (>1/10) adverse associated with the 2nd line hormonal therapies identified through the SMPCs where sufficient data is available across the relevant studies.

Clinical trials evaluating 2nd line hormonal therapy report a low incidence of serious adverse events, which are generally defined as an adverse event occurring during any study phase at any dose of the investigational product, comparator or placebo that fulfils one or more of the following criteria:

- results in death or is immediately life-threatening
- requires in-patient hospitalisation or prolongation of existing hospitalisation (including hospitalisation for tests related to AEs), except hospitalisation that has been planned before enrolment
- results in persistent or significant disability or incapacity
- is a congenital abnormality or birth defect
- is an important medical event that may jeopardise the patient or may require medical intervention to prevent one of the outcomes listed above.

Q11. In the economic model the occurrence of a serious adverse event will be associated with a hospital admission. Do you agree with this assumption?

Agree?_____→ If yes, please estimate the length of stay in hospital on average?_____ days

Disagree?_____→ If yes, please reasons why and suggest alternative health care resources:

Q12. In this population of patients with advanced breast cancer receiving 2nd line hormonal therapy, could you provide some examples of serious adverse events that you expect?

The health care resource utilisation associated with very common adverse events are assumed to be grade 1 and 2 since the clinical trials often state that the adverse events were mild to moderate in severity. Grade 1 and 2 adverse events associated with hormonal therapies have been previously estimated by clinical experts in Germany in 2007 for an economic evaluation of Faslodex by Lux et al. 2009.

Q13. Are the types and frequency of resource use associated with each grade 1 or 2 adverse event appropriate for the UK situation? If not, could you recommend alternative resource utilisation? *Please provide as much detail as possible (type of health care severe required, frequency per month).*

Very Common Adverse Events	**Estimated treatment**	**Estimate hospital visits**	**Other resources estimated**	**Agree or Disagree?**
Fatigue	None	None	None	Agree: ____ Disagree:____ → Suggest? _____
Headache	Ibuprofen 400 mg 3 x/d for 3 days	None	GP visit	Agree: ____ Disagree:____ → Suggest? _____
Hot Flushes	Venlafaxine 37,5 mg 2 x/d for 4 Weeks	None	GP visit	Agree: ____ Disagree:____ → Suggest? _____
Joint and musculoskeletal pain*	Ibuprofen 400 mg 3 x/d for 3 days	None	GP visit	Agree: ____ Disagree:____ → Suggest? _____

Very Common Adverse Events	Estimated treatment	Estimate hospital visits	Other resources estimated	Agree or Disagree?
Nausea	Zofran 8 mg 2 x daily for 2 days (also 32 mg)	None	GP visit	Agree: ____ Disagree:____ → Suggest? _____
Injection pain/ reaction	Venlafaxin 75 mg 2 x/d for 4 weeks	None	GP visit	Agree: ____ Disagree:____ → Suggest? _____

**Includes arthralgia and less often limb pain, osteoarthritis, back pain, arthritis, myalgia and joint stiffness*

Q14. Please identify if there are any other key common adverse events that should be considered that are associated with 2nd line hormonal therapy which are associated with significant resource utilisation and/or have a significant impact to the patient. Please identify any resources associated with the suggested adverse events.

Q15. The economic model assumes the same resource utilisation is associated with third-line hormonal therapy for adverse event management as for second-line hormonal therapy for both serious adverse events and very common grade 1 and 2 adverse events. In your expert clinical opinion, is this a reasonable assumption? If not, please state why and suggest alternative resource use recommendations.

15 Final Comments

Q16. Would you have any additional comments regarding the treatment pathway and subsequent lines of treatment for the management of advanced breast cancer in postmenopausal ER+ women following second-line hormonal therapy?

Q17. Would you have any additional comments regarding resource utilisation for the treatment of advanced breast cancer in the context of the Faslodex 500 mg economic model?

1.3 Appendix 15: Post-progression health state costs (section 6.5.6)

The table below shows the 18 strategies used to estimate the average cost associated with chemotherapy and supportive palliative care, which was based on the cost-utility analysis undertaken by NICE in the advanced breast

cancer guidelines. The proportion of patients estimated to receive each strategy in England was based on expert opinion.

Table 1. Duration, costs, and proportion of patients per chemotherapy sequence

Sequence #	First line	Second line	Third line	Total expected time (months)	Total Expected Costs (£)	Proportion of patients
1	DOC+CAP	VIN	No Chemo	**15.2**	**£19,787**	**0%**
2	DOC+CAP	No Chemo	No Chemo	**10.9**	**£14,882**	**0%**
3	GEM+DOC	CAP	VIN	**23.1**	**£30,313**	**0%**
4	GEM+DOC	CAP	No Chemo	**18.5**	**£22,544**	**0%**
5	GEM+DOC	VIN	CAP	**23.0**	**£30,284**	**0%**
6	GEM+DOC	VIN	No Chemo	**15.9**	**£26,765**	**0%**
7	GEM+DOC	No Chemo	No Chemo	**11.5**	**£19,215**	**0%**
8	PAC	CAP	VIN	**19.6**	**£21,995**	**18%**
9	PAC	CAP	No Chemo	**14.9**	**£16,692**	**11%**
10	PAC	VIN	CAP	**19.6**	**£21,966**	**18%**
11	PAC	VIN	No Chemo	**12.4**	**£18,430**	**11%**
12	PAC	No Chemo	No Chemo	**8.0**	**£13,441**	**18%**
13*	DOC	CAP	VIN	**21.3**	**£23,055**	**4%**
14*	DOC	CAP	No Chemo	**16.7**	**£18,118**	**3%**
15*	DOC	VIN	CAP	**21.3**	**£23,027**	**5%**
16	DOC	VIN	No Chemo	**14.2**	**£19,527**	**3%**
17	DOC	No Chemo	No Chemo	**9.8**	**£14,590**	**4%**
18	DOXO	No Chemo	No Chemo	**20.2**	**£9,340**	**5%**
Average duration and cost of chemotherapy				**15.8**	**£18,449**	NA

DOC+CAP= Docetaxel+ capecitabine; GEM+DOC= Gemcitabine + docetaxel; PAC= Paclitaxel; DOC= Docetaxel; VIN= Vinorelbine; No Chemo= Supportive palliative care only; CAP= Capecitabine;

1.4 Appendix 16: OS base case and scenario network meta-analysis

The Akaike's Information Criterion values in the table below support the selection of the Weibull distribution in terms of providing the best fit to the data.

Akaike's Information Criterion (AIC) goodness of fit for OS based on CONFIRM study

OS	Fulvestrant 250		Fulvestrant 500	
	Model Log likelihood	**AIC**	***Model Log likelihood***	**AIC**
Weibull	-910.00	1820.0	-814.70	1629.4
Log logistic	-912.70	1825.4	-814.90	1629.8
Log normal	-917.70	1835.4	-817.60	1635.2

The WinBUGs code is presented below.

Fixed effects network meta-analysis model for hazard ratios:

$\ln(hr_{jk}) \sim \text{Normal}(d_{bk}, \sigma^2) \sim \text{Normal}(d_{Ak} - d_{Ab}, \sigma^2)$ (Fixed effects model)

Note : $d_{AA} = 0$

d_{Ak}~Normal(−,−) (Prior distributions)

σ~Uniform(−,−)

j = study

b = control group, can be treatment A, B, C

k = treatment group, can be treatment B, C, D

$\ln(hr_{jk})$ = mean log hazard ratio for treatment k in study j

σ^2_{jk} = variance for the difference of treatment k in study j

d_{bk} = pooled difference

d_{Ak} = pooled difference for treatment k versus A

d_{Ab} = pooled difference for treatment b versus A

WinBUGS coding for fixed-effect hazard ratios:

```
model{

# Model for change in outcome parameter
 for(i in 1:N){
                    prec.d[i]<- 1/(se[i]*se[i])
                    diff[i] ~ dnorm(delta[i],prec.d[i])
                    delta[i]<- d[t[i]] - d[b[i]]
                    }
# Residual Deviance for data i
 for(i in 1:N){
 dev[i] <- (diff[i]-delta[i])* (diff[i]-delta[i])/(se[i]*se[i])
                    }
resdev <- sum(dev[])

# All pair wise effect sizes between treatments
for (c in 1:(NT-1)) {
for (k in (c+1):NT) { D[c,k] <-(d[k] - d[c] )
Prob_better[c,k]<- step(D[c,k])
}}

for (c in 1:(NT-1)) {
for (k in (c+1):NT) { hr[c,k] <- exp(D[c,k])

}}

# Ranking and prob{treatment k is best}
# Ranking and prob{treatment k is best}
for (k in 1:NT) {
          dneg[k] <- -1 * d[k]
          rk[k]<- rank(dneg[],k)
          best[k]<-equals(rk[k],1)}

# vague priors for basic parameters
          d[1]<-0
          for (k in 2:NT) {d[k] ~ dnorm(0,.00001) }
}
```

Base case analysis

Extent of data in network presented in section 5.7.4.

Base case: OS data set analyzed for Post-AO

Treatment	HR	Ln(HR)	SE	Baseline comparator	Reference
F500 mg	0.84	-0.174	0.102	F250 mg	CONFIRM
F250 mg	0.98	-0.020	0.078	Anas 1	Howell 2005
Anas 1	0.78	-0.248	0.127	MA	Buzdar 1996+1998
Letro 0.5	0.79	-0.236	0.122	MA	Buzdar 2001
Letro 2.5	0.92	-0.083	0.120	MA	Buzdar 2001

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg;

Results presented in section 5.7.6.

Scenario analysis

Network for TTP for post-AO/AI scenario

#	References	F500	F250	F250 LD	Anas 1	Anas 10	MA	Letro 0.5	Letro 2.5	EXE
1	CONFIRM	☑	☑							
2	Howell 2002		☑		☑					
3	Osborne 2002		☑		☑					
4	Buzdar 1996				☑	☑	☑			
4	Buzdar 1998				☑	☑	☑			
5	Buzdar 2001						☑	☑	☑	
6	Chia 2008 (EFFECT)			☑						☑
7	Kaufmann 2000						☑			☑
8	Dombernowsky 1998						☑	☑	☑	
9	Gershanovich 1998							☑	☑	

Scenario: OS data set analyzed in for the post-AO/AI scenario

Treatment	HR	Ln(HR)	SE	Baseline comparator	Reference
F500	0.84	-0.174	0.102	F250	CONFIRM
F250	0.98	-0.020	0.078	Anas 1	Howell 2005
Anas 1	0.78	-0.248	0.127	MA	Buzdar 1996+1998
Letro 0.5	0.79	-0.236	0.122	MA	Buzdar 2001
Letro 2.5	0.92	-0.083	0.120	MA	Buzdar 2001
MA	1.17	0.155	0.109	Exe	Kaufmann 2000
Letro 0.5	1.12	0.113	0.129	MA	Dombernowsky 1998
Letro 2.5	0.82	-0.198	0.137	MA	Dombernowsky 1998
Letro 2.5	0.64	-0.446	0.141	AG	Gershanovich 1998

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg; Exe=Exemestane 1mg;

Scenario: OS MTC results for the post-AO/AI scenario

Treatment	HR	2.5th percentile	97.5th percentile
Fulvestrant 500 mg	0.84	0.69	1.03
Anastrozole 1 mg	1.02	0.88	1.19
Megestrol acetate 160 mg**	1.30	0.98	1.74
Letro 0.5 mg*	1.22	0.87	1.71
Letro 2.5 mg	1.14	0.81	1.60
Exemestane 1 mg	1.12	0.78	1.60
Aminoglutethimide 250mg*	1.78	1.15	2.76

*Letrozole 0.5 mg was not included in the economic evaluation as this dose is not licensed and AG was not a treatment of interest. ** Megestrol acetate was not included in the economic model as this was not defined as a relevant comparator

1.5 Appendix 17: TTP base case and scenario network meta-analysis

For time-to-event data such as the TTP, the usual approach is to pool hazard ratios. This requires the assumption of a hazard ratio to be constant over time, including the post trial period. Given that the log-normal distribution was the best fitting distribution for the TTP for both fulvestrant 250 and fulvestrant 500 based on the fit of the patient level data from the CONFIRM study (see Table XX), the assumption of a constant hazard ratio is not valid. Therefore, instead of pooling the hazard ratios, the difference in the scale and the difference in the log shape parameters were pooled across the studies.

Table XX. Akaike's Information Criterion (AIC) goodness of fit for TTP based on CONFIRM study

TTP	Fulvestrant 250		Fulvestrant 500	
	Model Log likelihood	**AIC**	***Model Log likelihood***	**AIC**
Weibull	-1041.80	2083.6	-1036.7	2073.4
Log logistic	-1013.4	2026.8	-1017.7	2035.4
Log normal	-1011.9	2023.8	-1012.6	2025.2

Data extraction of Kaplan Meier Curves

The transformed survival proportion and corresponding variance was calculated according to Kalbfleisch and Prentice [72]taking into account that the overlap of the sequence of events and the sequence of censoring is unknown (the number of terms in the sum of Kalbfleisch and Prentice is overestimated by assuming death before censoring, while the values of the terms themselves are overestimated by assuming death after censoring). In order to use the methods described by Kalbfleish and Prentice to assess the uncertainty at least one event must have occurred. Therefore a conservative approach was used when selecting the time points to avoid underestimating the uncertainty so that at least 5 events had taken place between each pair of adjacent time points (i.e. time points for which the number at risk was less than 5 were not extracted). When the numbers at risk were not provided, the median follow-up period was used, together with the percentage still alive at median follow-up, in order to obtain an estimate of the censoring during the trial (100%- 50%/% alive). Data for time points after median follow-up were not used in that situation, as it was not possible to estimate the number at risk for those time points. The percentage censoring was used analogous as described above. For two studies, a lower bound for the time after the last patient started participation was known. Discontinuation rates were used to obtain an upper bound for censoring. Again, censoring was used in such a way that uncertainty was overestimated in order to be conservative.

Fixed effects network meta-analysis model for shape and scale:

The fixed effects model for network meta-analysis assuming a log-normal parametric survival curve can be defined according to:

Likelihood

$$\ln(-\ln(S)) \sim N(\theta_{jkt}, \sigma^2_{jkt})$$

Model

$$\Phi^{-1}(1-\exp(-\exp(\theta_{jkt}))) = \exp(\varphi_{jk})\left(\ln(t)+\mu_{jk}\right)$$

$$\begin{pmatrix}\mu_{jk}\\ \varphi_{jk}\end{pmatrix} = \begin{cases} \begin{pmatrix}\mu_{1jb}\\ \mu_{2jb}\end{pmatrix} & b = A,B,C,\ldots \text{ if } k = b \\ \begin{pmatrix}\mu_{1jb}\\ \mu_{2jb}\end{pmatrix} + \begin{pmatrix}d_{1bk}\\ d_{2bk}\end{pmatrix} = \begin{pmatrix}\mu_{1jb}\\ \mu_{2jb}\end{pmatrix} + \begin{pmatrix}d_{1Ak}\\ d_{2Ak}\end{pmatrix} - \begin{pmatrix}d_{1Ab}\\ d_{2Ab}\end{pmatrix} & \text{if } k \text{ 'alfabetically' after } b \end{cases}$$

Priors

$$\begin{pmatrix}\mu_{1jb}\\ \mu_{2jb}\end{pmatrix} \sim N\left(\begin{pmatrix}0\\ 0\end{pmatrix}, \tau^2_{\mu}\right) \qquad \tau^2_{\mu} = \begin{pmatrix}10^4 & 0\\ 0 & 10^4\end{pmatrix}$$

$$\begin{pmatrix}d_{1Ak}\\ d_{2Ak}\end{pmatrix} \sim N\left(\begin{pmatrix}0\\ 0\end{pmatrix}, \tau^2_{d}\right) \qquad \tau^2_{d} = \begin{pmatrix}10^4 & 0\\ 0 & 10^4\end{pmatrix}$$

with Φ^{-1} the inverse of the cumulative normal distribution, s_{jkt} and σ^2_{jkt} are obtained as transformation of the Kaplan Meier survival percentage and its variance (specifying the likelihood), while the expectation θ_{jkt} is ascribed to the parameters μ_{jk} and φ_{jk} of the log-normal distribution, taking into account the time point *t*, from which the corresponding survival percentage (and its variance) is obtained. The vector $\begin{pmatrix}d_{1Ak}\\ d_{2Ak}\end{pmatrix}$ denotes the difference in the parameters μ_{jk} and φ_{jk} between treatment *k* and the overall placebo/overall baseline comparator *A* (analogous for $\begin{pmatrix}d_{1Ab}\\ d_{2Ab}\end{pmatrix}$). Finally, $\begin{pmatrix}d_{1Ak}\\ d_{2Ak}\end{pmatrix}$ is assigned to a normal prior distribution with uncertainty τ^2_d, while the baseline values $\begin{pmatrix}\mu_{1jb}\\ \mu_{2jb}\end{pmatrix}$ are assigned per trial *j* to a prior distribution with uncertainty τ^2_{μ}.

The WinBUGs code is presented below.

WinBUGS coding for fixed effects network meta-analysis model for shape and scale:

```
Model{

for (i in 1:N){

#step 1: from ln(-ln(S)) to S
#normal distribution for ln(-ln(S))
#Input regarding ln(-ln(S)): se_ln_hazard

prec_ln_hazard[i] <- 1/pow(se_ln_hazard[i],2)
ln_hazard[i]  ~ dnorm(mean_hazard [i], prec_ln_hazard[i])
mean_hazard[i] <- log(-log(Survival_percentage[i]))


Survival_percentage[i] <- 1-normal_distribution_percentage[i]
probit(normal_distribution_percentage[i]) <- log_normal_model [i]*
indicator_between_lower_upper_probit[i]+upper[i]+lower[i]

log_normal_model[i] <- exp(log_shape[i])*(log(time[i])-log_scale[i])
#part2 > 0 if part 1 between -5 and 5
indicator_between_lower_upper_probit[i] <- step(5-log_normal_model[i])*step(log_normal_model[i]+5)
upper[i] <- step(log_normal_model[i]-5) *5
lower[i] <- step(-5- log_normal_model [i])*-5

log_scale[i]<-mu[s[i],1]+ d[t[i],1] - d[b[i],1]
log_shape[i]<-mu[s[i],2]+ d[t[i],2] - d[b[i],2]
}

# priors
d[1,1]<-0
d[1,2]<-0
for(j in 2 :NT){
d[j,1:2] ~ dmnorm(mean[1:2],prec2[,])
}
for(k in 1 :NS){
mu[k,1:2] ~ dmnorm(mean[1:2],prec2[,])
}


# output/results for baseline comparator = treatment 1
for (i in 1:NS){
        trial_log_scale[i,1] <- equals(baseline_short[i], 1)*mu[i,1]
        trial_log_shape [i,1] <- equals(baseline_short[i], 1)*mu[i,2]
        trial_count[i,1] <- equals(baseline_short[i], 1)
}

baseline_log_scale<-sum(trial_log_scale[,1])/sum(trial_count[,1])
baseline_log_shape<-sum(trial_log_shape[,1])/sum(trial_count[,1])

for (c in 1:NT) {
adjusted_log_scale[c]<-   d[c,1]+ baseline_log_scale
adjusted_log_shape[c]<- d[c,2]+ baseline_log_shape
adjusted_shape[c] <- exp(adjusted_log_shape[c])
}

for (c in 1:NT){
        for (tt in 1:30){
                probit(ST[c,tt]) <- adjusted_model[c,tt]*indicator_adjusted_model[c,tt]
                +indicator_adjusted_upper[c,tt]+indicator_adjusted_lower[c,tt]
```

```
            adjusted_model[c,tt] <- adjusted_shape[c]*(log(tt)-adjusted_log_scale[c])
            indicator_adjusted_model[c,tt] <- step(5-
            adjusted_model[c,tt])*step(adjusted_model[c,tt]+5)
            indicator_adjusted_upper[c,tt] <- step(adjusted_model[c,tt]-5) *5
            indicator_adjusted_lower[c,tt] <- step(-5- adjusted_model[c,tt])*-5

            Prob[c,tt] <- 1 - ST[c,tt]
        }
}
}
```

Base case analysis

Extent of data in network presented in section 5.7.4.

Time-to-progression as extracted from Kaplan-Meier curves of individual studies

	F250			F500			F250 LD		Anas 1			MA		Letro 2.5	Letro 0.5
	Finder 1	Finder 2	Howell '02	Confirm	Finder 1	Finder 2	Finder 1	Finder 2	Osborne '02	Buzdar '96+ '98	Howell '02	Buzdar '01	Buzdar '96+ '98	Buzdar '01	Buzdar '01
t	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)
0.92			0.93												
0.98									0.96						
1.00				0.98											
1.01										0.96					
1.02													0.94		
1.03											0.96				
1.07												0.96		0.96	
1.92															0.93
1.98										0.81					
1.99											0.84				
2.00				0.91								0.89		0.89	
2.02															
2.03			0.86						0.87						
2.05													0.81		
2.93											0.59				
2.97										0.59					
2.99															
3.00				0.65			0.86					0.55		0.55	
3.01					0.78	0.69		0.62							0.68
3.03	0.84	0.61													
3.04			0.62										0.61		
3.05									0.54						
3.92			0.56												
3.94												0.47		0.47	
3.96									0.48		0.53				

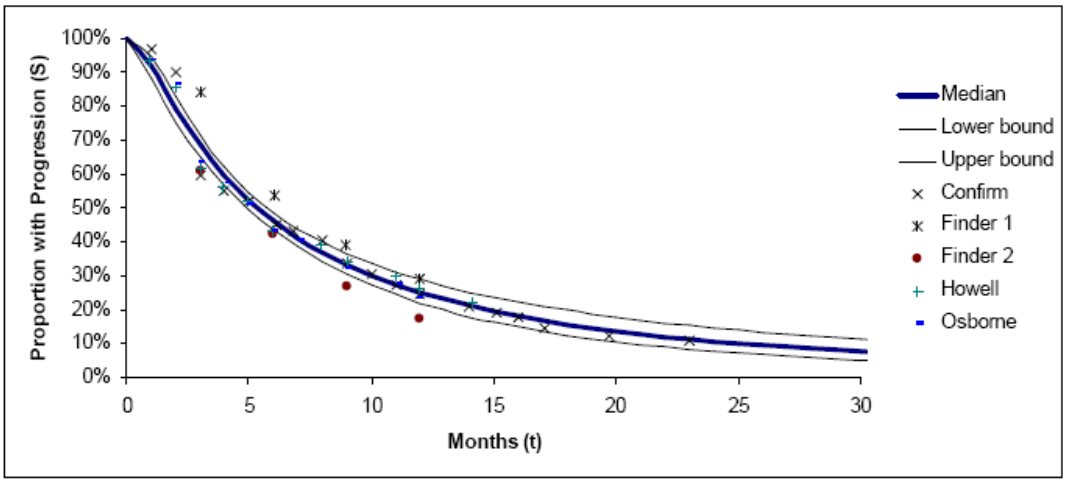
	F250			F500			F250 LD		Anas 1			MA		Letro 2.5	Letro 0.5
	Finder 1	Finder 2	Howell '02	Confirm	Finder 1	Finder 2	Finder 1	Finder 2	Osborne '02	Buzdar '96+ '98	Howell '02	Buzdar '01	Buzdar '96+ '98	Buzdar '01	Buzdar '01
t	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)
3.99															0.55
4.00				0.62									0.49		
4.03										0.48					
4.92			0.52								0.50				
4.99										0.42					
5.00				0.58											
5.02													0.42		
5.95											0.41				
5.96													0.37		
5.98												0.36		0.36	
5.99		0.42	0.43			0.50									
6.01							0.61	0.51							
6.02	0.54														
6.03									0.40						0.44
6.04					0.54										
6.05										0.35					
6.10				0.51											
6.91											0.37				
6.93													0.34		
7.01												0.31			
7.93			0.39												
7.95													0.33		
7.99									0.35	0.33					
8.05											0.34				
8.10				0.48											
8.96													0.28		
8.97									0.30			0.25			
8.98	0.39				0.43										0.37
8.99		0.27						0.38							
9.01										0.30					
9.02							0.43							0.28	
9.04			0.34								0.29				
9.10				0.43											
9.96											0.27				
9.99													0.25		
10.00				0.41					0.28						
11.00			0.30	0.38					0.25	0.28					
12.00	0.29	0.17	0.26	0.34	0.33	0.39	0.31	0.28	0.22	0.24		0.20	0.23	0.24	
12.10											0.23				0.30
13.00														0.20	
13.90											0.20				
14.00				0.30											
14.05													0.21		
14.10			0.22												
14.90										0.22					

	F250			F500			F250 LD		Anas 1			MA		Letro 2.5	Letro 0.5
	Finder 1	Finder 2	Howell '02	Confirm	Finder 1	Finder 2	Finder 1	Finder 2	Osborne '02	Buzdar '96+ '98	Howell '02	Buzdar '01	Buzdar '96+ '98	Buzdar '01	Buzdar '01
t	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)
15.00				0.28					0.17						
15.10												0.15			0.26
16.00														0.17	
16.90				0.24											
16.95										0.19			0.18		
18.00														0.14	0.22
19.10				0.21											
20.50				0.19											
20.90													0.15		
21.00										0.17					
23.95										0.14					
24.00				0.16											
24.95													0.12		
27.00				0.14											
28.10				0.12											
29.20				0.11											
32.30				0.09											
35.80				0.07											

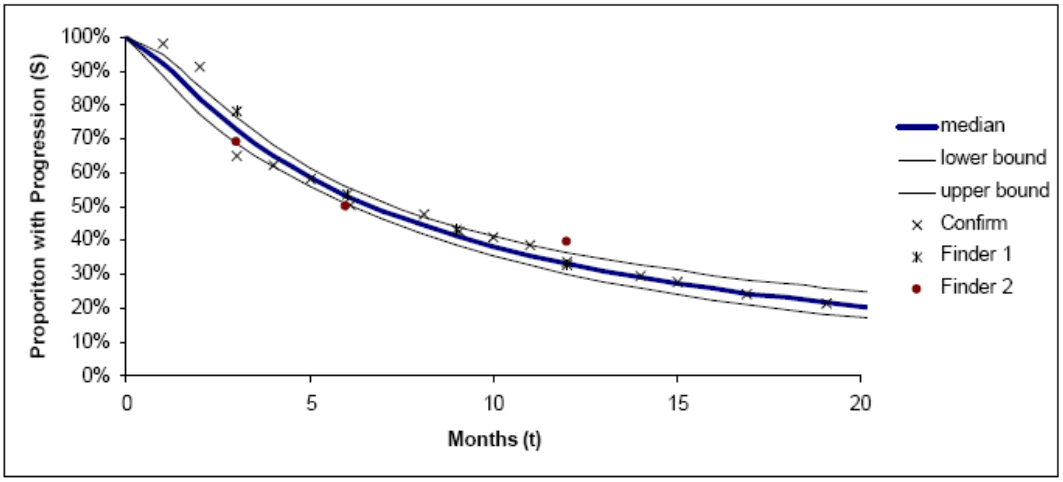
F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg;

Top-line results are presented in section 5.7.6.

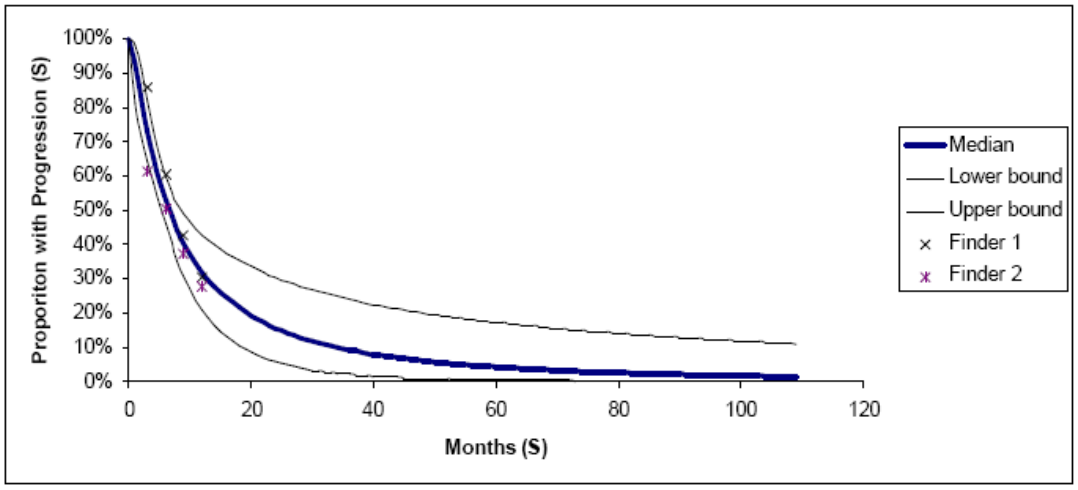
TTP as estimated with fixed effects log normal network meta-analysis model for fulvestrant 250 (and 2.5% and 97.5% credibility limits)



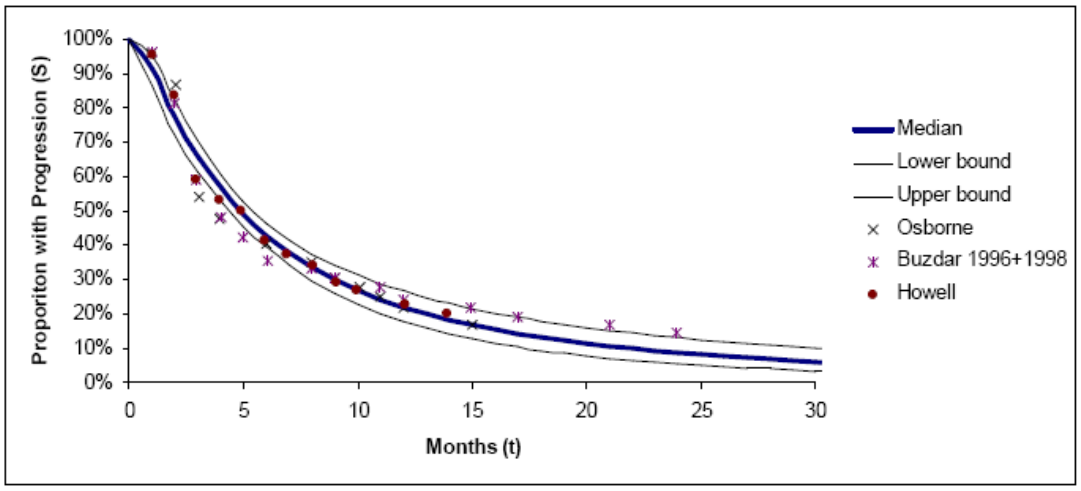
TTP as estimated with fixed effects log normal network meta-analysis model for fulvestrant 500 (and 2.5% and 97.5% credibility limits)



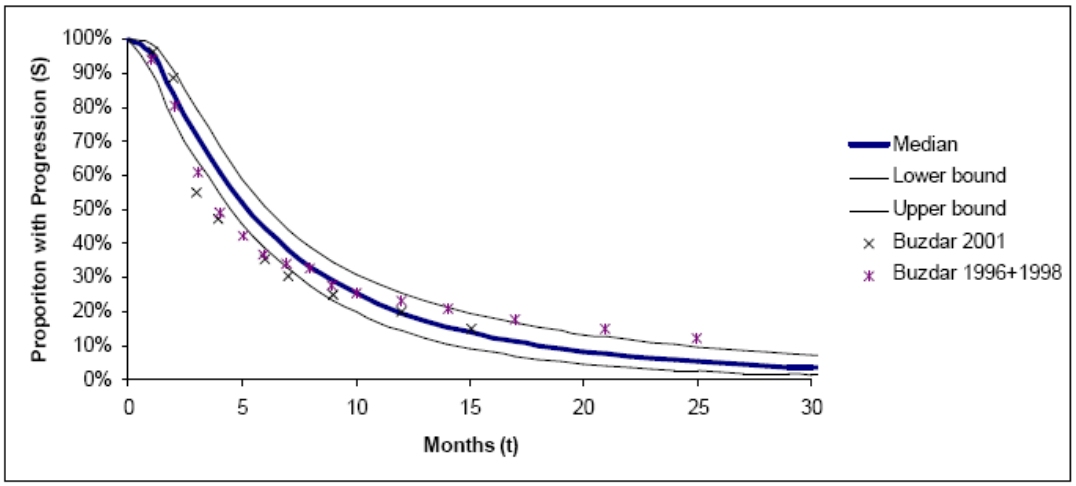
TTP as estimated with fixed effects log normal network meta-analysis model for fulvestrant 250 Loading Dose (LD) (and 2.5% and 97.5% credibility limits)



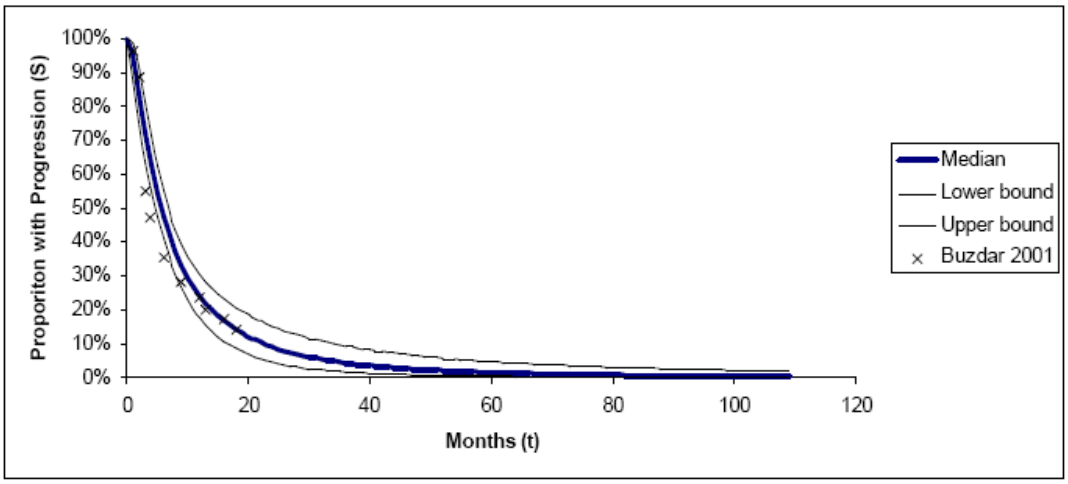
TTP as estimated with fixed effects log normal network meta-analysis model for anastrozole 1 mg (and 2.5% and 97.5% credibility limits)



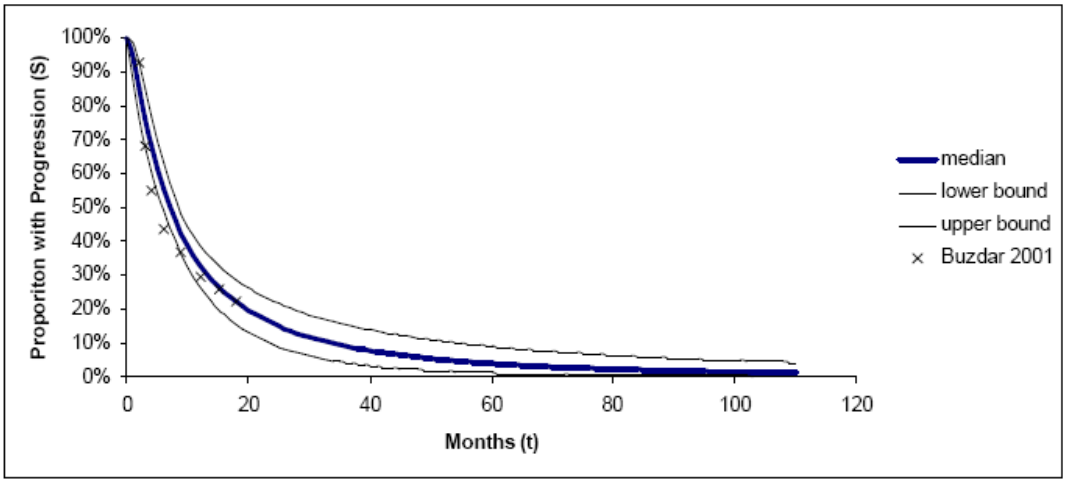
TTP as estimated with fixed effects log normal network meta-analysis model for megestrol acetate 160 mg (and 2.5% and 97.5% credibility limits)



TTP as estimated with fixed effects log normal network meta-analysis model for letrozole 2.5 mg (and 2.5% and 97.5% credibility limits)



TTP as estimated with fixed effects log normal network meta-analysis model for letrozole 0.5 mg (and 2.5% and 97.5% credibility limits)



Correlation matrix from the posterior distribution (WinBUGS output) for base case post-AO with all fulvestrant data

		Baseline (F250)		F250 LD		F500 mg		Anas 1 mg		MA		Letro 0.5		Letro 2.5	
		scale	log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape
Baseline (F250)	scale	1.00	0.04												
	log shape	0.04	1.00												
F250 mg LD	Δ scale			1.00	-0.27										
	Δ log shape			-0.27	1.00										
F500 mg	Δ scale					1.00	0.40								
	Δ log shape					0.40	1.00								
Anas 1 mg	Δ scale							1.00	0.26						
	Δ log shape							0.26	1.00						
MA	Δ scale									1.00	0.40				
	Δ log shape									0.40	1.00				
Letro 0.5	Δ scale											1.00	0.34		
	Δ log shape											0.34	1.00		
Letro 2.5	Δ scale													1.00	0.38
	Δ log shape													0.38	1.00

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg;

Scenario analysis

Network for TTP for post-AO/AI scenario with all fulvestrant data

#	References	F500	F250	F250 LD	Anas 1	Anas 10	MA	Letro 0.5	Letro 2.5	EXE
1	CONFIRM	☑	☑							
2	FINDER 1	☑	☑	☑						
3	FINDER 2	☑	☑	☑						
4	Howell 2002		☑		☑					
5	Osborne 2002		☑		☑					
6	Buzdar 1996				☑	☑	☑			
6	Buzdar 1998				☑	☑	☑			
7	Buzdar 2001						☑	☑	☑	
8	Chia 2008 (EFFECT)			☑						☑
9	Kaufmann 2000						☑			☑
10	Dombernowsky 1998						☑	☑	☑	
11	Gershanovich 1998							☑	☑	

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg; EXE=Exemestane 1mg;

Time-to-progression as extracted from Kaplan-Meier curves of additional studies included in the post-AO/AI scenario (studies from Table A4

	F250LD	MA	Letro 2.5		Letro 0.5		EXE		
	Chia	Kaufmann	Dombernovsky	Dombernovsky	Gershanovich 1998	Dombernovsky	Gershanovich 1998	Chia	Kaufmann
t	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)	S(t)
0.99					0.94				
1.02		0.98					0.96		0.98
1.04						0.94			
1.68	0.86							0.86	
1.92									0.73
1.97		0.69							
1.98						0.85			
2.01					0.85				
2.02				0.92					
2.03			0.88						
2.06							0.82		
2.98		0.60							
2.99									0.64
3.00			0.66			0.61			
3.01					0.60				
3.05				0.62					
3.06							0.57		
3.33	0.57							0.57	
3.96							0.47		
3.97			0.54	0.52					
4.00									0.52
4.01					0.47				
4.05		0.49							
4.06						0.51			
4.91		0.46							

	F250LD	MA	Letro 2.5		Letro 0.5		EXE		
	Chia	Kaufmann	Dombernovsky	Dombernovsky	Gershanovich 1998	Dombernovsky	Gershanovich 1998	Chia	Kaufmann
5.00	0.41							0.41	
5.02									0.49
5.93		0.36							0.43
5.99				0.47		0.39			
6.01					0.43				
6.04			0.43						
6.05							0.40		
6.77	0.28							0.28	
7.00			0.39						0.41
7.05		0.34		0.42					
7.91		0.32							
8.02							0.39		0.38
8.47	0.23							0.23	
8.95				0.39					
8.98						0.34			
9.00			0.32						
9.03		0.27							
9.04					0.37		0.32		
9.09									0.34
9.90							0.28		
9.95		0.25							
10.10			0.29						
10.17	0.17							0.17	
11.00									0.29
11.10		0.23							
11.57	0.14							0.14	
11.90							0.25		
12.00				0.34		0.30			
12.10			0.26		0.33				
13.50	0.12							0.12	
14.00			0.22						
14.90					0.27				
14.93	0.10							0.10	
15.00			0.18			0.26	0.21		
16.00						0.22			
17.00			0.14		0.25				
17.90				0.30					
18.00							0.18		
19.10					0.21				
19.90							0.16		

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg;

Network meta-analysis TTP results: Fulvestrant 250 mg (baseline comparator) for scenario analysis (post-AO/AI)

Treatment	Scale			Log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250 mg	1.665	1.592	1.733	-0.193	-0.332	-0.080

Network meta-analysis TTP results: Difference in log normal parameters for treatment alternatives versus fulvestrant 250 mg for scenario analysis (post-AO/AI)

Treatment	Difference in scale			Difference in log shape		
	Scale	2.5th percentile	97.5th percentile	Log shape	2.5th percentile	97.5th percentile
Fulvestrant 250 mg LD*	0.183	0.036	0.335	-0.015	-0.266	0.233
Fulvestrant 500 mg	0.228	0.162	0.294	-0.105	-0.191	-0.018
Anastrozole 1 mg	-0.106	-0.198	-0.017	0.006	-0.135	0.145
Megestrol acetate 160 mg*	-0.024	-0.152	0.103	0.203	0.020	0.371
Letrozole 0.5 mg*	0.104	-0.060	0.261	0.035	-0.188	0.252
Letrozole 2.5 mg	0.064	-0.096	0.217	-0.004	-0.230	0.214
Exemestane 1 mg	0.153	0.006	0.299	0.093	-0.148	0.327

*Excluded from the economic model; LD=Loading dose

Correlation matrix from the posterior distribution (WinBUGS output) for post-AO/AI scenario with all fulvestrant data

		Baseline (F250)		F250 LD		F500 mg		Anas 1 mg		MA		Letro 0.5		Letro 2.5		Exe	
		scale	log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape	Δ scale	Δ log shape
Base-line (F250)	scale	1.00	0.12														
	log shape	0.12	1.00														
F250 mg LD	Δ scale			1.00	0.21												
	Δ log shape			0.21	1.00												
F500 mg	Δ scale					1.00	0.44										
	Δ log shape					0.44	1.00										
Anas 1 mg	Δ scale							1.00	0.30								
	Δ log shape							0.30	1.00								
MA	Δ scale									1.00	0.40						
	Δ log shape									0.40	1.00						
Letro 0.5	Δ scale											1.00	0.39				
	Δ log shape											0.39	1.00				
Letro 2.5	Δ scale													1.00	0.39		
	Δ log shape													0.39	1.00		
Exe	Δ scale															1.00	0.23
	Δ log shape															0.23	1.00

F500=Fulvestrant 500mg; F250=Fulvestrant 250mg; F250LD=Fulvestrant 250mg + loading dose; Anas 1=Anastrozole 1mg; Letro 0.5=Letrozole 0.5mg; Letro 2.5=Letrozole 2.5mg Exe=Exemestane 1mg;

1.6 Appendix 18: Serious adverse event base case and scenario network meta-analysis

Base case analysis

Seven RCTs were used for the base case network meta-analysis for serious adverse events, which included the same as those used for the base case analysis for OS and TTP. This included CONFIRM, FINDER 1, FINDER 2, Buzdar 1996/98, Buzdar 2001, Osbourne 2002 and Howell 2002.

The WinBUGs code is presented below for fixed model.

```
model{


# Model for log-odds, for types of trial indicated by b[i]
 for(i in 1:N)
            {
            r[i] ~ dbin(p[i], n[i])
            logit(p[i]) <-mu[s[i]]+ d[t[i]] - d[b[i]]

# Residual Deviance for data i
            rhat[i] <- p[i]*n[i]
             dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i])) + (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
            }
            resdev <- sum(dev[])

# Fixed effect priors
            for(j in 1:NS){ mu[j]~dnorm(0,.0001)}
            prec <- 1/(sd*sd)
            sd~dunif(0,2)

# Give priors for log-odds ratios
                        d[1]<-0
                        for (k in 2:NT){d[k] ~ dnorm(0,.001)
                         }

# Absolute log odds on placebo treatment based on number of placebo controlled trials
for (i in 1:N){
                        mu1[i] <- mu[s[i]]*equals(t[i],1)
                        NN[i] <-     equals(t[i],1)
                        }
                        m<- sum(mu1[])/sum(NN[])

# Calculate treatment effects, T[k], on natural scale
for (k in 1:NT){
            logit(T[k]) <- m + d[k]
            }

# Log odds ratios and odds ratios
for (c in 1:(NT-1)){
            for (k in (c+1):NT){
                        lor[c,k] <- d[k] - d[c]
                        log(OR[c,k]) <- lor[c,k]
  pbOR[c,k]<- step((1-OR[c,k]))
  pblor[c,k]<- step(-lor[c,k])
                        }
}

# Relative risks
for (c in 1:(NT-1)) {
            for (k in (c+1):NT){
                        RR[c,k] <-T[k]/T[c]
                        pbRR[c,k]<-step(-1*(1-RR[c,k]))
                        }
}

# Risk difference
for (c in 1:(NT-1)) {
            for (k in (c+1):NT){
                        RD[c,k] <-T[k]-T[c]
                        pbRD[c,k]<- step(-RD[c,k])
                        pbRD05[c,k]<- step(-RD[c,k]-0.05)
                        }
}

# Relative risks reduction
for (c in 1:(NT-1)) {
            for (k in (c+1):NT) {
                        RRR[c,k] <-RD[c,k]/T[c]
                        }
}

# Rank the treatment effects (with 1=best) & record the best treatment
 for (k in 1:NT) {
            rk[k]<- rank(T[],k)
```

```
            best[k]<-equals(rk[k],1)
            }
}
```

```
list(NT = 5, NS = 7, N = 14)
```

t[]	r[]	n[]	b[]	s[]
1	25	374	1	1
2	29	361	1	1
1	2	45	1	2
2	1	46	1	2
1	5	47	1	3
2	5	46	1	3
3	16	263	3	4
4	23	253	3	4
5	35	199	4	5
4	38	201	4	5
1	37	219	1	6
3	30	230	1	6
1	38	203	1	7
3	25	193	1	7

```
END

list(
d = c(NA,0,0,0,0),
mu = c(0,0,0,0,0,0,0),
sd = 0.7478990940134502)
```

The WinBUGs code is presented below for random effects model.

```
model{

# Model for log-odds of fractures, for  types of trial indicated by b[i]
 for(i in 1:N)
  {
  r[i] ~ dbin(p[i],n[i])
  logit(p[i])<-mu[s[i]]+ delta[i]*(1-equals(t[i],b[i]))

#Random effects model for log-odds ratios
  delta[i] ~ dnorm(md[i],prec)
  md[i] <- d[t[i]] - d[b[i]]

#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-rhat[i])))
  }
resdev <- sum(dev[])

#Fixed effect priors
for(j in 1:NS){ mu[j]~dnorm(0,.0001)}
prec <- 1/(sd*sd)
sd~dunif(0,2)

#Give priors for log-odds ratios
 d[1]<-0
 for (k in 2:NT){d[k] ~ dnorm(0,.001) }

# Absolute log odds on placebo treatment based on number of placebo controlled trials
for (i in 1: N){mu1[i] <- mu[s[i]]*equals(t[i],1)
NN[i] <- equals(t[i],1)
}
m<- sum(mu1[])/sum(NN[] )

# Calculate treatment effects, T[k], on natural scale
for (k in 1:NT){
 logit(T[k]) <- m + d[k]
 }

# Log odds ratios and odds ratios
```

```
for (c in 1:(NT-1)){
 for (k in (c+1):NT){
  lor[c,k] <- d[k] - d[c]
  log(OR[c,k]) <- lor[c,k]
  pbOR[c,k]<- step((1-OR[c,k]))
  pblor[c,k]<- step(-lor[c,k])
  }
}

# Relative risks
for (c in 1:(NT-1)) {
 for (k in (c+1):NT){
  RR[c,k] <-T[k]/T[c]
  pbRR[c,k]<-step(-1*(1-RR[c,k]))
  }
}

# Risk difference
for (c in 1:(NT-1)) {
 for (k in (c+1):NT){
  RD[c,k] <-T[k]-T[c]
  pbRD[c,k]<- step(-RD[c,k])
  pbRD05[c,k]<- step(-RD[c,k]-0.05)
  }
}

# Relative risks reduction
for (c in 1:(NT-1)) {
 for (k in (c+1):NT) {
  RRR[c,k] <-RD[c,k]/T[c]
  }
}

# Rank the treatment effects (with 1=best) & record the best treatment
     for (k in 1:NT) {
 rk[k]<- rank(T[],k)
 best[k]<-equals(rk[k],1)
 }
}


list(NT = 5, NS = 7, N = 14)
t[]             r[]             n[]             b[]             s[]
1               25              374             1               1
2               29              361             1               1
1               2               45              1               2
2               1               46              1               2
1               5               47              1               3
2               5               46              1               3
3               16              263             3               4
4               23              253             3               4
5               35              199             4               5
4               38              201             4               5
1               37              219             1               6
3               30              230             1               6
1               38              203             1               7
3               25              193             1               7
END

list(
d = c(NA,0,0,0,0),
delta = c(0,0,0,0,0,
0,0,0,0,0,
0,0,0,0),
mu = c(
-0,0,0,0,0,
0,0),
sd = 1.141575881811593)
```

The results from the network meta-analysis using a fixed and random effects model are shown in the tables below. The model selected was the one which

the lower deviance information criterion (DIC) and therefore the results from the fixed effects model for the base case was used in the economic model.

Results for the expected proportion of patients with a serious adverse event from the network meta-analysis using the fixed effects model (base case)

Treatment	Expected proportion of patients with an SAE	2.5% credible interval	97.5% credible interval
Faslodex 250 mg	9%	6%	12%
Faslodex 500 mg	10%	7%	15%
Anastrozole 1mg	6%	4%	10%
Letrozole 2.5mg	9%	4%	20%

Results for the expected proportion of patients with a serious adverse event from the network meta-analysis using the random effects model (base case)

Treatment	Expected proportion of patients with an SAE	2.5% credible interval	97.5% credible interval
Faslodex 250 mg	9%	6%	12%
Faslodex 500 mg	10%	4%	19%
Anastrozole 1mg	6%	3%	16%
Letrozole 2.5mg	9%	1%	47%

Model	Dbar	Dhat	pD	DIC
fixed effects	74	63	11	85
random effects	74	62	12	86

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes

Scenario analysis

Ten RCTs were used for the scenario network meta-analysis for serious adverse events, which included the same as those used for the base case analysis for OS and TTP. This included CONFIRM, FINDER 1, FINDER 2, Buzdar 1996/98, Buzdar 2001, Osbourne 2002, Howell 2002, Chia 2008, Dombernowsky 1998 and Gershanovich 1998. It was not possible to include Kaufmann 2000 in the network meta-analysis as no serious adverse event data was available.

The results from the network meta-analysis using a fixed and random effects model are shown in the tables below. The model selected was the one which the lowest deviance information criterion (DIC) and therefore the results from

the random effects model for the scenario was used in the economic model (see section 6.7.9).

Results for the expected proportion of patients with a serious adverse event from the network meta-analysis using the fixed-effects model (scenario)

Treatment	Expected proportion of patients with an SAE	2.5% credible interval	97.5% credible interval
Faslodex 250 mg	9%	7%	12%
Faslodex 500 mg	11%	7%	15%
Exemestane	24%	12%	41%
Anastrozole 1mg	7%	4%	10%
Letrozole 2.5mg	5%	2%	12%

Results for the expected proportion of patients with a serious adverse event from the network meta-analysis using the random-effects model (scenario)

Treatment	Expected proportion of patients with an SAE	2.5% credible interval	97.5% credible interval
Faslodex 250 mg	10%	7%	13%
Faslodex 500 mg	10%	4%	21%
Exemestane	24%	5%	66%
Anastrozole 1mg	7%	2%	17%
Letrozole 2.5mg	5%	1%	28%

Model	Dbar	Dhat	pD	DIC
Fixed effects	134.254	117.356	16.898	151.152
Random effects	126.653	105.741	20.912	147.565

Dbar = post.mean of -2logL; Dhat = -2LogL at post.mean of stochastic nodes