National Institute for Health and Care Excellence

Early and locally advanced breast cancer: diagnosis and management

[R] Testicular function suppression

NICE guideline NG101

Evidence reviews underpinning recommendations 1.7.5 to 1.7.9 and research recommendations in the NICE guideline

February 2025

Draft for consultation

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1 Testicular function suppression

1.1 Review question

What is the clinical and cost effectiveness of testicular function suppression combined with an aromatase inhibitor compared to tamoxifen or an aromatase inhibitor alone in people with ER positive invasive breast cancer who have male reproductive organs?

1.1.1 Introduction

The 2018 update of NICE guideline on early and locally advanced breast cancer recommends that both premenopausal women and men with oestrogen receptor (ER) positive early or locally advanced invasive breast cancer are offered tamoxifen as an initial adjuvant endocrine therapy. However, there are currently no recommendations on the use of testicular function suppression taken in combination with other endocrine therapy in people with male reproductive organs. (When we mention people with male reproductive organs, we mean this to cover men, trans women and non-binary people who currently have testes.) The evidence in this area will be reviewed as part of this update. This update will not look at testicular function suppression as a means of preserving fertility during treatment for breast cancer.

1.1.2 Summary of the protocol

Table 1: PICOS inclusion criteria

Population	**Inclusion:** 1. Adults (18 and over) with invasive* oestrogen receptor (ER) positive breast cancer who have male reproductive organs. (* any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0)). 2. If limited or no data is identified for the population above, then we will look at data for adults (18 and over) with ER positive metastatic breast cancer who have male reproductive organs. **Exclusion:** Adults (18 and over) with: • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
Interventions	• Endocrine therapy using an aromatase inhibitor combined with testicular function suppression
Comparator	• Tamoxifen • An aromatase inhibitor
Outcomes	**Primary outcomes (critical outcomes)** • Overall survival or mortality if overall survival not reported • Disease-free survival • Quality of life **Secondary outcomes (important outcomes)**

	• Breast cancer specific survival or cancer-specific mortality if breast cancer specific survival is not reported
	• Serum oestradiol levels
	• Serum testosterone levels
	• Adverse events
	  ○ treatment-related mortality
	  ○ treatment-related morbidity
	• Local and/or locoregional recurrence
	• New contralateral disease
	• Adherence to or completion of treatment (early cessation of treatment)

Study type	• Randomised controlled trials (RCTs)
	• Observational studies
	  ○ Cohort studies
	  ○ Case series

For the full protocol see appendix A.

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and methods in appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

Additional methods considerations specific to this review:

1. Oestradiol levels and testosterone levels were reported as medians by Reinisch et al. (2021) in their RCT. Therefore, these 2 outcomes could not be evaluated using GRADE.

2. The RCT (Reinisch et al. 2021) was a 3-arm study. We extracted data from 2 of the arms (an aromatase inhibitor combined with testicular function suppression and tamoxifen alone). We did not extract data from the third arm (tamoxifen combined with testicular function suppression) because this intervention was not listed in our protocol.

3. There was limited data for adults with invasive ER positive breast cancer who had male reproductive organs (1 RCT reported by Reinisch et al. 2021). Based on our protocol (see appendix A), we looked at data for adults with ER positive metastatic breast cancer who had male reproductive organs. We included a case series review (Zagouri et al. 2015) which had 1 relevant case series study (Zagouri et al. 2013) to be included in this update. However, the case series review did not report enough information on study details and baseline characteristics for the case series study, so we then took this additional information from Zagouri et al. (2013). Both Zagouri et al. 2015 and Zagouri et al. 2013 reported overall survival. We did not extract overall survival from Zagouri et al. 2015 because it was reported as a pooled estimate across all included case studies and most of them did not meet the inclusion criteria in our protocol apart from Zagouri et al. 2013. We could not extract overall survival from Zagouri et al. 2013 because it was a non-comparative study. Therefore, we extracted data from Zagouri et al. 2015 which reported the number of participants who survived or died for each participant from case study.

4. The committee agreed that some adverse events were likely to be experienced by people receiving endocrine therapy with tamoxifen alone or with an aromatase inhibitor combined with testicular function suppression. Adverse events considered important for decision-making were chosen by committee consensus prior to data extraction (see appendix M for the list of adverse events of interest). We planned to extract data from adverse events that were grade 2 and above with the exception of cardiovascular adverse events where only grade 3 and 4 events were to be extracted (as per committee consensus) and that adverse events would be extracted and reported separately as grade 2 and grade 3 and above where possible.

5. In the protocol for all outcomes without a published minimally important difference (MID) threshold, any statistically significant difference was deemed to be clinically important, and we used the line of no effect as one of the downgrades for imprecision. The quality of the outcome was therefore downgraded once for imprecision if either end of the 95% confidence interval crossed the line of no effect. To be consistent with previous work on this guideline from 2018 we planned to use an event size of 300 events for the second downgrade based on 2018 optimal information size calculations that suggested that at least 300 events were needed to adequately detect an effect. If this information was not readily available, we planned to use sample size instead to ensure that all studies would have the potential to be downgraded twice. A minimum sample size of 500 was selected to allow for the possibility of 300 events. As a result, the quality was downgraded a second time if the number of participants for an outcome was less than 500.

1.1.3.1 Search methods

The searches for the effectiveness evidence were run on 17 09 2024. The following databases were searched: Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley); Embase (Ovid); Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 24 09 2024. The following databases were searched: Embase (Ovid); Econlit (Ovid); International Health Technology Assessment Database (INAHTA), NHS EED (CRD) and Medline ALL (Ovid). Full search strategies for each database are provided in Appendix B.

A NICE senior information specialist (SIS) conducted the searches. The MEDLINE strategy was quality assured by another NICE SIS. All translated search strategies were peer reviewed to ensure their accuracy. The QA procedures were adapted from the 2015 PRESS Guideline Statement.

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

A systematic search carried out to identify potentially relevant studies found 525 references (see appendix B for the literature search strategy). Evidence identified by other sources (1 reference) and evidence identified from the list of references of included studies (2 references) was also reviewed.

These 528 references were screened at title and abstract level against the review protocol, with 518 excluded at this level. 10% of references were screened separately by two reviewers with 100% agreement.

The full texts of 1 randomised controlled trial, 1 observational study, 2 reviews, and 6 case series were ordered for closer inspection. Three of these studies (1 RCT, 1 review of case series and 1 case series study) met the criteria specified in the review protocol (appendix A). For a summary of the 3 included studies see Table 2, Table 3, and Table 4.

The clinical evidence study selection is presented as a PRISMA diagram in appendix C.

See section 1.1.13 References for the full references of the included studies.

1.1.4.2 Excluded studies

Details of studies excluded at full text, along with reasons for exclusion are given in appendix J.

1.1.5 Summary of studies included in the effectiveness evidence

Invasive ER positive breast cancer

Table 2 Randomised controlled trial

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias Applicability
Reinisch, (2021) Location: Germany Duration of follow-up: 6 months	Median age (range): 61.5 (37 to 83) Total sample size: 35 Key inclusion criteria: Male patients with hormone receptor positive (oestrogen receptor and/or progesterone receptor positive) breast cancer; Karnofsky Performance Status of 60% or greater; No history or evidence of prostate cancer Key exclusion criteria: None reported	An aromatase inhibitor combined with testicular function suppression (sample size: 18) Exemestane: 25 mg/d orally. Gonadotropin-releasing hormone analogue was administered subcutaneously every 3 months. Treatment was given for 6 months in the neoadjuvant, adjuvant, or metastatic setting. Subsequent treatment with tamoxifen, 20 mg/d orally, alone was conducted regardless of study treatment. Chemotherapy use: 61.1% with prior chemotherapy Oestradiol levels at baseline: median 27.5 ng/L (range 17.0 to 113.0) Testosterone levels at baseline:	Tamoxifen alone (sample size: 17) Tamoxifen: 20 mg/d orally. Treatment was given for 6 months in the neoadjuvant, adjuvant, or metastatic setting. Subsequent treatment with tamoxifen, 20 mg/d orally, alone was conducted regardless of study treatment. Chemotherapy use: 64.7% with prior chemotherapy Oestradiol levels at baseline: median 27.0 ng/L (range 5.0 to 46.0)	• Serum oestradiol levels • Serum testosterone levels • Adverse events • Adherence to or completion of treatment • Quality of life	High Directly applicable

		median 4.0 µg/L (range 1.1 to 15.0)	Testosterone levels at baseline: median 3.7 µg/L (range 1.2 to 7.1)		

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1 **ER positive metastatic breast cancer**

2 **Table 3 Case series review (for full details of included primary studies, see Zagouri et al. 2015)**

Author (year)	Primary studies from Zagouri et al. 2015, included in the NICE review	Population covered by case series review	Intervention	Comparison	Outcomes	Risk of bias/Applicability of the case series review
Zagouri (2015) Number of included studies: 15	• Zagouri 2013 (see Table 4 for details)	**Inclusion criteria:** • All reports or studies (regardless of sample size) that examined the efficacy of AIs in metastatic male breast cancer • Only the first administration of AI was considered eligible • The first time of co-administration of AI and GnRH analogues, was considered eligible **Exclusion criteria:**	• An aromatase inhibitor combined with testicular function suppression	• An aromatase inhibitor alone	• Overall survival	High Partially applicable (participants had metastatic breast cancer)

Author (year)	Primary studies from Zagouri et al. 2015, included in the NICE review	Population covered by case series review	Intervention	Comparison	Outcomes	Risk of bias/Applicability of the case series review
		• Studies with AIs administration in male breast cancer patients without reporting any data on efficacy • Cases with co-administration of AI with other chemotherapeutic agents or hormonal manipulations other than GnRH analogues				

1 **Table 4 Case series study**

Study details	Participants	Intervention	Comparator	Outcomes	Risk of bias Applicability
Zagouri, (2013) Location: Austria and Greece Duration of follow-up: median overall survival was 39 months	Mean age (SD): 64.4 (6.5) Total sample size: 23 Key inclusion criteria: • Male patients with metastatic breast cancer who have been treated with an aromatase inhibitor with or without a gonadotropin-releasing hormone analogue Key exclusion criteria, patients who: • received an aromatase inhibitor in the adjuvant setting • had HER2 positive breast tumours • received concomitant chemotherapy, trastuzumab and/or radiotherapy • received previous gonadotropin-releasing hormone analogue administration • did not have at least one measurable or assessable non-measurable lesion • had oestrogen receptor and progesterone receptor	An aromatase inhibitor combined with testicular function suppression (sample size: 17) An oral aromatase inhibitor (either exemestane 25 mg or letrozole 2.5 mg or anastrozole 1 mg) was administered daily, combined with testicular function suppression with a gonadotropin-releasing hormone (GnRH) analogue (goserelin acetate 3.6 mg on day 1 in four weekly intervals). Treatment was continued until disease progression or unacceptable toxicity. Chemotherapy use: 100% with adjuvant chemotherapy	An aromatase inhibitor alone (sample size: 6) An oral aromatase inhibitor (either exemestane 25 mg or letrozole 2.5 mg or anastrozole 1 mg) was administered daily. Treatment was continued until disease progression or unacceptable toxicity. Chemotherapy use: 100% with adjuvant chemotherapy	• Overall survival (reported as number of people who died)	High Partially applicable (participants had metastatic breast cancer)

	negative primary and/or metastatic breast cancer				

AI: aromatase inhibitor; **GnRH:** gonadotropin hormone-releasing hormone; **SD:** standard deviation

See appendix D for full evidence tables.

1.1.6 Summary of the effectiveness evidence

Interpreting the effectiveness evidence

In the absence of published minimally important differences (MIDs) clinical decision thresholds were agreed with the committee and used to interpret the evidence. The line of no effect (in this case represented by 1.0 for dichotomous outcomes) was used as a clinical decision threshold.

The following criteria were used to interpret the effect (column of 'Interpretation of effect' below) in the summary GRADE tables:

For outcomes without a published MID or where the clinical decision threshold is set as the line of no effect, the results are divided into 2 groups as follows:

- The evidence showed that there is an effect if the 95% CI does not cross the line of no effect. (Where there an effect, we will state the direction of the effect.)

- It was not possible from the evidence to differentiate between comparators if the 95% CI crosses the line of no effect (shortened to 'could not differentiate').

Invasive ER positive breast cancer: an aromatase inhibitor combined with testicular function suppression compared to tamoxifen alone

Quality of life

Table 5 Quality of life – 6 months follow-up

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with an AI combined with TFS				
Quality of life (people who reported to have reduced quality of life) - 6 months follow-up (RR less than 1 favours an AI combined with TFS)	813 per 1,000	650 per 1,000 (423 to 991)	RR 0.80 (0.52 to 1.22)	33 (1 RCT)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ** See full GRADE tables in appendix F for reasons for downgrading. **AI:** aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression.

Adherence to or completion of treatment

Table 6 Adherence to or completion of treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with tamoxifen alone	Risk with an AI combined with TFS				
Adherence to or completion of treatment (participants with treatment discontinuation) (RR less than 1 favours an AI combined with TFS)	56 per 1,000	53 per 1,000 (3 to 786)	RR 0.95 (0.06 to 14.04)	20 (1 RCT)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ** See full GRADE tables in appendix F for reasons for downgrading. **AI:** aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression.

Adverse events

Table 7 Adverse events – 6 months follow up

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with an AI combined with TFS				
Hot flushes - grade 2 (RR less than 1 favours an AI combined with TFS)	Not estimable**	Not estimable**	RR 6.63 (0.37 to 119.59)	35 (1 RCT)	Very low	Could not differentiate

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)***	Interpretation of effect
	Risk with tamoxifen alone	Risk with an AI combined with TFS				
Sleep disorder - grade 2 (RR less than 1 favours an AI combined with TFS)	Not estimable**	Not estimable**	RR 2.84 (0.12 to 65.34)	35 (1 RCT)	Very low	Could not differentiate
Fatigue - grade 2 (RR less than 1 favours an AI combined with TFS)	Not estimable**	Not estimable**	RR 6.63 (0.37 to 119.59)	35 (1 RCT)	Very low	Could not differentiate
Decreased libido - grade 2 (RR less than 1 favours an AI combined with TFS)	118 per 1,000	278 per 1,000 (62 to 1,000)	RR 2.36 (0.53 to 10.58)	35 (1 RCT)	Very low	Could not differentiate
Erectile dysfunction - grade 2 (RR less than 1 favours an AI combined with TFS)	59 per 1,000	55 per 1,000 (4 to 819)	RR 0.94 (0.06 to 13.93)	35 (1 RCT)	Very low	Could not differentiate
Erectile dysfunction - grade 3 or more (RR less than 1 favours an AI combined with TFS)	Not estimable**	Not estimable**	RR 4.74 (0.24 to 92.07)	35 (1 RCT)	Very low	Could not differentiate
Arthralgia - grade 2 (RR less than 1 favours an AI combined with TFS)	Not estimable**	Not estimable**	RR 4.74 (0.24 to 92.07)	35 (1 RCT)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). **Absolute effects could not be estimated because there were 0 events in one of the arms. *** See full GRADE tables in appendix F for reasons for downgrading. **AI:** aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression.

Oestradiol and testosterone levels reported as median and range (GRADE could not be used with outcomes reported as medians)

Table 8 Oestradiol levels (ng/L) – change from baseline to 6 months

№ of studies	Outcome	AI plus TFS, N = 15	Tamoxifen alone, N = 17
1 (Reinisch 2021)	**Oestradiol levels, median (range)** (ng/L)	-17.0 (-102.0 to 6.0)	12.0 (-23.0 to 50.0)

Lower values are better; p values were not reported

Evidence from 1 RCT at high risk of bias showed that oestradiol levels decreased between baseline and 6 months, median -17.0 ng/L (range -102.0 to 6.0 ng/L) for people with male reproductive organs who have ER+ invasive breast cancer treated with an AI combined with testicular function suppression.

Evidence from 1 RCT at high risk of bias showed that oestradiol levels increased between baseline and 6 months, median 12.0 ng/L (range -23.0 to 50.0 ng/L) for people with male reproductive organs who have ER+ invasive breast cancer treated with tamoxifen alone.

Table 9 Testosterone levels (g/L) – change from baseline to 6 months

№ of studies	Outcome	An AI plus combined with TFS, N = 15	Tamoxifen alone, N = 17
1 (Reinisch 2021)	**Testosterone levels, median (range)** (g/L)	-3.5 (-14.7 to 1.0)	1.6 (-3.1 to 8.3)

Evidence from 1 RCT at high risk of bias showed that testosterone levels decreased between baseline and 6 months, median -3.5 ng/L (range -14.7 to 1.0 ng/L) for people with male reproductive organs who have ER+ invasive breast cancer treated with an AI combined with testicular function suppression.

Evidence from 1 RCT at high risk of bias showed that oestradiol levels increased between baseline and 6 months, median 1.6 ng/L (range -3.1 to 8.3 ng/L) for people with male reproductive organs who have ER+ invasive breast cancer treated with tamoxifen alone.

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Mortality

Table 10 Mortality – 3 years follow-up

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)**	Interpretation of effect
	Risk with AI alone	Risk with an AI combined with TFS				
Mortality - 3 years follow-up (median 38 months; range: 9 to 79 months)	1,000 per 1,000	930 per 1,000 (700 to 1,000)	RR 0.93 (0.70 to 1.22)	23 (1 case series)	Very low	Could not differentiate

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). ** See full GRADE tables in appendix F for reasons for downgrading. **AI:** aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression.

See appendix F for full GRADE tables.

1.1.7 Economic evidence

A literature search was conducted to identify published economic evaluations of relevance to the review question on testicular function suppression (see Appendix B). This search retrieved 62 studies, and one study was included at title and abstract level but was then excluded based on the study perspective and comparison included (see Appendix G).

1.1.7.1 Included studies

No economic studies were included for this review.

1.1.7.2 Excluded studies

One study was excluded at full text review as the comparison did not include the intervention of interest, and the study was in a US setting (see Appendix J).

1.1.8 Summary of included economic evidence

No economic evidence was included for this review.

1.1.9 Economic model

No economic modelling was included for this review.

1.1.10 Unit costs

Unit costs for the interventions considered in this review are presented in Table 11 and Table 12. Drug costs are taken from the Drugs and pharmaceutical electronic market information tool (eMIT) where possible and otherwise from the British National Formulary (BNF), and dosing information is taken from the BNF. Procedure costs are taken from the NHS National Schedule of Reference costs.

Table 11 Unit costs- endocrine therapies

Resource	Unit costs	Source
Tamoxifen, 20mg tablet	£0.10	eMIT: pack of 30 tablets, weighted average pack price £2.87 (SD £0.36), 20mg per day
Anastrozole, 1mg tablet	£0.02	eMIT: pack of 28 tablets, weighted average pack price £0.50 (SD £1.65), 1mg per day
Letrozole, 2.5mg tablet	£0.03	eMIT: pack of 28 tablets, weighted average pack price £0.86 (SD £0.96), 2.5mg per day
Exemestane, 25mg tablet	£0.14	eMIT: pack of 30 tablets, weighted average pack price £4.20 (SD £7.35), 25mg per day

Table 12 Unit costs – testicular function suppression

Resource	Unit costs	Source
Goserelin	£70.00	BNF: 3.6mg every 28 days, 3.6mg pre-filled disposable injection

Resource	Unit costs	Source
Triptorelin	£69.00	BNF: 3mg every 4 weeks, 3mg vial
Leuprorelin acetate	£75.24	BNF: 3.75mg every month (or 11.25mg every 3 months), 3.75mg pre-filled disposable injection (or 11.25mg pre-filled disposable injection at equivalent price per mg)
Bilateral orchidectomy	£2,894.95	NHS National Schedule of Reference costs 2021/22: weighted average of cost codes LB52A and LB52B, Major Open, Scrotum, Testis or Vas Deferens Procedures, Day case

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1.1.11 The committee's discussion and interpretation of the evidence

Terminology in this discussion

- When we mention people with male reproductive organs, we mean this to cover men, trans women and non-binary people who currently have testes.
- When we mention people with female reproductive organs, we mean this to cover women, trans men and non-binary people who currently have ovaries.

1.1.11.1. The outcomes that matter most

The evidence for this review focused on people with male reproductive organs who have oestrogen receptor (ER) positive invasive breast cancer. In these people, testicular function suppression (TFS) combined with an aromatase inhibitor (AI) aims to improve long-term cancer related outcomes. Therefore, the committee agreed that the critical outcomes for this review were overall survival (OS), disease-free survival (DFS) and quality of life, which can be severely affected by the side effects of these treatments.

ER positive tumours require oestrogen to grow. In people with male reproductive organs, there is both testosterone (an androgen) and oestrogens. Treatment of ER positive breast cancer involves the reduction of oestrogens. Androgens are converted to oestrogens by the aromatase enzyme. An aromatase inhibitor can block this conversion, but oestradiol suppression is incomplete with an aromatase inhibitor alone. Data on the critical outcomes discussed above was expected to be limited, therefore the committee agreed that serum oestradiol levels and serum testosterone levels were important secondary outcomes because these could provide information about whether the intervention is having the intended physiological effect on oestradiol/testosterone levels.

In addition, the committee acknowledged the importance of other outcomes including mortality due to breast cancer, local and/or locoregional recurrence, and new contralateral disease. Breast cancer mortality was not expected to be widely reported and therefore it was considered important but not critical to decision-making. The risk of local and/or locoregional recurrence and new contralateral disease were included because they could be reduced by treatment with TFS combined with an AI.

The committee also noted that the risk of adverse events and types of adverse events that people may experience with these treatments play an important role in their decision-making about whether to accept endocrine treatment, which treatment to take and whether to continue taking it. Therefore, they agreed that specific adverse events (see appendix M) and completion of treatment were also important outcomes for decision making.

1.1.11.2 The quality of the evidence

All outcomes were judged to be of very low quality with the main reasons for downgrading being due to risk of bias, data only available from single studies, and imprecision of the evidence. Results from case series studies were interpreted with caution because these are the lowest type of study in the hierarchy of evidence. The evidence from the randomised controlled trial (RCT) was judged to be at high risk of bias due to poor reporting and loss to follow-up without reporting reasons for the loss.

There was only 1 RCT with evidence for people with male reproductive organs who have ER positive invasive breast cancer. Therefore, additional evidence was included from people with male reproductive organs who have ER positive metastatic breast cancer as the

committee agreed that they could extrapolate any effectiveness data from this setting to the non-metastatic population. The evidence was from 1 case series review and 1 case series study, which were judged to be at high risk of bias due to poor reporting and partially applicable due to participants having metastatic breast cancer. All data was downgraded for imprecision as all the 95% confidence intervals (CIs) for all outcomes crossed the line of no effect. The studies had a sample size of less than 500 participants and were also downgraded a second time for imprecision as there were likely to be too few participants to reliably detect an effect.

Outcome data was reported for 2 of the critical outcomes: mortality (OS was reported graphically; hazard ratio and 95% CIs could not be extracted) and quality of life. There was also outcome data for serum oestradiol levels, serum testosterone levels, adverse events (treatment-related morbidity), and adherence (reported as treatment discontinuation). No data was reported for DFS, breast cancer specific survival, treatment-related mortality, local and/or locoregional recurrence, and new contralateral disease.

1.1.11.3 Benefits and harms

An AI combined with TFS compared to tamoxifen alone

The committee discussed the evidence for TFS combined with an AI compared to tamoxifen alone for people with male reproductive organs who have ER positive invasive breast cancer. They noted that there was limited evidence and of very low quality with data from a single study. It was not possible from the evidence to differentiate between TFS combined with an AI compared to tamoxifen alone for quality of life, serum oestradiol levels, serum testosterone levels**Error! Reference source not found.**, adherence reported as treatment d iscontinuation), and adverse events: hot flushes, sleep disorder, fatigue, decreased libido, erectile dysfunction, and arthralgia. The committee noted that it was likely that there were not enough participants (the total number was 35) in this study to be able to detect a difference between the 2 interventions of interest.

An AI combined with TFS compared to an AI alone

The committee discussed the evidence for TFS combined with an AI compared to an AI alone for people with male reproductive organs who have ER positive metastatic breast cancer. It came from a single, partially applicable study with very low quality evidence and it was not possible from the evidence to differentiate between TFS combined with an AI compared to an AI alone for mortality). The committee noted that it was likely that there were not enough participants (the total number of participants was 23) in this study to be able to detect a difference between the 2 interventions of interest.

Drafting recommendations

In 2018 the committee made a recommendation to offer tamoxifen as the initial adjuvant endocrine therapy for men and premenopausal women with ER positive invasive breast cancer. However, no recommendations were made on the use of TFS taken in combination with an AI in people with male reproductive organs. As part of this update and another review looking at ovarian function suppression in premenopausal/ perimenopausal people (see review Q) the committee decided to split the original recommendation into 2 parts to cover men (updated to say people with male reproductive organs) and premenopausal/ perimenopausal people separately.

It was not possible from the evidence presented to the committee to differentiate between TFS combined with an AI compared to either tamoxifen alone or an AI alone for any of the limited outcome data identified. The committee acknowledged the uncertainty of this evidence, and they tried to use their own expertise to address this. They were aware of indirect evidence from studies in healthy people with male reproductive organs showing that an AI alone does not suppress oestrogen effectively (Giordano SH 2018) and so they thought that AI alone would be unlikely to lower oestrogen levels sufficiently to reduce tumour growth. Taking this into account, the committee made a recommendation that an AI should not be used alone in people with male reproductive organs who have ER positive invasive breast cancer. They were also aware of the American Society of Clinical Oncology (ASCO) guideline on management of male breast cancer which identified the same evidence on healthy men and drew similar conclusions. However, they agreed that from the expected physiological mechanism of action of TFS, using this treatment in combination with an AI may help overcome the lack of complete oestradiol suppression sometimes seen in men treated with an AI alone.

The committee highlighted that the evidence for people with female reproductive organs (see review Q on ovarian function suppression) showed an increased risk of adverse events with ovarian function suppression (OFS) in combination with an AI compared to tamoxifen alone. They agreed that there were no biological reasons to suppose that people with male reproductive taking this combined therapy would be at any less risk of adverse events than people with female reproductive organs using OFS drugs and many of the types of adverse events experienced would be similar. Adverse events reported by the evidence in this review were: hot flushes, sleep disorder, fatigue, decreased libido, erectile dysfunction and arthralgia. In addition, also noted that more side effects are expected with TFS combined with an AI compared to tamoxifen alone. Due to the lack of evidence about the benefits of having TFS combined with an AI there was uncertainty about whether any potential improvement in survival and reductions in recurrence would outweigh the increased risk of adverse events associated with these treatments. As a result, the committee agreed that tamoxifen should still be offered as the first treatment option. However, they made a consider recommendation for the use of TFS combined with an AI as an alternative to tamoxifen in circumstances where tamoxifen is not suitable or tolerated because this drug combination could plausibly have a physiological effect on oestradiol/testosterone levels and thus improve clinical outcomes for people with male reproductive organ who have ER positive breast cancer and who are unable to take tamoxifen.

The committee agreed that there should be a balance between clinical outcomes and patient-reported outcomes when making decisions about adjuvant endocrine therapy options. However, the limited evidence for people with male reproductive organs makes this challenging. The committee included lay members (one of whom was male) who were able to bring their own experiences, and those of people in the patient networks they are involved in, of using these treatments to the discussions. Taking the experiences and expertise of the committee into account they agreed that it is important to have a discussion about the benefits and risks of the treatment options to help the individual decide whether to accept treatment with tamoxifen or TFS combined with an AI if tamoxifen is not suitable or tolerated. This should cover the potential side effects of the relevant endocrine therapy or therapies, which could be extrapolated in part from the evidence on adverse events for people with female reproductive organs (see review Q on ovarian function suppression). It should also highlight side effects that are specific to people with male reproductive organs such as erectile dysfunction and gynaecomastia.

The committee also agreed that bone mineral density should be assessed in people with male reproductive organs who are using an AI in combination with TFS. This assessment is already recommended in the section on bone health in NG101 for women who have ER positive invasive breast cancer and who start adjuvant therapy using an AI because the use of an AI is associated with an increased risk of bone density loss. The effects of aromatase inhibitors on bone density can also be experienced by people with male reproductive organs and so to promote equality the committee made a separate recommendation for people with male reproductive organs to reflect this. Due to the small numbers of people with male reproductive organs who have ER positive invasive breast cancer and who are expected to take an aromatise inhibitor (in combination with TFS in our recommendation), this is not expected to be a resource intensive recommendation.

The committee highlighted that some health professionals are reluctant to use TFS combined with an AI in the adjuvant setting for people with male reproductive organs who have ER positive invasive breast cancer because there is a lack of evidence about the effectiveness of this treatment combination. To try to address the gaps in the evidence base, the committee also made two research recommendations that could be carried out using real world evidence due to the expected difficulty recruiting sufficient numbers of people to randomised controlled trials. The first recommendation for research was to look at the clinical and cost effectiveness of TFS combined with an AI compared to tamoxifen alone or an AI alone in people with ER-positive invasive breast cancer who have male reproductive organs. The committee also noted the uncertainty around the types and severity of side effects in people with male reproductive organs who are using tamoxifen alone or using TFS combined with an AI. Therefore, they made a second recommendation for research to gather evidence about this.

1.1.11.4 Cost effectiveness and resource use

No health economic studies were identified and *de novo* economic modelling was not undertaken for this review question.

The committee were presented with costs of different treatment regimens. The cost of tamoxifen and aromatase inhibitors were shown to have a low cost per day (tamoxifen estimated to cost around £34.95 a year and aromatase inhibitors between £6.52 and £51.14 a year). The overall costs were relatively similar to each other and therefore unlikely to drive the relative cost effectiveness of aromatase inhibitors or tamoxifen containing regimens. The combination of TFS to an AI regimen would constitute the cost of the monthly or 3-monthly injection and would also include an appointment with a nurse for administration (£8.83 for a 10-minute appointment) however very few people are expected to receive TFS combined with an AI because the population of people with male reproductive organs and breast cancer is very small.

The committee noted that both tamoxifen alone and TFS combined with an AI are associated with adverse events that would have cost and quality of life impacts, and due to the different mechanism of action, would expect the side effect profiles to be different and therefore have differences in the resources required to manage these effects. However, without sufficient comparative clinical evidence this impact cannot be quantified.

1.1.11.5 Other factors the committee took into account

The committee noted that the equality and health inequalities assessment that accompanies this review highlighted a large number of issues that could affect people with male

reproductive organs who have ER positive invasive breast cancer constraining their decisions about whether to accept an endocrine therapy or TFS combined with an AI. However, they noted that many of these issues were societal and not within the committee's ability to address. For example, problems associated with being able to afford to take time off work and having access to affordable transport to take them to appointments or limited availability of healthcare facilities and long waiting times in their local areas. However, they noted that there are local initiatives in some places that provide free transport and extended or weekend hours that may help those who require this type of support.

Some of the issues related to communication of information in a way that is accessible for people with a range of needs (including those with low health literacy, people who have severe learning disabilities, people who are neurodiverse). The committee had previously drafted a new recommendation in the systemic anti-cancer therapy planning section of NG101 (as part of review O on neoadjuvant chemotherapy) that provides links to core NICE guidelines aimed at facilitating the decision-making process and ensuring that patients are able to fully participate. These were the sections on enabling patients to actively participate in their care in the NICE guideline on patient experience in adult NHS services, and communicating risks, benefits and consequences in the NICE guideline on shared decision making.

However, the committee also discussed some more specific issues that could affect uptake of endocrine therapy. They noted the importance of discussing the person's preferences and asking about their personal circumstances as part of the discussions around treatment choice. They noted that treatment with TFS combined with an AI is given as injections every 4 weeks or every 12 weeks and that this could be more inconvenient for the patient than treatment with tamoxifen alone. In addition, people having injections every 12 weeks may need to switch to having them every 4 weeks because the effect of TFS can wear off before 12 weeks in some people. The committee agreed that the treatment schedule may affect the choice of whether to accept TFS treatment for people who have childcare and other caring responsibilities, or those who will have to take unpaid time off from work, for example.

The committee acknowledged that TFS does affect fertility, and this should be discussed with the person who is deciding whether to accept this treatment. In addition, the use of endocrine therapy in people with male reproductive organs and ER positive invasive breast cancer who are undergoing gender reassignment may have effects on any hormone therapy they are taking as part of this process. The committee were aware of specialist services for people with breast cancer who are undergoing gender reassignment that could be consulted as part of decision making around whether to use and the choice of endocrine treatments.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.7.5 to 1.7.9 and the research recommendation on the use of testicular function suppression combined with an aromatase inhibitor compared to tamoxifen alone or an aromatase inhibitor alone and the research recommendation on the side effects (and severity) of tamoxifen or testicular function suppression combined with an aromatase inhibitor.

1.1.13 References – included studies

1.1.13.1 Effectiveness

References for studies including adults with invasive ER positive breast cancer

Reinisch, Mattea, Seiler, Sabine, Hauzenberger, Tanja et al. (2021) Efficacy of Endocrine Therapy for the Treatment of Breast Cancer in Men: Results from the MALE Phase 2 Randomized Clinical Trial. JAMA oncology 7(4): 565-572

References for studies including adults with ER positive metastatic breast cancer

Zagouri F, Sergentanis TN, Azim HA et al. (2015) Aromatase inhibitors in male breast cancer: a pooled analysis. Breast cancer research and treatment 151(1): 141-147

Zagouri, F, Sergentanis, T N, Koutoulidis, V et al. (2013) Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series. British journal of cancer 108(11): 2259-63

1.1.14 References – other

Giordano, S.H. (2018) Breast cancer in men. New England Journal of Medicine 378(24): 2311-2320

Hassett, M.J., Somerfield, M.R., Baker, E.R. et al. (2020) Management of male breast cancer: ASCO guideline. Journal of Clinical Oncology 38(16): 1849-1863

Appendices

Appendix A – Review protocols

Review protocol for the clinical and cost effectiveness of testicular function suppression combined with an aromatase inhibitor in people with oestrogen receptor (ER) positive invasive breast cancer who have male reproductive organs

ID	Field	Content
1.	Review title	RQ 2.2 Clinical and cost effectiveness of testicular function suppression combined with an aromatase inhibitor in people with oestrogen receptor (ER) positive invasive breast cancer who have male reproductive organs.
2.	Review question	RQ 2.2 What is the clinical and cost effectiveness of testicular function suppression combined with an aromatase inhibitor compared to tamoxifen or an aromatase inhibitor alone in people with ER-positive invasive breast cancer who have male reproductive organs?
3.	Objective	To assess the clinical and cost effectiveness of testicular function suppression combined with an aromatase inhibitor in people with ER positive invasive breast cancer who have male reproductive organs.
4.	Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Embase • MEDLINE ALL For the economics review the following databases will be searched: • Embase • MEDLINE ALL • Econlit • INAHTA • NHS EED Searches will be restricted by: • English language • Human studies • Abstracts, conference presentations, and theses will be excluded. • RCTs and Observational studies

		The full search strategies will be published in the final review.
5.	Condition or domain being studied	Oestrogen receptor positive invasive breast cancer in people who have male reproductive organs.
6.	Population	Inclusion: 1. Adults (18 and over) with invasive* ER positive breast cancer who have male reproductive organs. (* any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0)). 2. If limited or no data is identified for the population above, then we will look at data for adults (18 and over) with ER positive metastatic breast cancer who have male reproductive organs. Exclusion: Adults (18 and over) with: • invasive breast cancer who have male reproductive organs and are not ER positive. • invasive breast cancer who do not have male reproductive organs. • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
7.	Intervention	• Endocrine therapy using an aromatase inhibitor combined with testicular function suppression Aromatase inhibitors of interest are anastrozole, letrozole, and exemestane Testicular function suppression is using orchiectomy or luteinising hormone releasing hormone agonists (LHRH, also known as gonadotrophin releasing hormone (GnRH) agonists): buserelin, goserelin, leuprorelin, nafarelin, and triptorelin. Studies using radiotherapy to induce TFS will also be included.
8.	Comparator	• Tamoxifen • An aromatase inhibitor

9.	Types of study to be included	• RCTs
		• Observational studies
		  ○ Cohort studies
		  ○ Case series

10.	Other exclusion criteria	• Abstracts, conference presentations, theses and narrative reviews • Non-human studies • Non-English language studies • Studies where the LHRH agonists have been used for <12 months if there is data available for 12 or more months (but shorter use of LHRH agonists may be accepted if no other data is available).
11.	Context	The current guideline recommends that both premenopausal women and men with ER receptor positive early or locally advanced invasive breast cancer are offered tamoxifen as an initial adjuvant endocrine therapy. However, there are currently no recommendations on use of testicular function suppression taken in combination with endocrine therapy in people with male reproductive organs.
12.	Primary outcomes (critical outcomes)	• Overall survival (time to event data) or mortality (dichotomous data) if overall survival not reported • Disease-free survival (time to event data) • Quality of life (using validated measures such as the EQ-5D; MID: values from the literature where available) **Minimal important differences** Quality of life MID values from the literature: • EQ-5D: 0.08 for UK-based scores and 0.07 for VAS scores • FACT-G total: 3-7 points • FACT-B total: 7-8 points • TOI (trial outcome index) of FACT-B: 5-6 points • BCS of FACT-B: 2-3 points • WHOQOL-100: 1 point Any statistically significant difference will be used for overall survival and disease-free survival. **Time points** The longest follow-up periods will be prioritised if multiple time points are reported.
13.	Secondary outcomes (important outcomes)	• Breast cancer specific survival (time to event data) or cancer-specific mortality (dichotomous data) if breast cancer specific survival is not reported • Serum oestradiol levels (continuous outcome)

		• Serum testosterone levels (continuous outcome) • Adverse events (dichotomous outcome) • treatment-related mortality • treatment-related morbidity (specific adverse outcomes of interest only- see appendix M for a list of adverse events of interest for this review) • Local and/or locoregional recurrence (dichotomous outcome) • New contralateral disease (dichotomous outcome) • Adherence to or completion of treatment (early cessation of treatment; dichotomous outcome) **Minimal important differences** Any statistically significant difference will be used for all important outcomes. **Time points** The longest follow-up periods will be prioritised if multiple time points are reported.
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4).
15.	Risk of bias (quality) assessment	• Risk of bias for RCTs will be assessed using the Cochrane Risk of Bias v.2.0 • Risk of bias for cohort studies will be assessed using the Cochrane ROBINS-I tool • Risk of bias for case series will be assessed using the Institute of Health Economics (IHE) checklist for case series studies As described in Developing NICE guidelines: the manual.
16.	Strategy for data synthesis	Where possible, meta-analyses of outcome data will be conducted for all comparators that are reported by more than one study, with reference to the Cochrane Handbook for Systematic Reviews of Interventions. Hazard ratios will be pooled using the generic inverse-variance method.

		Pooled relative risks will be calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Absolute risks will be presented where possible. Continuous outcomes will be analysed as mean differences, unless multiple scales are used to measure the same factor. In these cases, standardised mean differences will be used instead. Any pooled SMDs will be back converted to a suitable scale to aid committee interpretation. Fixed- and random-effects models (der Simonian and Laird) will be fitted for all comparators, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models will be deemed to be inappropriate if one or both of the following conditions is met: • Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. • The presence of significant statistical heterogeneity in the meta-analysis, defined as I2≥50%. GRADE will be used to assess the quality of the outcomes. Data from randomised controlled trials will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point. Data from cohort studies assessed using ROBINS-I will also be rated as high quality while data from case series will be rated as low quality to begin with and downgraded from there. Where 10 or more studies are included as part of a single meta-analysis, a funnel plot will be produced to graphically (visually) assess the potential for publication bias.
17.	Analysis of sub-groups	None
18.	Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
19.	Language	English

20.	Country	England		
21.	Anticipated or actual start date	September 2024		
22.	Anticipated completion date	March 2025		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☐	☐
		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	5a. Named contact NICE Topic Hub 1 5b Named contact e-mail breastcancerupdate@nice.org.uk 5e Organisational affiliation of the review National Institute for Health and Care Excellence (NICE)		
25.	Review team members	• Marie Harrisingh, Topic Lead • Sarah Boyce, Senior technical analyst • Yolanda Martinez, Technical analyst • Lindsay Claxton, Health economics Adviser • Hannah Tebbs, Senior technical health economist • Andrea Heath, Information specialist • Gareth Haman, Editor		
26.	Funding sources/sponsor	This systematic review is being completed by NICE.		
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any		

		decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Early and locally advanced breast cancer: diagnosis and management - Neoadjuvant chemotherapy and ovarian function suppression (update).
29.	Other registration details	None
30.	Reference/URL for published protocol	N/A
31.	Dissemination plans	N/A
32.	Keywords	Male reproductive organs, endocrine therapy, testicular function suppression
33.	Details of existing review of same topic by same authors	N/A
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued
35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

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Appendix B – Literature search strategies

Background and development

Search design and peer review

A NICE Senior Information Specialist (SIS) conducted the literature searches for the evidence review. The searches were run on 17 September 2024 and the cost effectiveness searches were run on 24 September 2024.

This search report is compliant with the requirements of the PRISMA Statement for Reporting Literature Searches in Systematic Reviews (for further details see: Rethlefsen M et al. PRISMA-S. *Systematic Reviews*, 10(1), 39).

The MEDLINE strategies below were quality assured (QA) by a trained NICE SIS. All translated search strategies were peer reviewed by another SIS to ensure their accuracy. Both procedures were adapted from the Peer Review of Electronic Search Strategies Guideline Statement (for further details see: McGowan J et al. PRESS 2015 Guideline Statement. *Journal of Clinical Epidemiology*, 75, 40-46).

The principal search strategies were developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using a two-step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess "low-probability" matches. All decisions made for the review can be accessed via the deduplication history.

Search limits and other restrictions

Formats

Limits were applied in adherence to standard NICE practice and the review protocol to exclude:

- Animal studies
- Editorials, letters, news items and commentaries
- Conference abstracts and posters
- Registry entries for ongoing clinical trials or those that contain no results
- Theses and dissertations
- Papers not published in the English language.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from:

Dickersin K, Scherer R & Lefebvre C. (1994) Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Date limits

No date limits were applied to the effectiveness search in adherence to the review protocol. A date limit of 2010 to date was applied for the cost-effectiveness search.

Search filters and classifiers

Effectiveness searches

Randomised controlled trials filter

The MEDLINE RCT filter was McMaster Therapy – Medline - "best balance of sensitivity and specificity" version.

The standard NICE modifications were used: the MeSH heading *randomized controlled trial/*, which is equivalent *to randomized controlled trial.pt* was exploded to capture newer, narrower *terms equivalence trial/ and pragmatic clinical trial*. The free-text term *randomized.mp* was also changed to the (more inclusive) alternative *randomi?ed.mp.* to capture both UK and US spellings.

The Embase RCT filter was McMaster Therapy – Embase "best balance of sensitivity and specificity" version.

The standard NICE filters for cohort studies were used, which are in-house developments based on BMJ Best Practice and Waffenschmidt S et al. (2020) Development and validation of study filters for identifying controlled non-randomized studies in PubMed and Ovid MEDLINE. *Research Synthesis Methods*, 11(5): 617-626

Cost effectiveness searches

The following search filter was applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Note: Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

Translations of the databases for the effectiveness and cost-effectiveness searches were done as appropriate to the size and interface of the individual databases.

Effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	17/09/24	Wiley	Cochrane Central Register of Controlled Trials Issue 8 of 12, August 2024	46
Embase	17/09/24	Ovid	Embase <1974 to 2024 September 16>	473
MEDLINE ALL	17/09/24	Ovid	Ovid MEDLINE(R) ALL <1946 to September 16, 2024>	154

Search strategy history

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

Searches	
#1	MeSH descriptor: [Breast Neoplasms] explode all trees 20444
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees 1021
#3	MeSH descriptor: [Carcinoma, Lobular] this term only 219
#4	MeSH descriptor: [Carcinoma, Medullary] this term only 21
#5	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] this term only 311
#6	{OR #1-#5} 20757
#7	MeSH descriptor: [Breast] explode all trees 1161
#8	breast*:ti,ab 62904
#9	#7 or #8 63013
#10	(breast NEXT milk):ti,ab 2817
#11	(breast NEXT tender*):ti,ab 272
#12	#10 or #11 3088
#13	#9 not #12 59925
#14	MeSH descriptor: [Neoplasms] explode all trees 126379
#15	#13 and #14 20785
#16	(breast* NEAR/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 44941

Searches
#17 (mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)):ti,ab 291
#18 {OR #15-#17} 45982
#19 #6 or #18 47419
#20 MeSH descriptor: [Breast Neoplasms, Male] this term only 77
#21 (male or men or man):ti,ab 193197
#22 #20 or #21 193255
#23 #19 and #22 1246
#24 MeSH descriptor: [Castration] this term only 215
#25 MeSH descriptor: [Orchiectomy] this term only 438
#26 (orchiectomy or orchidectom* or castrat* or gonadectom*):ti,ab 4184
#27 (remov* near/3 (testi* or gonad*)):ti,ab 48
#28 ((radiation or irradiation or radiotherap*) near/3 testi*):ti,ab 99
#29 MeSH descriptor: [Testis] explode all trees 387
#30 MeSH descriptor: [Radiation] explode all trees 8228
#31 MeSH descriptor: [Radiotherapy] explode all trees 10096
#32 #30 or #31 16765
#33 #29 and #32 8
#34 ((testi* or gonad*) near/3 (suppress* or ablat*)):ti,ab 378
#35 #24 or #25 or #26 or #27 or #28 or #33 or #34 4874
#36 MeSH descriptor: [Luteinizing Hormone] explode all trees 2003
#37 (lutein* next hormon* next releas*):ti,ab 590
#38 (LHRH* or LH-RH*):ti,ab 1144
#39 MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees 3338
#40 (gonado* next releas* next hormon*):ti,ab 2493
#41 (GnRH* or GnRHA*):ti,ab 4747
#42 (goserelin* or zolade* or ici NEXT 118630* or ici118630* or ly NEXT 01005* or ly01005* or novimp* or prozoladex* or reseligo* or zd NEXT 9393* or zd9393* or zoreline*):ti,ab 1074
#43 (buserelin* or suprefact* or suprecur* or hoe NEXT 706* or hoe706* or hoe NEXT 766* or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*):ti,ab 423
#44 (leuprolid* or leuprorelin* or lupron* or prostap* or a NEXT 43818* or a43818* or abbott NEXT 43818* or abbott43818* or cam NEXT 2032* or cam2032* or camcevi* or carcinil* or ckd NEXT 841* or ckd841* or daronda* or depo NEXT lupron* or eligard* or eliprogel* or elityran* or elityran NEXT depot* or enanton* or enantone* or fensolvi* or fp NEXT 001* or fp001* or ginecrin* or klebrocid* or la NEXT 2575* or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or nh NEXT 901* or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or sot NEXT 375* or sot375* or staladex* or tap NEXT 144* or tap144* or tapros* or tol NEXT 2506* or tol2506* or trenantone* or viadur* or vp NEXT 4896* or Vp4896* or zeulide*):ti,ab 1284
#45 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or rs NEXT 94991* or rs94991* or rsynarel* or synrelin*):ti,ab 144
#46 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or ay NEXT 25650* or ay25650* or bim NEXT 21003* or bim21003* or bn NEXT 52014* or Bn52014* or cl NEXT

Searches
118532* or cl118532* or debio NEXT 8200* or debio NEXT 8206* or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or isr NEXT 048* or isr NEXT 48* or isr048* or isr48* or ly NEXT 01007* or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or wy NEXT 42422* or wy NEXT 42462* or wy42422* or wy42462*):ti,ab 797
#47 (hormon* near/3 (suppress* or ablat*)):ti,ab 565
#48 {OR #36-#47} 10317
#49 #35 or #48 14178
#50 MeSH descriptor: [Aromatase Inhibitors] explode all trees 952
#51 (aromatase near/2 (inhibit* or block*)):ti,ab 2628
#52 (exemestane* or aromasi* or fce NEXT 24304* or fce24304* or nakides* or nikidess* or pnu NEXT 155971* or pnu15597*):ti,ab 1010
#53 (anastrozole* or anastrazole* or arimidex* or ici NEXT d1033* or icid1033* or zd NEXT 1033* or zd1033* or zeneca* or femathina* or mpi NEXT 674* or mpi NEXT676* or mpi674* or mpi676* or trozolet*):ti,ab 5154
#54 (letrozole* or femar* or cgs NEXT 20267* or cgs20267* or loxifan*):ti,ab 2632
#55 {OR #50-#54} 9253
#56 MeSH descriptor: [Tamoxifen] explode all trees 2981
#57 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or ici NEXT 47699* or ici47699* or tomaxithen* or zitazonium* or ebefen* or kessar* or nsc NEXT 180973* or nsc180973* or pt NEXT 101* or pt101* or tamoplac* or tamoxasta*):ti,ab 5008
#58 #56 or #57 5972
#59 #23 and #49 and #55 74
#60 #23 and #55 192
#61 #23 and #58 75
#62 #59 or #60 or #61 in Trials 211
#63 ((clinicaltrials or trialsearch* or trial-registry or trials-registry or clinicalstudies or trialsregister* or trialregister* or trial-number* or studyregister* or study-register* or controlled-trials-com or current-controlled-trial or AMCTR or ANZCTR or ChiCTR* or CRiS or CTIS or CTRI* or DRKS* or EU-CTR* or EUCTR* or EUDRACT* or ICTRP or IRCT* or JAPIC* or JMCTR* or JRCT or ISRCTN* or LBCTR* or NTR* or ReBec* or REPEC* or RPCEC* or SLCTR or TCTR* or UMIN*):so or (ctgov or ictrp)):an 534051
#64 "conference":pt 247486
#65 #63 or #64 781537
#66 #62 not #65 46

1 **Database name: Embase**

Searches
1 exp breast cancer/ 609181
2 exp breast carcinoma/ 100989
3 exp medullary carcinoma/ 13216
4 ductal breast carcinoma in situ/ 3633
5 exp breast tumor/ 692430
6 lobular carcinoma/ 3643
7 or/1-6 704055
8 exp breast/ 130742

Searches
9 breast*.ti,ab,kw. 819322
10 8 or 9 852600
11 (breast adj milk).ti,ab,kw. 21027
12 (breast adj tender*).ti,ab,kw. 789
13 11 or 12 21810
14 10 not 13 830790
15 exp neoplasm/ 5852229
16 14 and 15 632880
17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 631826
18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 44583
19 16 or 17 or 18 709320
20 7 or 19 838148
21 male breast cancer/ 1916
22 (male or men or man).ti,ab. 2909126
23 21 or 22 2909341
24 20 and 23 32514
25 castration/ 17609
26 exp orchiectomy/ 20978
27 (orchiectomy or orchidectom* or castrat* or gonadectom*).ti,ab. 64091
28 ((radiation or irradiation or radiotherap*) adj3 testi*).ti,ab. 1642
29 (remov* adj3 (testi* or gonad*)).ti,ab. 2221
30 exp testis/ 113994
31 exp radiation/ 788887
32 exp radiotherapy/ 694809
33 31 or 32 1405225
34 30 and 33 3447
35 ((testi* or gonad*) adj3 (suppress* or ablat*)).ti,ab. 3949
36 or/25-29,34-35 85977
37 exp luteinizing hormone/ 71812
38 exp gonadorelin derivative/ 85032
39 (lutein* adj hormon* adj releas*).ti,ab. 7611
40 (LHRH* or LH-RH*).ti,ab. 12848
41 exp growth hormone releasing factor derivative/ 10344
42 (gonado* adj releas* adj hormon*).ti,ab. 23479
43 (GnRH* or GnRHA*).ti,ab. 35987
44 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 2166
45 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2607

Searches
46 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 4961
47 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 785
48 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1902
49 (hormon* adj3 (suppress* or ablat*)).ti,ab. 6815
50 or/37-49 163864
51 36 or 50 238137
52 exp aromatase inhibitor/ 41854
53 (aromatase adj2 (inhibit* or block*)).ti,ab. 16148
54 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 3026
55 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 7080
56 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 8015
57 or/52-56 47428
58 tamoxifen/ 75835
59 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 40576
60 58 or 59 80613
61 and/24,51,57 350
62 24 and 57 959
63 24 and 60 1371
64 or/61-63 1873
65 random:.tw. 2120643
66 placebo:.mp. 545820
67 double-blind:.tw. 255927
68 or/65-67 2406035
69 cohort analysis/ 1218953
70 longitudinal study/ 221325
71 prospective study/ 940745
72 retrospective study/ 1683317

Searches
73 follow up/ 2246518
74 ((follow up* or followup* or concurrent* or incidence* or population*) adj3 (study* or studies* or analy* or observation* or design* or method* or research*)).ti,ab. 866836
75 (longitudinal* or prospective* or retrospective* or cohort*).ti,ab. 4430563
76 case study/ 103111
77 case series.ti,ab. 161434
78 or/69-77 6688482
79 68 or 78 8368297
80 64 and 79 834
81 limit 80 to english language 815
82 nonhuman/ not human/ 5529930
83 81 not 82 808
84 (conference abstract* or conference review or conference paper or conference proceeding or editorial or letter).db,pt,su. 8184412
85 83 not 84 473

1 **Database name: MEDLINE ALL**

Searches
1 exp Breast Neoplasms/ 358488
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 48761
3 Carcinoma, Lobular/ 6194
4 Carcinoma, Medullary/ 3427
5 Carcinoma, Intraductal, Noninfiltrating/ 10916
6 or/1-5 379197
7 exp Breast/ 55038
8 breast*.ti,ab,kw. 590703
9 7 or 8 600719
10 (breast adj milk).ti,ab,kw. 16517
11 (breast adj tender*).ti,ab,kw. 601
12 10 or 11 17115
13 9 not 12 583604
14 exp Neoplasms/ 4019667
15 13 and 14 376776
16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 439457
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 37367
18 or/15-17 496525
19 6 or 18 554932
20 Breast Neoplasms, Male/ 3457
21 (male or men or man).ti,ab. 1982267
22 20 or 21 1983462

Searches	
23	19 and 22 18656
24	Castration/ 22071
25	Orchiectomy/ 15664
26	(orchiectomy or orchidectom* or castrat* or gonadectom*).ti,ab. 47010
27	((radiation or irradiation or radiotherap*) adj3 testi*).ti,ab. 1179
28	(remov* adj3 (testi* or gonad*)).ti,ab. 1613
29	exp Testis/ 82781
30	exp Radiation/ 534670
31	exp Radiotherapy/ 213622
32	30 or 31 706663
33	29 and 32 2736
34	((testi* or gonad*) adj3 (suppress* or ablat*)).ti,ab. 3158
35	or/24-28,33-34 72683
36	exp Luteinizing Hormone/ 48619
37	(lutein* adj hormon* adj releas*).ti,ab. 6940
38	(LHRH* or LH-RH*).ti,ab. 9943
39	exp Gonadotropin-Releasing Hormone/ 35036
40	(gonado* adj releas* adj hormon*).ti,ab. 19955
41	(GnRH* or GnRHA*).ti,ab. 26472
42	(goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 1368
43	(buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2185
44	(leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 3002
45	(nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 547
46	(triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1140
47	(hormon* adj3 (suppress* or ablat*)).ti,ab. 5270
48	or/36-47 91376
49	35 or 48 154891
50	exp Aromatase Inhibitors/ 10341

Searches
51 (aromatase adj2 (inhibit* or block*)).ti,ab. 9746
52 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 1559
53 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 2599
54 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 4166
55 or/50-54 16214
56 exp Tamoxifen/ 23089
57 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 26089
58 56 or 57 33277
59 and/23,49,55 68
60 23 and 55 255
61 23 and 58 454
62 or/59-61 630
63 exp Randomized Controlled Trial/ 623253
64 randomi?ed.mp. 1141389
65 placebo.mp. 260069
66 or/63-65 1209815
67 exp Cohort studies/ 2650761
68 ((follow up* or followup* or concurrent* or incidence* or population*) adj3 (study* or studies* or analy* or observation* or design* or method* or research*)).ti,ab. 514412
69 (longitudinal* or prospective* or retrospective* or cohort*).ti,ab. 2794454
70 epidemiologic methods/ and (197* or 198*).yr. 10282
71 case series.ti,ab. 114301
72 or/67-71 4114375
73 66 or 72 4978188
74 62 and 73 183
75 limit 74 to english language 172
76 Animals/ not (Animals/ and Humans/) 5224962
77 75 not 76 170
78 limit 77 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or letter) 16
79 77 not 78 154

Cost-effectiveness searches

Database results

Databases	Date searched	Database platform	Database segment or version	No. of results downloaded
Embase	24/09/24	Ovid	Embase <1974 to 2024 September 23>	36
Econlit	24/09/24	Ovid	Econlit <1886 to September 12, 2024>	12
INAHTA	24/09/24	INAHTA		14
Medline ALL	24/09/24	Ovid	Ovid MEDLINE(R) ALL <1946 to September 23, 2024>	8
NHS EED	24/09/24	CRD		0

Search strategy history

Database name: Econlit

Searches
1 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 409
2 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 1
3 or/1-2 410
4 (male or men or man).ti,ab,kw. 27543
5 3 and 4 13
6 limit 5 to yr="2010 -Current" 12

Database name: Embase

Searches
1 exp breast cancer/ 610788
2 exp breast carcinoma/ 101116
3 exp medullary carcinoma/ 13234
4 ductal breast carcinoma in situ/ 3654
5 exp breast tumor/ 694075
6 lobular carcinoma/ 3648
7 or/1-6 705715

Searches
8 exp breast/ 130855
9 breast*.ti,ab,kw. 821180
10 8 or 9 854476
11 (breast adj milk).ti,ab,kw. 21068
12 (breast adj tender*).ti,ab,kw. 791
13 11 or 12 21853
14 10 not 13 832623
15 exp neoplasm/ 5862771
16 14 and 15 634523
17 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 633471
18 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 44652
19 16 or 17 or 18 711044
20 7 or 19 840042
21 male breast cancer/ 1921
22 (male or men or man).ti,ab. 2913515
23 21 or 22 2913730
24 20 and 23 32565
25 castration/ 17639
26 exp orchiectomy/ 21000
27 (orchiectomy or orchidectom* or castrat* or gonadectom*).ti,ab. 64278
28 ((radiation or irradiation or radiotherap*) adj3 testi*).ti,ab. 1643
29 (remov* adj3 (testi* or gonad*)).ti,ab. 2221
30 exp testis/ 114070
31 exp radiation/ 790024
32 exp radiotherapy/ 694119
33 31 or 32 1405665
34 30 and 33 3449
35 ((testi* or gonad*) adj3 (suppress* or ablat*)).ti,ab. 3955
36 or/25-29,34-35 86181
37 exp luteinizing hormone/ 71873
38 exp gonadorelin derivative/ 85086
39 (lutein* adj hormon* adj releas*).ti,ab. 7610
40 (LHRH* or LH-RH*).ti,ab. 12848
41 exp growth hormone releasing factor derivative/ 10372
42 (gonado* adj releas* adj hormon*).ti,ab. 23499
43 (GnRH* or GnRHA*).ti,ab. 36010
44 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 2173
45 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2608

Searches
46 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid* or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 4969
47 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 785
48 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1905
49 (hormon* adj3 (suppress* or ablat*)).ti,ab. 6830
50 or/37-49 164011
51 36 or 50 238471
52 exp aromatase inhibitor/ 41927
53 (aromatase adj2 (inhibit* or block*)).ti,ab. 16184
54 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 3031
55 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 7158
56 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 8031
57 or/52-56 47570
58 tamoxifen/ 75926
59 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 40636
60 58 or 59 80705
61 and/24,51,57 352
62 24 and 57 963
63 24 and 60 1372
64 or/61-63 1878
65 exp Health Economics/ 1094572
66 exp "Health Care Cost"/ 358625
67 exp Pharmacoeconomics/ 246638
68 Monte Carlo Method/ 54930
69 Decision Tree/ 25935
70 econom$.tw. 539497
71 cba.tw. 14694
72 cea.tw. 43767

Searches
73 cua.tw. 2000
74 markov$.tw. 42797
75 (monte adj carlo).tw. 65439
76 (decision adj3 (tree$ or analys$)).tw. 44697
77 (cost or costs or costing$ or costly or costed).tw. 1072236
78 (price$ or pricing$).tw. 78493
79 budget$.tw. 50300
80 expenditure$.tw. 96335
81 (value adj3 (money or monetary)).tw. 4582
82 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 10013
83 or/65-82 2418921
84 64 and 83 85
85 limit 84 to english language 84
86 limit 85 to yr="2010 -Current" 67
87 nonhuman/ not human/ 5536033
88 86 not 87 64
89 (conference abstract* or conference review or conference paper or conference proceeding or editorial or letter).db,pt,su. 8198016
90 88 not 89 36

1 **Database name: INAHTA**

Searches
(("breast neoplasms"[mhe] OR "neoplasms, ductal, lobular, and medullary"[mhe] OR "carcinoma, lobular"[mh] OR "carcinoma, medullary"[mh] OR "carcinoma, intraductal, noninfiltrating"[mh]) OR ((breast* AND (neoplasm* or cancer* or tumor* or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))) OR ((mammar* AND (neoplasm* or cancer* or tumor*or tumour* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))))
AND
("breast neoplasms, male"[mh] OR (male or men or man))

2 **Database name: MEDLINE ALL**

Searches
1 exp Breast Neoplasms/ 358706
2 exp "Neoplasms, Ductal, Lobular, and Medullary"/ 48797
3 Carcinoma, Lobular/ 6194
4 Carcinoma, Medullary/ 3428
5 Carcinoma, Intraductal, Noninfiltrating/ 10925
6 or/1-5 379437
7 exp Breast/ 55054
8 breast*.ti,ab,kw. 591343

Searches
9 7 or 8 601359
10 (breast adj milk).ti,ab,kw. 16548
11 (breast adj tender*).ti,ab,kw. 600
12 10 or 11 17145
13 9 not 12 584214
14 exp Neoplasms/ 4022038
15 13 and 14 377021
16 (breast* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 439953
17 (mammar* adj5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*)).ti,ab,kw. 37375
18 or/15-17 497045
19 6 or 18 555474
20 Breast Neoplasms, Male/ 3459
21 (male or men or man).ti,ab. 1984526
22 20 or 21 1985721
23 19 and 22 18680
24 Castration/ 22071
25 Orchiectomy/ 15668
26 (orchiectomy or orchidectom* or castrat* or gonadectom*).ti,ab. 47065
27 ((radiation or irradiation or radiotherap*) adj3 testi*).ti,ab. 1179
28 (remov* adj3 (testi* or gonad*)).ti,ab. 1615
29 exp Testis/ 82801
30 exp Radiation/ 534936
31 exp Radiotherapy/ 213657
32 30 or 31 706965
33 29 and 32 2737
34 ((testi* or gonad*) adj3 (suppress* or ablat*)).ti,ab. 3164
35 or/24-28,33-34 72748
36 exp Luteinizing Hormone/ 48630
37 (lutein* adj hormon* adj releas*).ti,ab. 6942
38 (LHRH* or LH-RH*).ti,ab. 9944
39 exp Gonadotropin-Releasing Hormone/ 35043
40 (gonado* adj releas* adj hormon*).ti,ab. 19962
41 (GnRH* or GnRHA*).ti,ab. 26487
42 (goserelin* or zolade* or "ici 118630*" or ici118630* or "ly 01005*" or ly01005* or novimp* or prozoladex* or reseligo* or "zd 9393*" or zd9393* or zoreline*).ti,ab. 1370
43 (buserelin* or suprefact* or suprecur* or "hoe 706*" or hoe706* or "hoe 766*" or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*).ti,ab. 2187
44 (leuprolid* or leuprorelin* or lupron* or prostap* or a 43818* or a43818* or "abbott 43818*" or abbott43818* or "cam 2032*" or cam2032* or camcevi* or carcinil* or "ckd 841*" or ckd841* or daronda* or "depo lupron*" or eligard* or eliprogel* or elityran* or elityran depot* or enanton* or enantone* or fensolvi* or "fp 001*" or fp001* or ginecrin* or klebrocid*

Searches
or "la 2575*" or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or "nh 901*" or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or "sot 375*" or sot375* or staladex* or "tap 144*" or tap144* or tapros* or "tol 2506*" or tol2506* or trenantone* or viadur* or "vp 4896*" or Vp4896* or zeulide*).ti,ab. 3004
45 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or "rs 94991*" or rs94991* or rsynarel* or synrelin*).ti,ab. 547
46 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or "ay 25650*" or ay25650* or "bim 21003*" or bim21003* or "bn 52014*" or Bn52014* or "cl 118532*" or cl118532* or "debio 8200*" or "debio 8206*" or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or "isr 048*" or isr 48* or isr048* or isr48* or "ly 01007*" or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or "wy 42422*" or "wy 42462*" or wy42422* or wy42462*).ti,ab. 1140
47 (hormon* adj3 (suppress* or ablat*)).ti,ab. 5271
48 or/36-47 91402
49 35 or 48 154979
50 exp Aromatase Inhibitors/ 10352
51 (aromatase adj2 (inhibit* or block*)).ti,ab. 9760
52 (exemestane* or aromasi* or "fce 24304*" or fce24304* or nakides* or nikidess* or "pnu 155971*" or pnu15597*).ti,ab. 1561
53 (anastrozole* or anastrazole* or arimidex* or "ici d1033*" or icid1033* or "zd 1033*" or zd1033* or zeneca* or femathina* or "mpi 674*" or "mpi 676*" or mpi674* or mpi676* or trozolet*).ti,ab. 2600
54 (letrozole* or femar* or "cgs 20267*" or cgs20267* or loxifan*).ti,ab. 4178
55 or/50-54 16238
56 exp Tamoxifen/ 23095
57 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or "ici 47699*" or ici47699 or tomaxithen* or zitazonium* or ebefen* or kessar* or "nsc 180973*" or nsc180973 or "pt 101*" or pt101 or tamoplac* or tamoxasta*).ti,ab. 26114
58 56 or 57 33302
59 and/23,49,55 68
60 23 and 55 255
61 23 and 58 456
62 or/59-61 632
63 Economics/ 27539
64 exp "Costs and Cost Analysis"/ 273327
65 Economics, Dental/ 1922
66 exp Economics, Hospital/ 25987
67 exp Economics, Medical/ 14446
68 Economics, Nursing/ 4013
69 Economics, Pharmaceutical/ 3149
70 Budgets/ 11858
71 exp Models, Economic/ 16525
72 Markov Chains/ 16460
73 Monte Carlo Method/ 33316

Searches
74 Decision Trees/ 12355
75 econom$.tw. 446391
76 cba.tw. 11468
77 cea.tw. 28280
78 cua.tw. 1515
79 markov$.tw. 34006
80 (monte adj carlo).tw. 62645
81 (decision adj3 (tree$ or analys$)).tw. 33968
82 (cost or costs or costing$ or costly or costed).tw. 809285
83 (price$ or pricing$).tw. 57692
84 budget$.tw. 38183
85 expenditure$.tw. 72921
86 (value adj3 (money or monetary)).tw. 3444
87 (pharmacoeconomic$ or (pharmaco adj economic$)).tw. 4684
88 or/63-87 1550152
89 62 and 88 12
90 limit 89 to english language 12
91 limit 90 to yr="2010 -Current" 10
92 Animals/ not (Animals/ and Humans/) 5226930
93 91 not 92 8
94 limit 93 to (case reports or clinical conference or comment or consensus development conference or consensus development conference, nih or editorial or letter) 0
95 93 not 94 8

1 **Database name: NHS EED**

Searches
1 MESH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES
2 MESH DESCRIPTOR Neoplasms, Ductal, Lobular, and Medullary EXPLODE ALL TREES
3 MESH DESCRIPTOR Carcinoma, Lobular
4 MESH DESCRIPTOR Carcinoma, Medullary
5 MESH DESCRIPTOR Carcinoma, Intraductal, Noninfiltrating
6 #1 or #2 or #3 or #4 or #5
7 MESH DESCRIPTOR Breast EXPLODE ALL TREES
8 breast*
9 #7 or #8
10 (breast NEXT milk)
11 (breast NEXT tender*)
12 #10 or #11
13 #9 not #12
14 MESH DESCRIPTOR Neoplasms EXPLODE ALL TREES
15 #13 and #14

Searches
16 (breast* NEAR5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
17 (mammar* near5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular or malignan*))
18 #15 or #16 or #17
19 #6 or #18
20 MESH DESCRIPTOR Breast Neoplasms, Male
21 (male or men or man)
22 #20 or #21
23 #19 and #22
24 MESH DESCRIPTOR Castration
25 MESH DESCRIPTOR Orchiectomy
26 (orchiectomy or orchidectom* or castrat* or gonadectom*)
27 (remov* near3 (testi* or gonad*))
28 ((radiation or irradiation or radiotherap*) near3 testi*)
29 MESH DESCRIPTOR Testis EXPLODE ALL TREES
30 MESH DESCRIPTOR Radiation EXPLODE ALL TREES
31 MESH DESCRIPTOR Radiotherapy EXPLODE ALL TREES
32 #30 or #31
33 #29 and #32
34 ((testi* or gonad*) near3 (suppress* or ablat*))
35 #24 or #25 or #26 or #27 or #28 or #33 or #34
36 MESH DESCRIPTOR Luteinizing Hormone EXPLODE ALL TREES
37 (lutein* next hormon* next releas*)
38 (LHRH* or LH-RH*)
39 MESH DESCRIPTOR Gonadotropin-Releasing Hormone EXPLODE ALL TREES
40 (gonado* next releas* next hormon*)
41 (GnRH* or GnRHA*)
42 (goserelin* or zolade* or ici NEXT 118630* or ici118630* or ly NEXT 01005* or ly01005* or novimp* or prozoladex* or reseligo* or zd NEXT 9393* or zd9393* or zoreline*)
43 (buserelin* or suprefact* or suprecur* or hoe NEXT 706* or hoe706* or hoe NEXT 766* or hoe766* or bigonist* or etilamide* or ethylamide* or profact* or receptal* or superfact* or supremon* or tiloryth*)
44 (leuprolid* or leuprorelin* or lupron* or prostap* or a NEXT 43818* or a43818* or abbott NEXT 43818* or abbott43818* or cam NEXT 2032* or cam2032* or camcevi* or carcinil* or ckd NEXT 841* or ckd841* or daronda* or depo NEXT lupron* or eligard* or eliprogel* or elityran* or elityran NEXT depot* or enanton* or enantone* or fensolvi* or fp NEXT 001* or fp001* or ginecrin* or klebrocid* or la NEXT 2575* or la2575* or leptoprol* or lerin* or leuplin* or leupro* or leuprogel* or leuprol* or leuprostin* or lorelin* or lucrin* or lupride* or luprolex* or lupron* or lutrate* or nh NEXT 901* or nh901* or ovarest* or politrate* or procren* or procrin* or prostaplant* or reliser* or sixantone* or sot NEXT 375* or sot375* or staladex* or tap NEXT 144* or tap144* or tapros* or tol NEXT 2506* or tol2506* or trenantone* or viadur* or vp NEXT 4896* or Vp4896* or zeulide*)
45 (nafarelin* or synarel* or gonadorelin* or napharelin* or nasanyl* or rs NEXT 94991* or rs94991* or rsynarel* or synrelin*)

Searches
46 (triptorelin* or decapeptyl* or gonapeptyl* or arvekap* or ay NEXT 25650* or ay25650* or bim NEXT 21003* or bim21003* or bn NEXT 52014* or Bn52014* or cl NEXT 118532* or cl118532* or debio NEXT 8200* or debio NEXT 8206* or debio8200* or debio8206* or detryptorelin* or diphereline* or fertipeptil* or isr NEXT 048* or isr NEXT 48* or isr048* or isr48* or ly NEXT 01007* or ly01007* or microrelin* or moapar* or ovugel* or pamorelin* or salvacyl* or spherotide* or trelstar* or triptodur* or triptofem* or wy NEXT 42422* or wy NEXT 42462* or wy42422* or wy42462*)
47 (hormon* near3 (suppress* or ablat*))
48 #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47
49 #35 or #48
50 MESH DESCRIPTOR Aromatase Inhibitors EXPLODE ALL TREES
51 (aromatase near2 (inhibit* or block*))
52 (exemestane* or aromasi* or fce NEXT 24304* or fce24304* or nakides* or nikidess* or pnu NEXT 155971* or pnu15597*)
53 (anastrozole* or anastrazole* or arimidex* or ici NEXT d1033* or icid1033* or zd NEXT 1033* or zd1033* or zeneca* or femathina* or mpi NEXT 674* or mpi NEXT676* or mpi674* or mpi676* or trozolet*)
54 (letrozole* or femar* or cgs NEXT 20267* or cgs20267* or loxifan*)
55 #50 or #51 or #52 or #53 or #54
56 MESH DESCRIPTOR Tamoxifen EXPLODE ALL TREES
57 (tamoxifen* or tamofen* or tamone* or nolvadex* or soltamox* or ici NEXT 47699* or ici47699* or tomaxithen* or zitazonium* or ebefen* or kessar* or nsc NEXT 180973* or nsc180973* or pt NEXT 101* or pt101* or tamoplac* or tamoxasta*)
58 #56 OR #57
59 #23 AND #49 AND #55
60 #23 AND #55
61 #23 AND #58
62 #59 OR #60 OR #61
63 (#62) IN NHSEED FROM 2010 TO 2024

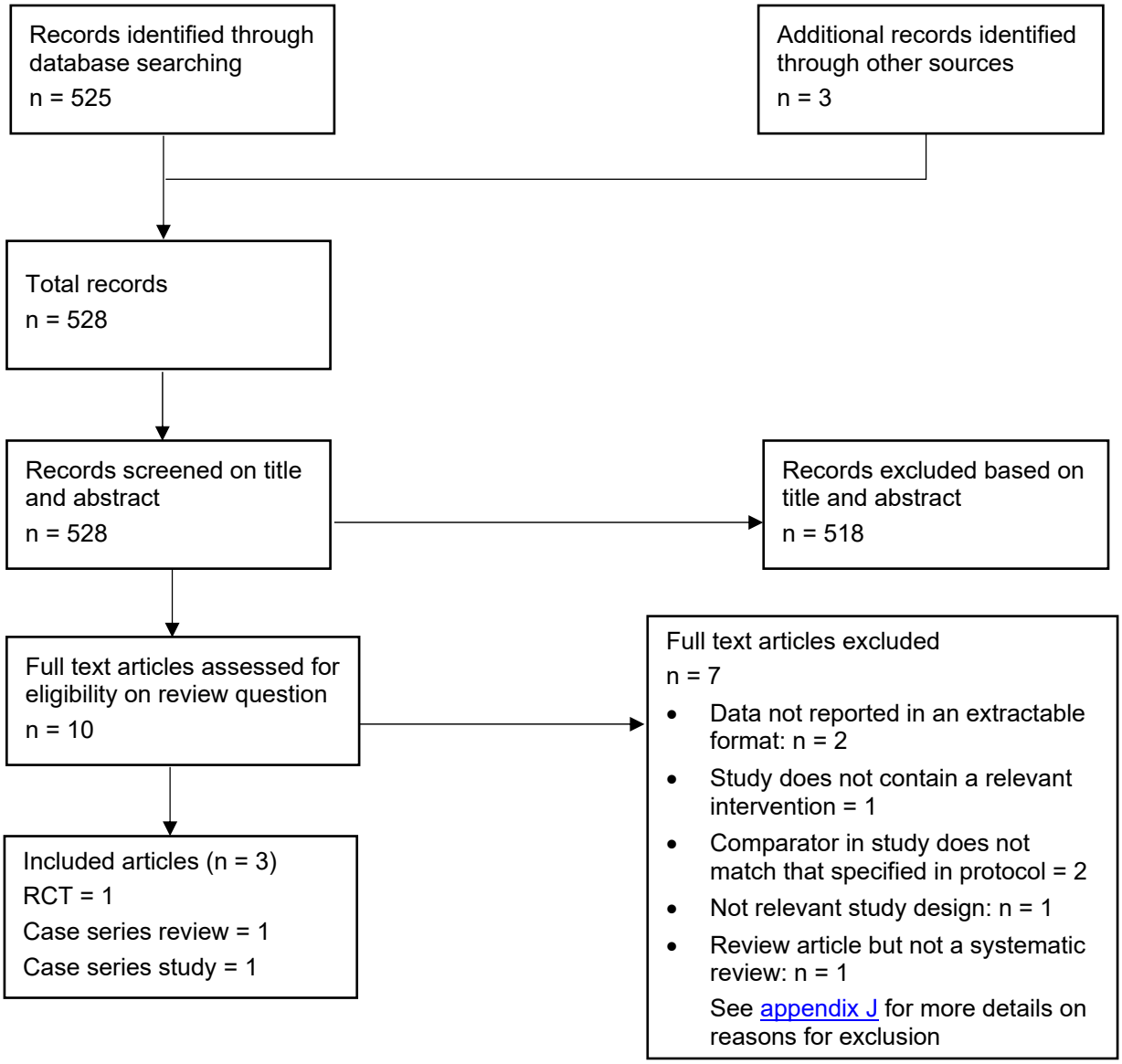
Additional search methods – Technical Team action

Date of action	24/10/2024
No. of results added	3
How the results were processed	1 reference (Zagouri et al. 2015) was highlighted by the clinical adviser and 2 references (Giordano et al. 2002; Giordano et al. 2006) were included by Zagouri et al. 2015.
How the results were selected	All 3 references were included at title and abstract sift. Zagouri et al. 2015 was included at full text sift and data has been extracted from it. The other 2 references (Giordano et al. 2002; Giordano et al. 2006) were excluded at full text sift because none of them met the inclusion criteria of the protocol

List of results added	Zagouri F, Sergentanis TN, Azim HA et al. (2015) Aromatase inhibitors in male breast cancer: a pooled analysis. Breast cancer research and treatment 151(1): 141-147 Giordano SH, Valero V, Buzdar AU et al. (2002) Efficacy of anastrozole in male breast cancer. American journal of clinical oncology 25(3): 235-237 Giordano SH and Hortobagyi GN (2006) Leuprolide acetate plus aromatase inhibition for male breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24(21): e42

1

Appendix C – Effectiveness evidence study selection



1 Appendix D – Effectiveness evidence

2 Randomised controlled trial

3 Reinisch, 2021

Bibliographic Reference	Reinisch, Mattea; Seiler, Sabine; Hauzenberger, Tanja; Kamischke, Axel; Schmatloch, Sabine; Strittmatter, Hans-Joachim; Zahm, Dirk-Michael; Thode, Christian; Furlanetto, Jenny; Strik, Dominika; Mobus, Volker; Reimer, Toralf; Sinn, Bruno Valentin; Stickeler, Elmar; Marme, Frederik; Janni, Wolfgang; Schmidt, Marcus; Rudlowski, Christian; Untch, Michael; Nekljudova, Valentina; Loibl, Sibylle; Efficacy of Endocrine Therapy for the Treatment of Breast Cancer in Men: Results from the MALE Phase 2 Randomized Clinical Trial.; JAMA oncology; 2021; vol. 7 (no. 4); 565-572

4 Study details

Trial registration number and/or trial name	NCT01638247 / GBG-54 MALE
Study type	Randomised controlled trial (RCT)
Study location	Germany
Study setting	Breast units
Study dates	October 2012 and May 2017
Sources of funding	Drug supply (exemestane) was provided by Pfizer, Germany. The study was sponsored by German Breast Group and supported by the Claudia von Schilling Foundation.
Inclusion criteria	Male patients with hormone receptor positive (oestrogen receptor and/or progesterone receptor positive) breast cancer Karnofsky Performance Status of 60% or greater No history or evidence of prostate cancer
Exclusion criteria	None reported
Intervention(s)	An aromatase inhibitor (exemestane) combined with gonadotropin-releasing hormone analogue
Comparator	Tamoxifen alone
Outcome measures	Quality of life The International Index of Erectile Function (IIEF) questionnaire assesses the sexual function and includes dimensions of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. It divides patients into 2 groups with “potential for erectile dysfunction” (score <21) or “no signs of erectile dysfunction” (score ≥21). The Aging Male Symptom (AMS) Score was used to evaluate patients’ quality of life by capturing aspects of psychological, physical, and sexual well-being, which are supposed to be associated with androgen decline in

	aging men. A score of 27 or higher has been defined to be suggestive for androgen deficiency. Serum oestradiol levels Changes in 17-β-oestradiol (oestradiol) levels at 6 months. Reference ranges for men (and minimum detectable values) were 27 to 52 (5) ng/L for oestradiol. In the case of early study discontinuation, blood samples were taken at the time of discontinuation. Serum testosterone levels Change in the level of testosterone at 6 months. Reference ranges for men (and minimum detectable values) were 2.8 to 8.8 (0.1) µg/L for testosterone. In the case of early study discontinuation, blood samples were taken at the time of discontinuation. Adverse events The National Cancer Institute Common Toxicity Criteria version 4.0 (Common Terminology Criteria for Adverse Events, CTCAE) and the corresponding grading system were used to grade adverse events. Adherence to or completion of treatment Compliance parameters: treatment interruption or permanent discontinuation.
Number of participants	35
Duration of follow-up	6 months
Methods of analysis	Because the test of normality failed, the Kruskal-Wallis test was used to compare decreases in hormone levels between arms after 6 months of treatment. Pairwise comparisons of an AI combined with gonadotropin-releasing hormone analogue and tamoxifen were planned hierarchically in case the overall primary test was significant and were performed, using the non-parametric Mann-Whitney test; no other adjustments for multiplicity were performed. For the questionnaire, per each score changes from baseline were compared for the treatment groups using the Kruskal-Wallis test. The categorized AMS and IIEF were compared between arms at baseline and at 3 and 6 months with the χ test. Additionally, for all continuous parameters at 6 months, a nonparametric analysis of covariance sensitivity analysis was performed, covariate adjusted for the baseline value. SAS version 9.4 (SAS Institute) and R version 3.2.2 (for box plots and nonparametric ANCOVA) were used for analyses.
Additional comments	Study was a 3-arm trial. In the third arm participants received tamoxifen combined with gonadotropin-releasing hormone analogue. This arm was not included in the NICE review because it did not meet the inclusion criteria listed in the protocol.

Study arms

An AI combined with TFS (N = 18)

Loss to follow-up	4 (1 treatment discontinuation due to patient's request and 3 missing blood samples)

Exemestane: 25 mg/d orally. Gonadotropin-releasing hormone analogue was administered subcutaneously every 3 months. Treatment was given for 6 months in the neoadjuvant, adjuvant, or metastatic setting. Subsequent treatment with tamoxifen, 20 mg/d orally, alone was conducted regardless of study treatment.

Tamoxifen alone (N = 17)

Loss to follow-up	1 (1 treatment discontinuation due to disease progression)

Tamoxifen: 20 mg/d orally. Treatment was given for 6 months in the neoadjuvant, adjuvant, or metastatic setting. Subsequent treatment with tamoxifen, 20 mg/d orally, alone was conducted regardless of study treatment.

Characteristics

Arm-level characteristics

Characteristic	An AI combined with TFS (N = 18)	Tamoxifen alone (N = 17)
Age (years) Median (range) Custom value	66 (45 to 80)	59 (37 to 83)
Setting - Neoadjuvant No of events	n = 0 ; % = 0	n = 0 ; % = 0
Setting - Adjuvant No of events	n = 18 ; % = 100	n = 14 ; % = 82.4
Setting - Metastatic No of events	n = 0 ; % = 0	n = 3 ; % = 17.6
Tumour stage - T1 No of events	n = 8 ; % = 44.4	n = 7 ; % = 43.8
Tumour stage - T2 No of events	n = 9 ; % = 50	n = 7 ; % = 43.8
Tumour stage - T3 No of events	n = 0 ; % = 0	n = 0 ; % = 0
Tumour stage - T4 No of events	n = 1 ; % = 5.6	n = 2 ; % = 12.5
Tumour stage - Missing No of events	n = 0	n = 1
Breast cancer grade - G1 No of events	n = 2 ; % = 11.1	n = 3 ; % = 17.6
Breast cancer grade - G2 No of events	n = 12 ; % = 66.7	n = 9 ; % = 52.9
Breast cancer grade - G3 No of events	n = 4 ; % = 22.2	n = 5 ; % = 29.4
Histological tumour type - Ductal or ductal-lobular invasive	n = 17 ; % = 94.4	n = 16 ; % = 94.1

Characteristic	An AI combined with TFS (N = 18)	Tamoxifen alone (N = 17)
No of events		
Histological tumour type - Lobular invasive No of events	n = 0 ; % = 0	n = 0 ; % = 0
Histological tumour type - Other No of events	n = 1 ; % = 5.6	n = 1 ; % = 5.9
Lymph node status - N0 No of events	n = 10 ; % = 55.6	n = 7 ; % = 46.7
Lymph node status - N+ No of events	n = 8 ; % = 44.5	n = 8 ; % = 53.3
Lymph node status - Missing No of events	n = 0	n = 2
Metastatic lesion - M0 No of events	n = 18 ; % = 100	n = 15 ; % = 88.2
Metastatic lesion - M1 No of events	n = 0 ; % = 0	n = 2 ; % = 11.8
Metastatic lesion - Missing No of events	n = 0 ; % = 0	n = 0 ; % = 0
Prior chemotherapy - No No of events	n = 11 ; % = 61.1	n = 11 ; % = 64.7
Prior chemotherapy - Yes No of events	n = 7 ; % = 38.9	n = 6 ; % = 35.3

Outcomes

Study timepoints

- Baseline
- 6 month

Oestradiol levels (ng/L)

Outcome	6 month, an AI combined with TFS, N = 15	6 month, Tamoxifen alone, N = 17
Oestradiol levels, median (range) (ng/L) Change in oestradiol levels from baseline to 6 months Custom value	-17.0 (-102.0 to 6.0)	12.0 (-23.0 to 50.0)

Oestradiol levels, median (range) - Polarity - Lower values are better

Change in oestradiol levels from baseline to 6 months

Testosterone levels (µg/L)

Outcome	6 month, an AI combined with TFS, N = 15	6 month, Tamoxifen alone, N = 17
Testosterone levels, median (range) (g/L) Change in testosterone levels from baseline to 6 months Custom value	-3.5 (-14.7 to 1.0)	1.6 (-3.1 to 8.3)

Testosterone levels, median (range) - Polarity - Lower values are better

Change in testosterone levels from baseline to 6 months

Sexual function

Outcome	An AI combined with TFS, Baseline, N = 18	An AI combined with TFS, 6 month, N = 17	Tamoxifen alone, Baseline, N = 17	Tamoxifen alone, 6 month, N = 16
Sexual function Participants reporting erectile dysfunction No of events	n = 7 ; % = 38.88	n = 13 ; % = 76.47	n = 5 ; % = 29.41	n = 4 ; % = 25

Sexual function - Polarity - Lower values are better

The International Index of Erectile Function questionnaire was used to assesses sexual function. Score less than 21: potential for erectile dysfunction; score 21 or more: no signs of erectile dysfunction.

Quality of life

Outcome	An AI combined with TFS, Baseline, N = 18	An AI combined with TFS, 6 month, N = 17	Tamoxifen alone, Baseline, N = 17	Tamoxifen alone, 6 month, N = 16
Quality of life Participants reporting reduced quality of life No of events	n = 9 ; % = 50	n = 11 ; % = 64.7	n = 11 ; % = 64.7	n = 13 ; % = 81.25

Quality of life - Polarity - Lower values are better

The Aging Male Symptom Score was used to evaluate patients' quality of life. A score of 27 or higher was defined to be suggestive for androgen deficiency.

Adverse events

Outcome	6 month, an AI combined with TFS, N = 18	6 month, Tamoxifen alone, N = 17
Hot flushes Grade 2 No of events	n = 3 ; % = 16.7	n = 0 ; % = 0

Outcome	6 month, an AI combined with TFS, N = 18	6 month, Tamoxifen alone, N = 17
Sleep disorder Grade 2 No of events	n = 1 ; % = 5.6	n = 0 ; % = 0
Fatigue Grade 2 No of events	n = 3 ; % = 16.7	n = 0 ; % = 0
Decreased libido Grade 2 No of events	n = 5 ; % = 27.8	n = 2 ; % = 11.1
Erectile dysfunction Grade 2 No of events	n = 1 ; % = 5.6	n = 1 ; % = 5.6
Erectile dysfunction Grade 3 or more No of events	n = 2 ; % = 11.1	n = 0 ; % = 0
Arthralgia (Myalgia and bone pain pooled) Grade 2 No of events	n = 2 ; % = 11.2	n = 0 ; % = 0

1 Hot flushes - Polarity - Lower values are better
2 Sleep disorder - Polarity - Lower values are better
3 Fatigue - Polarity - Lower values are better
4 Decreased libido - Polarity - Lower values are better
5 Erectile dysfunction - Polarity - Lower values are better
6 Erectile dysfunction - Polarity - Lower values are better
7 Arthralgia - Polarity - Lower values are better
8 Numbers calculated from percentages

9 Adherence to or completion of treatment

Outcome	An AI combined with TFS, 6 month, N = 19	Tamoxifen alone, 6 month, N = 18
Adherence to or completion of treatment Participants with treatment discontinuation No of events	n = 1 ; % = 5.26	n = 1 ; % = 5.55

10 Adherence to or completion of treatment - Polarity - Lower values are better
11 Participants with treatment discontinuation

1 Critical appraisal - Cochrane Risk of Bias tool (RoB 2.0) RCT

2 Risk of bias for objective outcomes: change in oestradiol levels

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions; proportions of missing data on oestradiol and testosterone levels differed between groups: tamoxifen alone (no missing data), an AI combined with TFS (3 participants [16.6%] without blood samples at 6 months); reasons for missing blood samples were not reported)
Overall bias and Directness	Overall Directness	Directly applicable

3 Risk of bias for objective outcomes: change in testosterone levels

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions; proportions of missing data on oestradiol and testosterone levels differed between groups: tamoxifen alone (no missing data), an AI combined with TFS (3 participants [16.6%] without blood samples at 6 months); reasons for missing blood samples were not reported)
Overall bias and Directness	Overall Directness	Directly applicable

4 Risk of bias for subjective outcomes: sexual function

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions; it is likely that assessment of the outcome was influenced by knowledge of the intervention received)
Overall bias and Directness	Overall Directness	Directly applicable

5 Risk of bias for subjective outcomes: quality of life

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions; it is likely

Section	Question	Answer
		that assessment of the outcome was influenced by knowledge of the intervention received)
Overall bias and Directness	Overall Directness	Directly applicable

1 **Risk of bias for subjective outcomes: adverse events**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions; it is likely that assessment of the outcome was influenced by knowledge of the intervention received)
Overall bias and Directness	Overall Directness	Directly applicable

2 **Risk of bias for subjective outcomes: adherence to or completion of treatment**

Section	Question	Answer
Overall bias and Directness	Risk of bias judgement	High (No information on whether allocation sequence was concealed until participants were enrolled and assigned to interventions; it is likely that assessment of the outcome was influenced by knowledge of the intervention received)
Overall bias and Directness	Overall Directness	Directly applicable

3 **Case series review**

4 **Zagouri, 2015**

Bibliographic Reference	Zagouri F; Sergentanis TN; Azim HA; Chrysikos D; Dimopoulos MA; Psaltopoulou T; Aromatase inhibitors in male breast cancer: a pooled analysis.; Breast cancer research and treatment; 2015; vol. 151 (no. 1)

5 **Study Characteristics**

Study design	Case series review
Study details	Dates searched From 1 January 1980 to 15 October 2014 Databases searched PUBMED Sources of funding Not reported

Inclusion criteria	All reports or studies that examined the efficacy (response and/or survival) of third-generation AIs (anastrozole, letrozole, exemestane) in metastatic male breast cancer and reported data regarding efficacy, regardless of sample size In case of administration of AI in different lines of treatments, only the first administration of AI was considered eligible The first time of co-administration of AI and GnRH analogues, was considered eligible, irrespective of administration of GnRH analogues or AI in a previous line of treatment; in that case, the subjects were censored at the moment of transition to the second treatment (regarding the first treatment)
Exclusion criteria	Studies with AIs administration in male breast cancer patients without reporting any data on efficacy Cases with co-administration of AI with other chemotherapeutic agents or hormonal manipulations other than GnRH analogues
Outcome(s)	Overall survival
Number of studies included in the case series review	15
Studies from the case series review that are relevant for use in the current review	• Zagouri 2013
Studies from the case series review that are not relevant for use in the current review	• Zabolonty et al. 2005 (1 case report) • Arriola et al. 2007 (1 case report) • Giordano et al. 2006 (2 cases; both with an AI combined with TFS) • Italiano et al. 2004 (1 case report) • Carmona-Bayonas et al. 2007 (1 case report) • Di Lauro et al. 2013 (All participants received combination therapy with an aromatase inhibitor and testicular function suppression either as a first line or as a second line treatment) • Doyen et al. 2010 (none of the included participants received testicular function suppression) • Soon Wong et al. 2007 (1 case report) • Arrighi et al. 2005 (conference abstract with 3 cases) • Giordano et al. 2002 (an aromatase inhibitor combined with testicular function suppression was not included as an intervention) • Bighin et al. 2010 (none of the included participants received testicular function suppression) • Bradley et al. 2014 (none of the included participants received testicular function suppression) • Montero et al. 2011 (none of the included participants received testicular function suppression)

	• Fontana et al. 2007 (1 case report)
Additional comments	Extracted data was number of people who died.

Study arms

An AI combined with TFS (N = 39)

AI: aromatase inhibitor (anastrozole, letrozole or exemestane); TFS: testicular function suppression with gonadotropin-releasing hormone (GnRH) analogues

AI alone (N = 63)

AI: aromatase inhibitor alone (anastrozole, letrozole or exemestane)

Outcomes

Study timepoints

- 39 month (months of overall survival)

Mortality

Outcome	An AI combined with TFS, 39 month, N = 17	An AI alone, 39 month, N = 6
Mortality Number of people who died No of events	n = 15 ; % = 88.23	n = 6 ; % = 100

Mortality - Polarity - Lower values are better

Number of participants who died

Data from a single study (Zagouri et al. 2013)

Critical appraisal - ROBIS checklist

Risk of bias for mortality

Section	Question	Answer
Overall study ratings	Overall risk of bias	High (1 case reports were included; only 1 database was searched (PUBMED); study quality was not formally assessed; results are likely to be biased because between-study variation was not accounted for)
Overall study ratings	Applicability as a source of data	Partially applicable (Participants had metastatic breast cancer)

1 **Case series study**

2 **Zagouri, 2013**

Bibliographic Reference	Zagouri, F; Sergentanis, T N; Koutoulidis, V; Sparber, C; Steger, G G; Dubsky, P; Zografos, G C; Psaltopoulou, T; Gnant, M; Dimopoulos, M-A; Bartsch, R; Aromatase inhibitors with or without gonadotropin-releasing hormone analogue in metastatic male breast cancer: a case series.; British journal of cancer; 2013; vol. 108 (no. 11); 2259-63

3 **Study details**

Secondary publication of another included study- see primary study for details	Zagouri et al. 2015
Study type	Case series
Study location	Austria and Greece
Study setting	Academic breast centres
Study dates	Not reported
Sources of funding	Research grant from Hellenic Society for Medical Oncology (HeSMO)
Inclusion criteria	Male patients with metastatic breast cancer who have been treated with an aromatase inhibitor with or without a gonadotropin-releasing hormone analogue
Exclusion criteria	Patients who had received an aromatase inhibitor in the adjuvant setting Patients with HER2 positive breast tumours Patients who received concomitant chemotherapy, trastuzumab and/or radiotherapy Previous gonadotropin-releasing hormone analogue administration Patients without at least one measurable or assessable non-measurable lesion Oestrogen receptor and progesterone receptor negative primary and/or metastatic breast cancer
Outcome measures	Overall survival Defined as the interval between initiation of AI therapy and time of death
Number of participants	23
Duration of follow-up	Median overall survival was 39 months
Loss to follow-up	Not reported

Methods of analysis	Kaplan-Meier survival curves were estimated for the graphical presentation of results. Log-rank test for the equality of survivor functions was performed in order to assess whether co-administration of goserelin as well as the type of administered AI was associated with differences in terms of OS and PFS.
Additional comments	Outcome data was not reported in an extractable format. Therefore, outcome data was extracted from Zagouri et al. 2015

Study arms

An AI combined with TFS (N = 17)

An oral aromatase inhibitor (either exemestane 25 mg or letrozole 2.5 mg or anastrozole 1 mg) was administered daily, combined with testicular function suppression with a gonadotropin-releasing hormone (GnRH) analogue (goserelin acetate 3.6 mg on day 1 in four weekly intervals). Treatment was continued until disease progression or unacceptable toxicity.

AI alone (N = 6)

An oral aromatase inhibitor (either exemestane 25 mg or letrozole 2.5 mg or anastrozole 1 mg) was administered daily. Treatment was continued until disease progression or unacceptable toxicity.

Characteristics

Study-level characteristics

Characteristic	Study (N = 23)
Age (years) Mean (SD)	64.4 (6.5)
Oestrogen receptor expression (Allred score) Mean (SD)	6.61 (1.2)
Progesterone receptor expression (Allred score) Mean (SD)	4.91 (1.81)
Histological type - Invasive ductal carcinoma No of events	n = 18 ; % = 78.3
Histological type - Infiltrative lobular carcinoma No of events	n = 5 ; % = 21.7
Grade - 1 No of events	n = 2 ; % = 8.7
Grade - 2 No of events	n = 10 ; % = 43.5
Grade - 3 No of events	n = 11 ; % = 47.8
Adjuvant radiotherapy - Yes No of events	n = 22 ; % = 95.6

Characteristic	Study (N = 23)
Adjuvant radiotherapy - No No of events	n = 1 ; % = 4.4
Adjuvant chemotherapy - Anthracycline based No of events	n = 5 ; % = 21.7
Adjuvant chemotherapy - Taxane based No of events	n = 3 ; % = 13
Adjuvant chemotherapy - Anthracycline plus taxane based No of events	n = 13 ; % = 56.5
Adjuvant chemotherapy - Unknown No of events	n = 1 ; % = 4.4
Adjuvant chemotherapy - No No of events	n = 1 ; % = 4.4
Type of aromatase inhibitor administered - Non-steroidal (letrozole or anastrozole) No of events	n = 19 ; % = 82.6
Type of aromatase inhibitor administered - Steroidal (exemestane) No of events	n = 4 ; % = 17.4
Line of treatment - First No of events	n = 14 ; % = 60.9
Line of treatment - Second No of events	n = 9 ; % = 39.1

Critical appraisal - Institute of Health Economics checklist for case series studies

Section	Question	Answer
Overall Risk of Bias	Risk of Bias	Moderate *(Participants were recruited retrospectively; study did not provide estimates of the random variability in the data analysis of overall survival (these are confidence intervals or standard error or standard deviation))*
Overall Risk of Bias	Applicability	Partially directly applicable *(Participants had metastatic breast cancer)*

Appendix E – Forest plots

It was not possible to undertake any meta-analysis for this review question.

Appendix F – GRADE tables

Invasive ER positive breast cancer: an aromatase inhibitor combined with testicular function suppression compared to tamoxifen alone

Quality of life

Table 13 Quality of life – 6 months follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	An AI combined with TFS	Tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Quality of life (people who reported to have reduced quality of life) - 6 months follow-up (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	11/17 (64.7%)	13/16 (81.3%)	RR 0.80 (0.52 to 1.22)	162 fewer per 1,000 (from 390 fewer to 179 more)	Very low	CRITICAL

AI: aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression

Explanations

a. Study at high risk of bias, outcome was downgraded two levels

b. Data was only available from one study, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

Adherence to or completion of treatment

Table 14 Adherence to or completion of treatment

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	An AI combined with TFS	tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Adherence to or completion of treatment (participants with treatment discontinuation) (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	1/19 (5.3%)	18/1 (1800.0%)	RR 0.95 (0.06 to 14.04)	900 fewer per 1,000 (from 1,000 fewer to 1,000 more)	Very low	IMPORTANT

AI: aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression

Explanations

a. Study at high risk of bias, outcome was downgraded two levels

b. Data was only available from one study, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

Adverse events

Table 15 Adverse events (6 months follow up)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	An AI combined with TFS	Tamoxifen alone	Relative (95% CI)	Absolute (95% CI)		
Hot flushes - grade 2 (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	3/18 (16.7%)	0/17 (0.0%)	RR 6.63 (0.37 to 119.59)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT
Sleep disorder - grade 2 (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	1/18 (5.6%)	0/17 (0.0%)	RR 2.84 (0.12 to 65.34)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT
Fatigue - grade 2 (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	3/18 (16.7%)	0/17 (0.0%)	RR 6.63 (0.37 to 119.59)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**An AI combined with TFS**	**Tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Decreased libido - grade 2 (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	5/18 (27.8%)	2/17 (11.8%)	RR 2.36 (0.53 to 10.58)	160 more per 1,000 (from 55 fewer to 1,000 more)	Very low	IMPORTANT
Erectile dysfunction - grade 2 (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	1/18 (5.6%)	1/17 (5.9%)	RR 0.94 (0.06 to 13.93)	4 fewer per 1,000 (from 55 fewer to 761 more)	Very low	IMPORTANT
Erectile dysfunction - grade 3 or more (RR less than 1 favours an AI combined with TFS)												
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	2/18 (11.1%)	0/17 (0.0%)	RR 4.74 (0.24 to 92.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT
Arthralgia - grade 2 (RR less than 1 favours an AI combined with TFS)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**An AI combined with TFS**	**Tamoxifen alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Reinisch 2021)	randomised trials	very serious[a]	serious[b]	not serious	very serious[c]	none	2/18 (11.1%)	0/17 (0.0%)	RR 4.74 (0.24 to 92.07)	0 fewer per 1,000 (from 0 fewer to 0 fewer)	Very low	IMPORTANT

AI: aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression

Explanations

a. Study at high risk of bias, outcome was downgraded two levels

b. Data was only available from one study, outcome was downgraded one level

c. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

ER positive metastatic breast cancer: an aromatase inhibitor combined with testicular function suppression compared to an aromatase inhibitor alone

Mortality

Table 16 Mortality – 3 years follow-up

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**An AI combined with TFS**	**AI alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
Mortality - 3 years follow-up (median 38 months; range: 9 to 79 months) (RR less than 1 favours an AI combined with TFS)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**An AI combined with TFS**	**AI alone**	**Relative (95% CI)**	**Absolute (95% CI)**		
1 (Zagouri 2013)	case series	very serious[a]	serious[b]	serious[c]	very serious[d]	none	15/17 (88.2%)	6/6 (100.0%)	RR 0.93 (0.70 to 1.22)	70 fewer per 1,000 (from 300 fewer to 220 more)	Very low	CRITICAL

AI: aromatase inhibitor; **CI:** confidence interval; **RR:** risk ratio; **TFS:** testicular function suppression

Explanations

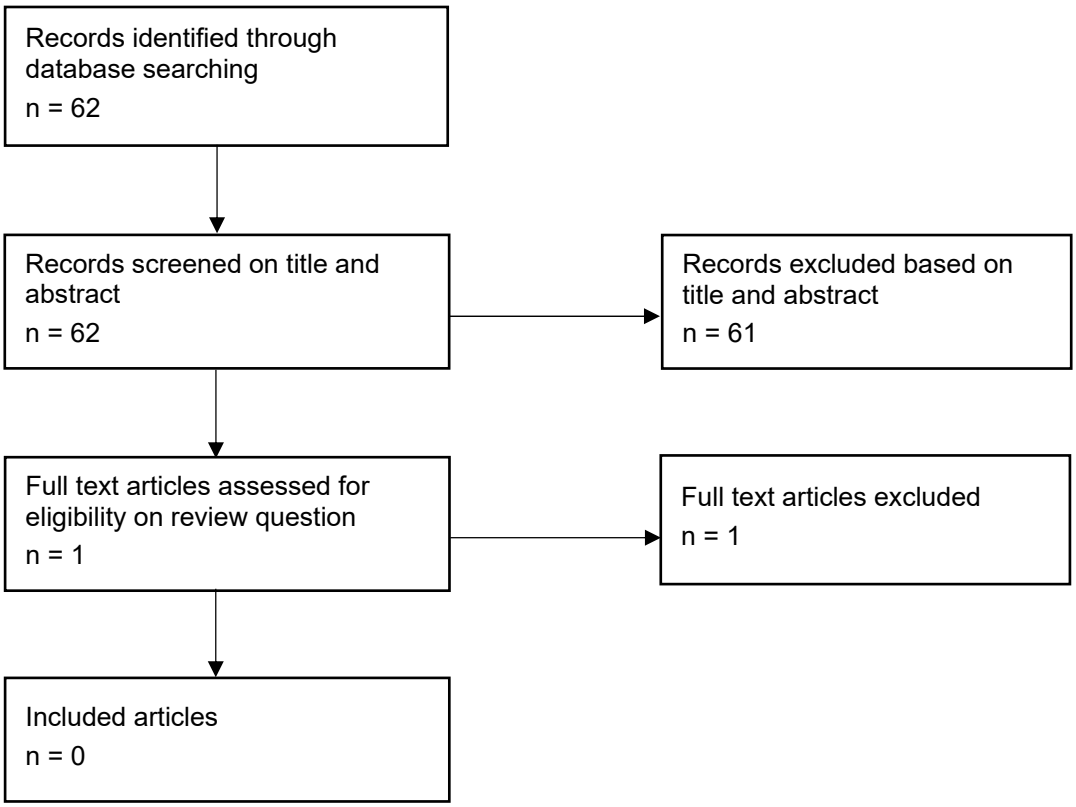
a. Study at high risk of bias, outcome was downgraded two levels

b. Data was only available from one study, outcome was downgraded one level

c. Participants had metastatic breast cancer

d. 95% confidence interval for the effect size crossed the line of no effect and the number of participants was less than 500, outcome was downgraded two levels

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

No economic evidence was included for this review question.

Appendix I – Health economic model

No economic modelling was conducted for this review question.

Appendix J – Excluded studies

Effectiveness studies

Study	Reason for exclusion
Di Lauro, Luigi, Pizzuti, Laura, Barba, Maddalena et al. (2015) Role of gonadotropin-releasing hormone analogues in metastatic male breast cancer: results from a pooled analysis. Journal of hematology & oncology 8: 53	- Data not reported in an extractable format *Data was not reported separately for an aromatase inhibitor with/without testicular function suppression*
Di Lauro, Luigi, Vici, Patrizia, Del Medico, Pietro et al. (2013) Letrozole combined with gonadotropin-releasing hormone analog for metastatic male breast cancer. Breast cancer research and treatment 141(1): 119-23	- Comparator in study does not match that specified in protocol *All participants received combination therapy with an aromatase inhibitor and testicular function suppression either as a first line or as a second line treatment*
Giordano SH and Hortobagyi GN (2006) Leuprolide acetate plus aromatase inhibition for male breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 24(21): e42	- Comparator in study does not match that specified in protocol *2 cases and both with an aromatase inhibitor combined with testicular function suppression; no comparator was included*
Giordano SH, Valero V, Buzdar AU et al. (2002) Efficacy of anastrozole in male breast cancer. American journal of clinical oncology 25(3): 235-237	- Study does not contain a relevant intervention *An aromatase inhibitor combined with testicular function suppression was not included as an intervention*
Giordano, S.H. (2018) Breast cancer in men. New England Journal of Medicine 378(24): 2311-2320	- Review article but not a systematic review
Hassett, M.J., Somerfield, M.R., Baker, E.R. et al. (2020) Management of male breast cancer: ASCO guideline. Journal of Clinical Oncology 38(16): 1849-1863	- Not a relevant study design *American Society of Clinical Oncology guideline*
Sirieix, J., Fraisse, J., Mathoulin-Pelissier, S. et al. (2020) Management and outcome of male metastatic breast cancer in the national multicenter observational research program Epidemiological Strategy and Medical Economics (ESME). Therapeutic Advances in Medical Oncology 12	- Data not reported in an extractable format *Overall survival was not reported separately for treatments included in our protocol*

Health Economic studies

Study	Reason
Huang, Yaping, Ke, Chengjie, Cai, Jiaqin et al. (2024) Cost-effectiveness of adjuvant endocrine treatment with tamoxifen for male breast cancer. Breast cancer (Tokyo, Japan) 31(5): 917-925	- Exclude - comparison does not include TFS - Exclude - US study perspective

Appendix K– Research recommendations – full details

K1.1 Research recommendation

What is the real-world evidence clinical and cost effectiveness of testicular function suppression in combination with an aromatase inhibitor compared to tamoxifen alone or an aromatase inhibitor alone in people with ER-positive invasive breast cancer who have male reproductive organs?

K1.1.1 Why this is important

The committee noted the lack of evidence in people with male reproductive organs who have ER positive invasive breast cancer. There was limited evidence from a single RCT comparing TFS combined with an AI to tamoxifen alone and reporting outcome data on quality of life, serum oestrogen levels, serum testosterone levels, adherence reported as treatment discontinuation, and adverse events. The RCT had a short-term follow-up (6 months) and a small sample size (35 participants) and did not report data on overall survival, disease-free survival, breast cancer specific survival, local and/or locoregional recurrence, and new contralateral disease. Therefore, the committee made a recommendation for research that could be carried out using real world evidence..

K1.1.2 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the clinical benefits and short and long-term risks associated with the use of TFS combined with an AI for people with male reproductive organs who have ER positive invasive breast cancer.
Relevance to NICE guidance	TFS combined with an AI has been considered in this guideline and there is a lack of data on long-term effectiveness and safety.
Relevance to the NHS	The outcome would affect the types of treatment for people with male reproductive organs who have ER positive invasive breast cancer provided by the NHS and may also predict future healthcare needs for people with male reproductive organs who have ER positive invasive breast cancer who have had endocrine therapy with TFS combined with an AI.
National priorities	No specific national priorities
Current evidence base	Limited data from 1 RCT with a small sample size (35 participants) and short-term follow-up (6 months)
Equality considerations	Gender reassignment Fertility Little is known about male breast cancer

K1.1.3 Modified PICO table

Population	**Inclusion:** 1. Adults (18 and over) with invasive* oestrogen receptor (ER) positive breast cancer who have male reproductive organs. (* any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0)). 2. If limited or no data is identified for the population above, then data could be collected for adults (18 and over) with ER positive metastatic breast cancer who have male reproductive organs. **Exclusion:** Adults (18 and over) with: • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
Intervention	• Endocrine therapy using an aromatase inhibitor combined with testicular function suppression
Comparator	• Tamoxifen alone • An aromatase inhibitor alone

Outcome	**Primary outcomes (critical outcomes)**
	• Overall survival or mortality if overall survival not reported
	• Disease-free survival
	• Quality of life
	Secondary outcomes (important outcomes)
	• Breast cancer specific survival or cancer-specific mortality if breast cancer specific survival is not reported
	• Serum oestradiol levels
	• Serum testosterone levels
	• Adverse events
	  ○ treatment-related mortality
	  ○ treatment-related morbidity
	• Local and/or locoregional recurrence
	• New contralateral disease
	• Adherence to or completion of treatment (early cessation of treatment)

Study design	Real word evidence: cohort study
Timeframe	Long term
Additional information	None

K1.2 Research recommendation

What is the real-world evidence on the types of side effects (and severity) that people with ER-positive invasive breast cancer who have male reproductive organs experience with tamoxifen alone or testicular function suppression in combination with an aromatase inhibitor?

K1.2.1 Why this is important

The committee noted that side effects in people with male reproductive organs who have ER positive invasive breast cancer are expected to be similar to those in premenopausal or perimenopausal people with ER-positive invasive breast cancer. However, there is a lack of evidence about the type and severity of the side effects and due to the small number of people who have invasive breast cancer and male reproductive organs RCTs are unlikely to be possible. Therefore, the committee made a recommendation for research that could be carried out using real world evidence.

K1.2.2 Rationale for research recommendation

Importance to 'patients' or the population	Little is known about the similarities or differences in side effects associated with the use of TFS combined with an AI for people with male reproductive organs who have ER positive invasive breast cancer compared to the side effects with the use of OFS combined with an AI in premenopausal or perimenopausal people with ER-positive invasive breast cancer. There is significant public and political concern about this.
Relevance to NICE guidance	TFS combined with an AI has been considered in this guideline and there is a lack of data on their safety.
Relevance to the NHS	The outcome would affect the types of treatment for people with male reproductive organs who have ER positive invasive breast cancer provided by the NHS and may also predict future healthcare needs for people with male reproductive organs who have ER positive invasive breast cancer who have had endocrine therapy with TFS combined with an+ AI.
National priorities	No specific national priorities
Current evidence base	Limited data from 1 RCT with a small sample size (35 participants with male reproductive organs who have ER positive invasive breast cancer) and short-term follow-up (6 months)
Equality considerations	Gender reassignment Fertility Little is known about male breast cancer

K1.2.3 Modified PICO table

Table title (caption style)

Population	**Inclusion:** 1. Adults (18 and over) with invasive* oestrogen receptor (ER) positive breast cancer who have male or female reproductive organs. (* any size (T1 to T4), with or without spread to locoregional lymph nodes (N0 to N3) and with no distant metastases (M0)). 2. If limited or no data is identified for the population above, then data could be collected for adults (18 and over) with ER positive metastatic breast cancer who have male or female reproductive organs. People with male reproductive organs covers men, trans women and non-binary people who currently have testes. People with female reproductive organs covers women, trans men and non-binary people who currently have ovaries.) **Exclusion:** Adults (18 and over) with: • newly diagnosed ductal carcinoma in situ (DCIS) with no invasive component. • Paget's disease of the breast with no invasive component.
Intervention	• Endocrine therapy using an aromatase inhibitor combined with testicular function suppression
Comparator	• Tamoxifen alone
Outcome	**Primary outcomes (critical outcomes)** • Adverse events ○ treatment-related morbidity
Study design	Real word evidence: cohort study
Timeframe	Long term
Additional information	None

Appendix L – Methods

Reviewing research evidence

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Searching for evidence

Evidence was searched for each review question using the methods specified in the 2024 NICE guidelines manual.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Incorporating published evidence syntheses

If published evidence syntheses were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting information from primary studies. Syntheses considered for inclusion in this way were quality assessed to assess their suitability using the appropriate checklist, as outlined in Table 17. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in Table 18, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Table 17 Checklists for published evidence syntheses

Type of synthesis	Checklist for quality appraisal
Systematic review of quantitative evidence	ROBIS

Each published evidence synthesis was classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in Table 18. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 18 Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full text papers of included studies were

Quality	Applicability	Use of published evidence synthesis
		still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Methods of combining evidence

Data synthesis for intervention studies

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. When there were 2 treatment alternatives, pairwise meta-analysis was used to compare interventions.

Pairwise meta-analysis

Pairwise meta-analyses were performed in Cochrane Review Manager (web version). A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the risk in the comparator arm of the meta-analysis (calculated as the total number events in the comparator arms of studies in the meta-analysis divided by the total number of participants in the comparator arms of studies in the meta-analysis).

Random-effects models were fitted when significant between-study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken. For all other syntheses, fixed- and random-effects models were fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if there was significant statistical heterogeneity in the meta-analysis, defined as $I2 \geq 50\%$.

However, in cases where the results from individual pre-specified subgroup analyses were less heterogeneous (with $I2 < 50\%$) the results from these subgroups were reported using fixed-effects models. This may have led to situations where pooled results were reported from random-effects models and subgroup results were reported from fixed-effects models.

Appraising the quality of evidence

Intervention studies (relative effect estimates)

RCTs were quality assessed using the Cochrane Risk of Bias Tool 2. Case series studies were quality assessed using the Institute of Health Economics checklist for case series studies. Risk of bias for single studies were conducted once for objective outcomes, once for subjective outcomes, and once for adverse events. Where there is a published approach to overall risk of bias judgement this should be used. Where there is no published approach developers should use their judgement and include a statement of the rationale for the overall judgement included in EPPI and evidence table. Evidence on each outcome for each individual study was classified into one of the following groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the following areas: population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Minimally important differences (MIDs) and clinical decision thresholds

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline that might aid the committee in identifying clinical decision thresholds for the purpose of GRADE. Identified MIDs were assessed to ensure they had been developed and validated in a methodologically rigorous way, and were applicable to the populations, interventions and outcomes specified in this guideline. In addition, the Guideline Committee were asked to prospectively specify any outcomes where they felt a consensus clinical decision threshold could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one treatment is not meaningfully worse than another) required a clinical decision threshold to be defined to act as a non-inferiority margin.

Clinical decision thresholds were used to assess imprecision using GRADE and aid interpretation of the size of effects for different outcomes. Clinical decision threshold that were used in the guideline are given in Table 19 and also reported in the relevant evidence reviews.

Table 19 Identified Clinical decision thresholds

Outcome	Clinical decision threshold	Source
Quality of life FACT-G total	3 to 7 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life FACT-B total	7 to 8 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life TOI (trial outcome index) of FACT-B	5 to 6 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life BCS of FACT-B	2 to 3 points	Eton DT, Cella D, Yost KJ, Yount SE, Peterman AH, Neuberg DS, Sledge GW, Wood WC. A combination of distribution- and anchor-based approaches determined minimally important differences (MIDs) for four endpoints in a breast cancer scale. J Clin Epidemiol. 2004 Sep;57(9):898-910. doi: 10.1016/j.jclinepi.2004.01.012. PMID: 15504633.
Quality of life WHOQOL-100	1 point	Den Oudsten, B.L., Zijlstra, W.P. & De Vries, J. The minimal clinical important difference in the World Health Organization Quality of Life instrument—100. Support Care Cancer 21, 1295–1301 (2013). https://doi.org/10.1007/s00520-012-1664-8

GRADE for intervention studies analysed using pairwise analysis

GRADE was used to assess the quality of evidence for the outcomes specified in the review protocol. Data from randomised controlled trials were initially rated as high quality. The quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in Table 20. These criteria were used to

apply preliminary ratings, but were overridden in cases where, in the view of the analyst or committee the uncertainty identified was unlikely to have a meaningful impact on decision making.

Table 20 Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than <50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 50% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than <50% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than >50% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than >50% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. Not serious: If the I^2 was less than <40%, the outcome was not downgraded. Serious: If the I^2 was between 41% and 60%, the outcome was downgraded one level or if data on the outcome was only available from one study. Very serious: If the I^2 was greater than >60%, the outcome was downgraded two levels.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

GRADE criteria	Reasons for downgrading quality
Publication bias	Where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias. When a funnel plot showed convincing evidence of publication bias, or the review team became aware of other evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

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Appendix M – Adverse events of interest for this review

Table 21 Adverse events of interest for this review

Type of adverse event
Vasomotor symptoms (= hot flushes, sweats, night sweats, vasodilation pooled)
Sleep disturbances, somnolence and insomnia pooled
Fatigue/ tiredness
Weight gain
Hypercholesterolemia
Glucose intolerance (including hyperglycaemia and hypoglycaemia as pooled terms)
Neurocognitive
Cognitive function (cognitive disorder, memory and concentration problems pooled)
Depression
Anxiety
Sexual function
Lower libido
Erectile dysfunction
Musculoskeletal
Fracture
Osteoporosis
Arthralgia =bone and muscle pain pooled with arthropathy (achy joints)
Loss of muscle mass
Cardiovascular (Grade 3 or 4 only)
DVT, PE (VTE umbrella term, thrombosis, embolism- pooled)
Stroke
Cardiac ischemia
Other cancers (pooled with footnotes): not graded, reported as any incidence