National Institute for Health and Care Excellence

Draft for Consultation

Early and locally advanced breast cancer: diagnosis and management

[D] Evidence reviews for endocrine therapy for invasive disease

NICE guideline tbc

Evidence reviews

January 2018

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Endocrine therapy for invasive disease

This evidence report contains information on 3 reviews relating to endocrine therapy for invasive disease.

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- Review question 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Review question 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Introduction

Treatment of women with oestrogen receptor-positive (ER-positive) early stage invasive breast cancer with adjuvant endocrine therapy for 5 years reduces recurrence rates in ER-positive breast cancer by about half and breast cancer mortality by about a third.

Tamoxifen, a selective oestrogen receptor modulator is effective in premenopausal or postmenopausal women and can therefore be used regardless of the menopausal status of the patient. Aromatase inhibitors reduce the non-ovarian production of oestrogen and can be used in postmenopausal women to greatly reduce systemic oestrogen levels and thus to avoid stimulation of ER-positive breast cancer.

Unlike most cancers, the risk of relapse for ER-positive invasive breast cancer remains significant even after completing 5 years of endocrine therapy. The aim of this review is to identify the optimal duration of endocrine therapy to minimise the risk of disease recurrence in women with ER-positive breast cancer.

PICO table

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women (18 or over) with oestrogen-receptor positive invasive breast cancer (M0) after surgery and/or radiotherapy
Intervention	Continuous endocrine therapy for more than 5 years
Comparison	Continuous endocrine therapy for 5 years
Outcome	**Critical** • Treatment-related morbidity • Disease-free survival • Overall survival **Important** • Compliance/adherence • Treatment-related mortality • HRQoL

HRQoL, Health-related quality of life

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Ten studies (number of participants, N=22,221) were included in the review (Davies, 2013; Fisher, 1996; Fisher, 2001; Goss, 2005; Jakesz, 2007; Mamounas, 2008; Muss, 2008; Stewart, 1996; Stewart, 2001; Tormey, 1996), which report data from 7 trials: Austrian Breast and Colorectal Cancer Study Group (ABCSG) 6a (number of publications, k=1), Adjuvant Tamoxifen Longer Against Shorter (ATLAS; k=1), National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 (k=2), NSABP B-33 (k=1), MA.17 trial (k=2), Scottish Adjuvant Tamoxifen Trial (k=2), and Tormey, 1996 (k=1).

Four trials compared tamoxifen taken for longer than 5 years with tamoxifen taken for 5 years only: the Scottish Adjuvant Tamoxifen Trial and Tormey (1996) compared tamoxifen to be taken indefinitely/until relapse with 5 years of adjuvant tamoxifen; the ATLAS and B-14 trials both compared 10 years of tamoxifen with 5 years of tamoxifen (with the addition of 5 years of placebo following tamoxifen in B-14).

Three trials compared tamoxifen followed by an aromatase inhibitor with tamoxifen alone: MA.17 compared 5 years of tamoxifen followed by 5 years of letrozole against 5 years of tamoxifen followed by 5 years of placebo, B-33 compared 5 years of tamoxifen followed by 5 years of exemestane with 5 years of tamoxifen followed by 5 years of placebo, and ABCSG 6a compared 5 years of tamoxifen followed by anastrozole for 3 years with 5 years of tamoxifen only.

Only one study (Jakesz, 2007) reported data for critical outcomes by any subgroups of interest; however, the only subgroup reported was individuals with grade 3 cancer. Due to significant heterogeneity and the critical nature of survival outcomes, unplanned subgroup analysis was conducted for disease-free and overall survival outcomes to investigate differences in estimated effects between those studies where tamoxifen was continued and those where individuals switched to an aromatase inhibitor.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 3). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 2: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Davies 2016	ATLAS	• Still on tamoxifen or stopped in the past year	• Intervention arm (TAM=10yrs): 20 mg of Nolvadex (tamoxifen) daily for a further 5 years (after a median of 5 years of tamoxifen prior to entry into the trial) resulting in 10 years of tamoxifen treatment. • Control arm (TAM=5yrs): no endocrine therapy (after a

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
			median of 5 years of tamoxifen prior to entry)
Fisher 1996	B-14	• Aged ≤70 years • Node negative • No second primary cancer	• Intervention arm (TAM=10yrs): 10 mg of tamoxifen orally twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial) • Control arm (TAM=5yrs): placebo twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial)
Fisher 2001	B-14	• Aged ≤70 years • Node negative • No second primary cancer	• Intervention arm (TAM=10yrs): 10 mg of tamoxifen orally twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial) • Control arm (TAM=5yrs): placebo twice a day for 5 years (following 10 mg of tamoxifen orally twice a day for 5 years during initial trial)
Goss 2005	MA.17	• Received prior adjuvant tamoxifen therapy for 4.5–6 years • ER and/or PR positive	• Intervention arm (ET>5yrs): 2.5 mg oral letrozole daily for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy) • Control arm (ET=5yrs): placebo for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy)
Jakesz 2007	ABCSG 6a	• Post-menopausal • ER and/or PR positive • Stage I or stage II • Aged ≤80 years • Excluded if: previous malignant disease (except cured squamous cell skin carcinoma and early-stage cervical cancer; preoperative antineoplastic treatment and irradiation; inflammatory breast cancer; more than 4 weeks between randomisation and starting treatment; Karnofsky Index >3; bilateral oophorectomy/ radiotherapy to ovaries.	• Intervention arm (ET=8yrs): 1 mg anastrozole daily for 3 years (commencing within 6 weeks of completing 5 years of adjuvant tamoxifen [4 0mg daily for 2 years followed by 20 mg daily for 3 years] during original trial ABCSG6) • Control arm (ET=5yrs): no further treatment (following 5 years of adjuvant tamoxifen [40 mg daily for 2 years followed by 20 mg daily for 3 years] during original trial ABCSG6)
Mamounas 2008	B-33	• Post-menopausal • Received tamoxifen for 57-66 months for T1-3, N0-1, M0 ER and/or PR positive invasive breast cancer • Interval between tamoxifen completion and random assignment <180 days	• Intervention arm (ET=10yrs): exemestane for 5 years (following approximately 5 years of tamoxifen) • Control arm (ET=5yrs): placebo for 5 years (following approximately 5 years of tamoxifen)

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		• Excluded if inadequate hematologic, hepatic and/or renal function	
Muss 2008	MA.17	• Received prior adjuvant tamoxifen therapy for 4.5–6 years • ER and/or PR positive • Willing to complete QOL questionnaires • Fluent in English or French	• Intervention arm (ET>5yrs): 2.5 mg oral letrozole daily for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy) • Control arm (ET=5yrs): placebo for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy)
Stewart1996	Scottish Adjuvant Tamoxifen Trial	• Women entering the parent trial before March 1980 were ineligible, as most had already stopped tamoxifen	• Intervention arm (TAM>5yrs): 20mg tamoxifen daily to be taken indefinitely (following 5 years of tamoxifen taken during parent trial) • Control arm (TAM=5yrs): no endocrine therapy (following 5 years of tamoxifen taken during parent trial)
Stewart 2001	Scottish Adjuvant Tamoxifen Trial	• Women entering the parent trial before March 1980 were ineligible, as most had already stopped tamoxifen	• Intervention arm (TAM>5yrs): 20mg tamoxifen daily to be taken indefinitely (following 5 years of tamoxifen taken during parent trial) • Control arm (TAM=5yrs): no endocrine therapy (following 5 years of tamoxifen taken during parent trial)
Tormey1996		• Tumour ≤5 cm in diameter • One or more positive axillary lymph nodes • Normal hematologic function, biochemical profiles, and bone scan	• Intervention arm (TAM>5yrs): 10 mg tamoxifen twice daily until relapse (following 5 years of 10 mg tamoxifen twice daily and 1 year of chemotherapy [at the beginning of tamoxifen treatment] during the parent trials) • Control arm (TAM=5yrs): no endocrine therapy (following 5 years of 10mg tamoxifen twice daily and 1 year of chemotherapy [at the beginning of tamoxifen treatment] during the parent trials)

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ATLAS, Adjuvant Tamoxifen Longer Against Shorter; ER, oestrogen receptor; ET, endocrine therapy; PR, progesterone receptor; QoL, quality of life; TAM, tamoxifen

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (duration of endocrine therapy) is presented in Table 3. The quality of evidence ranges from very low to high. Main reasons for downgrading evidence include significant heterogeneity and imprecision around the estimates due to a small number of events of interest and wide confidence intervals.

Table 3: Summary clinical evidence profile: Comparison 1. Endocrine therapy for greater than 5 years versus endocrine therapy for 5 years only

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: ET=5yrs	Corresponding risk: ET>5yrs			
Disease-free survival - Whole sample (2.5 to 15 year follow-up)	2.5yr DFS 93%	2.5yr DFS 94% (94% to 95%)	HR 0.85 (0.78 to 0.93)	16055 (7 studies)	Low[1,2]
Disease-free survival - Grade 3 (5 year follow-up)	NR	Cannot be calculated	HR 0.73 (0.29 to 1.84)	171 (1 study)	Number of events were not reported - insufficient information to judge imprecision, and therefore overall quality
Disease-free survival - Continued tamoxifen (5.6 to 15 year follow-up)	5.6yr DFS 67%	5.6yr DFS 69% (67% to 71%)	HR 0.92 (0.84 to 1.01)	8480 (4 studies)	Low[2,3]
Disease-free survival - Switched to AI (2.5 to 5 year follow-up)	2.5yr DFS 93%	2.5yr DFS 96% (95% to 96%)	HR 0.61 (0.5 to 0.74)	7575 (3 studies)	High
Overall survival (4 to 15 year follow-up)	4yr OS 98%	4yr OS 98% (98% to 98%)	HR 0.91 (0.83 to 1)	14555 (6 studies)	Moderate[4,5]
Overall survival - Continued tamoxifen (5.6 to 15 year follow-up)	5.6yr OS 89%	5.6yr OS 90% (89% to 91%)	HR 0.92 (0.84 to 1.02)	8533 (4 studies)	Moderate[5,6]
Overall survival - Switched to AI (4 to 5 year follow-up)	4yr OS 98%	4yr OS 98% (98% to 99%)	HR 0.85 (0.65 to 1.12)	6022 (2 studies)	Moderate[7]
Compliance - did not comply with/complete assigned treatment	87 per 1000	98 per 1000 (38 to 245)	RR 1.12 (0.44 to 2.81)	19558 (4 studies)	Low[2,8]
Treatment-related morbidity - hot flushes (2 month to 4 year follow-up)	475 per 1000	565 per 1000 (441 to 726)	RR 1.19 (0.93 to 1.53)	7157 (3 studies)	Very low[9,10]
Treatment-related morbidity - secondary cancer – Any (5.6 to 7.6 year follow-up)	125 per 1000	126 per 1000 (116 to 137)	RR 1.01 (0.93 to 1.1)	14581 (4 studies)	High[5]
Treatment-related morbidity - secondary cancer - Contralateral breast (6 to 7.6 year follow-up)	68 per 1000	61 per 1000 (54 to 70)	RR 0.9 (0.79 to 1.02)	14388 (3 studies)	High[2]
Treatment-related morbidity - secondary cancer – Endometrial (6 to 7.6 year follow-up)	10 per 1000	18 per 1000 (14 to 24)	RR 1.87 (1.4 to 2.5)	14388 (3 studies)	Moderate[7]
Treatment-related morbidity - bone fractures (2 month to 7.6 year follow-up)	21 per 1000	23 per 1000 (19 to 27)	RR 1.08 (0.9 to 1.3)	20438 (4 studies)	Moderate[10]
Treatment-related morbidity – arthralgia (2 month to 4 year follow-up)	163 per 1000	202 per 1000 (184 to 223)	RR 1.24 (1.13 to 1.37)	7567 (3 studies)	High
Treatment-related morbidity - cardiac disease/event (2 month to 7.6 year follow-up)	32 per 1000	29 per 1000 (22 to 39)	RR 0.91 (0.69 to 1.19)	18876 (3 studies)	High
Treatment-related morbidity – hypertension (4 year follow-up)	50 per 1000	51 per 1000 (40 to 64)	RR 1.01 (0.8 to 1.28)	5149 (1 study)	Low[11]
Treatment-related morbidity – osteoporosis (4 year follow-up)	60 per 1000	82 per 1000 (67 to 100)	RR 1.35 (1.11 to 1.65)	5126 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: ET=5yrs	Corresponding risk: ET>5yrs			
Treatment-related morbidity – myalgia (4 year follow-up)	120 per 1000	148 per 1000 (129 to 170)	RR 1.23 (1.07 to 1.41)	5149 (1 study)	High
Treatment-related morbidity - any grade 3+ toxicity (2.5 to 5.6 year follow-up)	68 per 1000	93 per 1000 (68 to 129)	RR 1.38 (1 to 1.9)	1755 (2 studies)	Low[12,13]
Treatment-related morbidity - vaginal dryness (2 month to 4 year follow-up)	53 per 1000	71 per 1000 (48 to 104)	RR 1.34 (0.91 to 1.96)	6005 (2 studies)	Moderate[10]
Treatment-related morbidity - vaginal bleeding (2 month to 4 year follow-up)	65 per 1000	70 per 1000 (19 to 266)	RR 1.09 (0.29 to 4.11)	6005 (2 studies)	Low[14]
Treatment-related morbidity - vaginal discharge (2 month to 4 year follow-up)	111 per 1000	137 per 1000 (51 to 366)	RR 1.24 (0.46 to 3.3)	2008 (2 studies)	Very low[11,15]
Treatment-related morbidity – stroke (7.6 year follow-up)	18 per 1000	20 per 1000 (16 to 26)	RR 1.09 (0.85 to 1.39)	12894 (1 study)	Low[13]
Treatment-related morbidity - irregular menstruation (4 year follow-up)	271 per 1000	252 per 1000 (206 to 303)	RR 0.93 (0.76 to 1.12)	1152 (1 study)	Moderate[16]
Treatment-related morbidity - phlebitis/thromboembolic events (2 month to 7.6 year follow-up)	3 per 1000	7 per 1000 (4 to 11)	RR 2.17 (1.32 to 3.57)	14902 (3 studies)	Moderate[7]
HRQoL - change in SF-36 scores from baseline (2 year follow-up) - Physical health		The mean HRQoL - change in SF-36 scores from baseline (2 year follow-up) - physical health in the intervention groups was 1 higher (0.73 lower to 2.73 higher)		382 (1 study)	High
HRQoL - change in SF-36 scores from baseline (2 year follow-up) - Mental health		The mean HRQoL - change in SF-36 scores from baseline (2 year follow-up) - physical health in the intervention groups was 0.6 lower (2.42 lower to 1.22 higher)		382 (1 study)	High
HRQoL - change in MENQOL scores from baseline (2 year follow-up) – Vasomotor		The mean HRQoL - change in MENQOL scores from baseline (2 year follow-up) - physical health in the intervention groups was 0.4 higher (0.15 to 0.65 higher)		386 (1 study)	High
HRQoL - change in MENQOL scores from		The mean HRQoL - change in MENQOL		379 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: ET=5yrs	Corresponding risk: ET>5yrs			
baseline (2 year follow-up) – Psychosocial		scores from baseline (2 year follow-up) - physical health in the intervention groups was 0.1 lower (0.31 lower to 0.11 higher)			
HRQoL - change in MENQOL scores from baseline (2 year follow-up) – Physical		The mean HRQoL - change in MENQOL scores from baseline (2 year follow-up) - physical health in the intervention groups was 0 higher (0.21 lower to 0.21 higher)		386 (1 study)	High
HRQoL - change in MENQOL scores from baseline (2 year follow-up) - Sexual		The mean HRQoL - change in MENQOL scores from baseline (2 year follow-up) - physical health in the intervention groups was 0.2 higher (0.08 lower to 0.48 higher)		263 (1 study)	High

Rates of disease-free survival and overall survival in the control group correspond to the trial with the shortest follow-up period

AI, aromatase inhibitor; CI: Confidence interval; DFS: disease-free survival; ET, endocrine therapy; HRQoL: health-related quality of life; MENQOL, menopause-specific quality of life; NR: Not reported; OS, overall survival; RR: Risk ratio; SF-36, 36-Item Short Form Survey

[1] Significant heterogeneity - I squared value 82% - heterogeneity explored in subgroup analyses

[2] Serious indirectness in Scottish Adjuvant Tamoxifen Trial due to population; however, this study does not have very much weight in the analysis

[3] Significant heterogeneity - I squared value 85% - not possible to further investigate heterogeneity as subgroups of interest identified by the GC were not reported for trials that contributed to this estimate

[4] Significant heterogeneity - I squared value 53% - heterogeneity explored in subgroup analyses

[5] Serious indirectness in Scottish Adjuvant Tamoxifen Trial and Tormey 1996 due to population; however, neither of these studies have much weight in the analysis

[6] Significant heterogeneity - I squared value 71% - not possible to further investigate heterogeneity as subgroups of interest identified by the GC were not reported for trials that contributed to this estimate

[7] <300 events

[8] Significant heterogeneity - I squared value 99%. High rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes.

[9] Random effects model with significant heterogeneity - I squared value 91% high rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes.

[10] 95% CI crosses both no effect (1) and GRADE default value for minimally important difference (1.25)

[11] <300 events and 95% CI crosses both boundaries for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

[12] Serious indirectness in Tormey 1996 due to population but study does not have much weight in the analysis

[13] <300 events and 95% crosses both no effect (1) and minimally important difference (1.25) based on GRADE default value

[14] 95% CI crosses both boundaries for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

[15] Significant heterogeneity - I squared value 87% - high rates of unexplained heterogeneity as subgroups of

interest were only identified by the GC for critical outcomes.
[16] 95% CI crosses both no effect (1) and minimally important difference (0.8) based on GRADE default value

See appendix F for full GRADE tables.

Economic evidence

Included studies

One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic; Erman 2014 (see appendix H and appendix I for summary and full evidence tables). The study considered the cost-effectiveness of extended tamoxifen or extended aromatase inhibitors in comparison to standard tamoxifen. The analysis was a cost-utility analysis measuring effectiveness in terms of quality adjusted life years (QALYs).

Excluded studies

See Supplement 1: Health economic literature search for the list of excluded studies.

Summary of studies included in the economic evidence review

The base case results of Erman 2014 showed that extended tamoxifen and extended aromatase inhibitors were both cost-effective in comparison to a standard tamoxifen regimen. Extended tamoxifen was found to be less costly and more effective than standard tamoxifen (i.e. dominant) while extended aromatase inhibitors were more effective and more costly but likely to be cost-effective with a very small ICER of $178 per QALY (CAD). Using dominance rank to determine the optimal strategy, it was found that extended aromatase inhibitors were more effective and more costly than extended tamoxifen with an ICER of $3,402 per QALY likely to be considered cost-effective.

Probabilistic sensitivity analysis showed that at a threshold of $50,000 per QALY (CAD), the probability of being cost-effective was 70% for extended aromatase inhibitors, 30% for extended tamoxifen and 0.003% for standard tamoxifen.

The analysis was deemed to be only partially applicable to the decision problem in the UK setting as it was conducted from the perspective of the Canadian health care system. Some potentially serious limitations were identified in the analysis including the absence of some potentially key input parameters from the sensitivity analysis (most notably utility weights).

Evidence statements

Comparison 1. Endocrine therapy for greater than 5 years versus endocrine therapy for 5 years only

Critical outcomes

Treatment-related morbidity

- There is very low quality evidence from 3 RCTs (N=7157) that there is no clinically important effect of duration of endocrine therapy on hot flushes at 2 month to 4 year follow-up.
- There is high quality evidence from 4 RCTs (N=14581) that there is no clinically important effect of duration of endocrine therapy on any secondary cancer at 5.6 to 7.6 year follow-up.
- There is high quality evidence from 3 RCTs (N=14388) that there is no clinically important effect of duration of endocrine therapy on contralateral breast cancer at 6 to 7.6 year follow-up.

- There is moderate quality evidence from 3 RCTs (N=14388) that endocrine therapy for greater than 5 years produces clinically meaningful increases in endometrial cancer at 6 to 7.6 year follow-up relative to endocrine therapy for 5 years only.
- There is moderate quality evidence from 4 RCTs (N=20438) that there is no clinically important effect of duration of endocrine therapy on bone fractures at 2 month to 7.6 year follow-up.
- There is high quality evidence from 3 RCTs (N=7567) that there is no clinically important effect of duration of endocrine therapy on arthralgia at 2 month to 4 year follow-up.
- There is high quality evidence from 3 RCTs (N=18876) that there is no clinically important effect of duration of endocrine therapy on cardiac disease/events at 2 month to 7.6 year follow-up.
- There is low quality evidence from 1 RCT (N=5149) that there is no clinically important effect of duration of endocrine therapy on hypertension at 4 year follow-up.
- There is high quality evidence from 1 RCT (N=5126) that endocrine therapy for greater than 5 years produces clinically meaningful increases in osteoporosis at 4 year follow-up relative to endocrine therapy for 5 years only.
- There is high quality evidence from 1 RCT (N=5149) that there is no clinically important effect of duration of endocrine therapy on myalgia at 4 year follow-up.
- There is low quality evidence from 2 RCTs (N=1755) that endocrine therapy for greater than 5 years produces clinically meaningful increases in grade 3+ toxicities at 2.5 to 5.6 year follow-up relative to endocrine therapy for 5 years only.
- There is moderate quality evidence from 2 RCTs (N=6005) that endocrine therapy for greater than 5 years produces clinically meaningful increases in vaginal dryness at 2 month to 4 year follow-up relative to endocrine therapy for 5 years only. However, this was not statistically significant.
- There is low quality evidence from 2 RCTs (N=6005) that there is no clinically important effect of duration of endocrine therapy on vaginal bleeding at 2 month to 4 year follow-up.
- There is very low quality evidence from 2 RCTs (N=2008) that there is no clinically important effect of duration of endocrine therapy on vaginal discharge at 2 month to 4 year follow-up.
- There is low quality evidence from 1 RCT (N=12894) that there is no clinically important effect of duration of endocrine therapy on stroke at 7.6 year follow-up.
- There is moderate quality evidence from 1 RCT (N=1152) that there is no clinically important effect of duration of endocrine therapy on irregular menstruation at 4 year follow-up.
- There is moderate quality evidence from 3 RCTs (N=14902) that endocrine therapy for greater than 5 years produces clinically meaningful increases in phlebitis/thromboembolic events at 2 month to 7.6 year follow-up relative to endocrine therapy for 5 years only.

Disease-free survival

- There is evidence from 1 RCT (N=171) that there is no clinically important effect of duration of endocrine therapy on disease-free survival at 5 year follow-up for women with grade 3 tumours. It was not possible to judge imprecision, and therefore the quality of this evidence, as number of events were not reported.
- There is low quality evidence from 4 RCTs (N=8480) that there is no clinically important effect of duration of endocrine therapy on disease-free survival at 5.6 to 15 year follow-up for women who continue tamoxifen.
- There is high quality evidence from 3 RCTs (N=7575) that endocrine therapy for greater than 5 years produces clinically meaningful increases in disease-free survival compared with endocrine therapy for 5 years only at 2.5 to 5 year follow-up for women who switch from tamoxifen to an aromatase inhibitor after 5 years.

Overall survival

- There is moderate quality evidence from 4 RCTs (N=8533) that there is no clinically important effect of duration of endocrine therapy on overall survival at 5.6 to 15 year follow-up for women who continue tamoxifen.
- There is moderate quality evidence from 2 RCTs (N=6022) that there is no clinically important effect of duration of endocrine therapy on overall survival at 4 to 5 year follow-up for women who switch from tamoxifen to an aromatase inhibitor after 5 years.

Important outcomes

Compliance/ adherence

- There is low quality evidence from 4 RCTs (N=19558) that there is no clinically important effect of duration of endocrine therapy on compliance.

Treatment-related mortality

- No evidence was found for this outcome.

Health-related quality of life

- There is high quality evidence from 1 RCT (N=382) that there is no clinically important effect of duration of endocrine therapy on HRQoL as measured change from baseline by SF-36 physical and mental health scores at 2 year follow-up.
- There is high quality evidence from 1 RCT (N=386) that there is no clinically important effect of duration of endocrine therapy on HRQoL as measured change from baseline by MENQOL vasomotor, psychosocial, physical and sexual scores at 2 year follow-up.

Economic evidence statement

- There is evidence from one cost-utility analysis showing that extended tamoxifen was dominant in comparison to standard tamoxifen, while extended aromatase inhibitors have an ICER of $178 per QALY in comparison to standard tamoxifen and an ICER of $3,402 per QALY in comparison to extended tamoxifen. The analysis was partially applicable with some potentially serious limitations.

Recommendations

D1. Offer extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor[a] for postmenopausal women with ER-positive invasive breast cancer who are at medium or high risk[b] of disease recurrence and who have been taking tamoxifen for 2 to 5 years.

D2. Consider extended therapy (total duration of endocrine therapy of more than 5 years) with an aromatase inhibitor[a] for postmenopausal women with ER-positive invasive breast cancer who are at low risk[b] of disease recurrence and who have been taking tamoxifen for 2 to 5 years.

D3. Consider extending the duration of tamoxifen therapy for longer than 5 years for both premenopausal and postmenopausal women with ER-positive invasive breast cancer.

a Please refer to the Summary of Product Characteristics for individual aromatase inhibitors because there are differences in their licensed indications.

b Risk can be estimated using a range of standardised tools and clinical expertise.

Rationale and impact

Why the committee made the recommendations

Good evidence showed that switching to an aromatase inhibitor after 5 years of tamoxifen improved disease-free survival compared with postmenopausal women who had only received tamoxifen for 5 years, with the benefits being greater in those women who had a greater risk of disease recurrence.

The evidence showed no benefit in terms of disease-free survival or overall survival from continuing tamoxifen beyond 5 years. However, some of the studies on tamoxifen were conducted in the 1980s and may not be relevant to current practice. In the committee's experience, continuing tamoxifen can be beneficial for some women.

However, evidence showed that being on endocrine therapy for more than 5 years can increase the risk of problems such as endometrial cancer, osteoporosis, toxicity and phlebitis. The committee agreed that people will often prioritise survival even if this means they will have a reduced quality of life, but that people need to be informed about the possible benefits and risks so they can make a choice.

Because of the risk of problems with taking endocrine therapy for more than 5 years, the committee agreed that healthcare professionals should discuss the potential benefits and risks with women to help them make an informed choice about treatment, based on their own risk factors.

Impact of the recommendations on practice

Some centres already review treatment at 5 years, and continue endocrine therapy with tamoxifen or an aromatase inhibitor when it could benefit women. Because a large number of women will be affected by these recommendations, the resource impact will be large for centres that are not currently providing treatment after 5 years.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

As this review question is related to the duration of therapy required to prevent disease recurrence, the committee identified disease-free survival and overall survival as critical outcomes. Treatment-related morbidities was also a critical outcome as extending treatment affords greater opportunity for side effects of treatment to occur, and the optimal duration may be a balance of effectiveness and potential side-effects. Compliance/adherence, treatment-related mortality and health-related quality of life were selected as important outcomes.

These outcomes are important to service users as increased survival is normally prioritised. However, the tolerability of, and adherence to, treatments will be affected by the severity of side effects and the impact these have on quality of life.

No evidence was identified for treatment-related mortality.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For disease-free survival the evidence was of a low quality for the mixed population and for those who continued tamoxifen due to large amount of heterogeneity. However, it was not possible to explore heterogeneity in the tamoxifen studies as the subgroups of interest to the committee

were not reported in trials that contributed to this estimate. For disease-free survival in the population who switched to an aromatase inhibitor, the evidence was of high quality.

For overall survival the evidence was of moderate quality. There was serious inconsistency in the tamoxifen studies (but again this could not be explored due to a lack of evidence reported for the subgroups) and only a small number of events of interest were reported for the population who switched to an aromatase inhibitor.

The quality of evidence for treatment-related morbidity ranged from very low to high quality. The low quality was mainly due to uncertainty around the estimate due to small number of events of interest and wide confidence intervals

Compliance evidence was all low quality due to unexplained heterogeneity (and as the subgroups of interest were only identified by the committee for critical outcomes this heterogeneity could not be investigated). Finally, for health-related quality of life the evidence was of high quality.

Based on the high quality of the evidence relating to improvements in disease-free survival in those who switched to an aromatase inhibitor after 5 years of tamoxifen, the committee made a strong recommendation. It was recommended that aromatase inhibitors were offered to post-menopausal women following 2 to 5 years of tamoxifen, rather than the 5 year evidence shown in the current review, as the previous guideline CG80 (NICE 2009) recommended an aromatase inhibitor was offered after 2-3 years of tamoxifen; this recommendation was retained (as the current review only examined >5 years of endocrine therapy compared with 5 years of treatment) and combined with the current recommendation for clarity. The low quality of evidence available for the tamoxifen studies meant that the committee were only able to make a weak recommendation here. There was also no evidence available that evaluated extended duration of treatment for those post-menopausal women who started endocrine therapy with an aromatase inhibitor. The committee were therefore unable to make a recommendation for this therapy option, but agreed that they did not need to make a research recommendation as there are already ongoing trials addressing issue.

Benefits and harms

The main benefit demonstrated by the evidence was an improved disease-free survival (an additional 3% of people were free from disease at 2.5 years when switched after 5 years from tamoxifen to an aromatase inhibitor).

However, the harms identified with the increased duration of endocrine therapy included increased rates of endometrial cancer, osteoporosis, grade 3 toxicities and phlebitis/thromboembolic events. The committee noted that some of these treatment-related morbidities were serious and may negate the beneficial effects of the additional duration of treatment, and that the additional duration of treatment may increase the likelihood of a patient experiencing any side-effect. However, the committee agreed that people prioritise survival over other outcomes, and that the evidence review had confirmed that extending treatment does not lead to a significant reduction in health-related quality of life.

Furthermore, the committee noted that the absolute differences in rates of side effects are small for the comparison between interventions, and that the numbers needed to harm (i.e. the number of people you would need to treat for one additional incidence of the side effect to occur, number need to harm, NNH) are large (based on moderate to high quality evidence). The NNH values are also lower than the number needed to treat (i.e. the number of people you would need to treat for one additional person to be free from disease at 2.5 years, NNT) as shown here:

- NNT for disease-free survival in those switched to an aromatase inhibitor = 33
- NNH for osteoporosis = 45
- NNH for endometrial cancer = 125

- NNH for phlebitis/thromboembolic events = 250

Finally, the committee recognised that the recommendations may lead to over-treatment in low risk individuals. However, as the committee also made a recommendation to discuss the benefits and harms with individual person, this should also mitigate the risk of over-treatment in people where the harms nay outweigh the benefits.

Cost effectiveness and resource use

One relevant study was identified in a literature review of published cost-effectiveness analyses on this topic; Erman 2014. The study considered the cost-effectiveness of extended tamoxifen or extended aromatase inhibitors in comparison to standard tamoxifen. The study was conducted from the perspective of the Canadian health care system and was therefore only partially applicable to the UK NHS context.

The base case results showed that extended tamoxifen and extended aromatase inhibitors were both cost-effective in comparison to standard tamoxifen. Extended tamoxifen was found to be less costly and more effective than standard tamoxifen (i.e. dominant) while extended aromatase inhibitors were more effective and more costly but likely to be cost-effective with a very small ICER of $178 per QALY (CAD). Using dominance rank to determine the optimal strategy, it was found that extended aromatase inhibitors were more effective and more costly than extended tamoxifen with an ICER of $3,402 per QALY likely to be considered cost-effective. Probabilistic sensitivity analysis showed that at a threshold of $50,000 per QALY (CAD), the probability of being cost-effective was 70% for extended aromatase inhibitors, 30% for extended tamoxifen and 0.003% for standard tamoxifen.

While the analysis was not directly applicable, it does suggest that that extended aromatase inhibitors or tamoxifen are cost-effective in comparison to standard tamoxifen. While the magnitude of the costs may vary between countries, it is likely that the same effects would be observed. Therefore, the additional costs of tamoxifen or aromatase inhibitors are likely to be offset, at least partially offset by downstream cost savings, while the improvements in clinical effectiveness would translate into QALY gains. It then seems likely that the strategy would be cost-effective in cost per QALY terms.

The committee carefully considered the potential resource impact in this topic area as they were aware of the large number of women that are likely to be affected by the recommendations. However, while the population affected may be large, the cost of interventions are very low. The cost of aromatase inhibitors and tamoxifen were estimated based on prices reported in the electronic market information tool (eMit). Letrozole 2.5mg was reported to cost £1.52 for a pack of 28, anastrozole 1mg was reported to cost £0.74 for a pack of 28, exemestane 25mg was reported to cost £4.16 for a pack of 30 and tamoxifen 20mg was reported to cost £1.44 for a pack of 30. This equates to an estimated cost per dose of £0.05, £0.03, £0.14 and £0.05 for letrozole, anastrozole, exemestane and tamoxifen, respectively. The committee discussed whether the extended treatment might require additional consultations but this was thought unlikely as consultations tend to occur frequently when treatment is commenced but stop after a few years of treatment. However, it is possible that there may be an additional consultation to review medications at 5 years.

The committee commented that the recommendations reflect current practice for some centres as some women already receive extended treatment. Therefore the overall cost impact of implementing the recommendation nationwide will be smaller and any cost increases associated with continued medication will vary based on current local protocols.

Overall, when taking all factors into account, it was thought that the recommendations were likely to be cost-effective and unlikely to have a substantial resource impact of more than £1 million per year.

Other factors the committee took into account

The committee questioned the relevance of the Scottish adjuvant tamoxifen trial and NSABP-14 trial as these were older trials in which people received treatment during the 1980s. However, no specific information in the publications was identified that was inconsistent with current practice so a sensitivity analysis was not performed to evaluate the inclusion of these trials.

The committee agreed that the ATLAS and Adjuvant Tamoxifen Treatment Offers More? (aTTom) trials are likely to be consistent with current standards. Evidence from ATLAS included in the current review showed a benefit in terms of disease-free survival (82% vs. 79%) and overall survival (81% vs. 79%) for individuals who continued tamoxifen to 10 years compared with those that took it for 5 years. It was not possible to include the results of the aTTom trial in the evidence review as they are only available in abstract form (Gray, 2013) with insufficient evidence to calculate hazard ratios. The results, however, are consistent with ATLAS which showed breast cancer recurrence rates of 17% vs. 19% and overall survival rates of 76% and 74% for individuals that continued tamoxifen to 10 years compared with those that took it for 5 years; risk ratios for both outcomes decreased (favouring continued tamoxifen) as the trial continued.

Based on the results of ATLAS and aTTom the committee agreed that extending the duration of tamoxifen should be considered, despite the non-significant pooled effects observed for disease-free survival and overall in the evidence review.

There were a number of trials in the current evidence review with relatively short follow-up periods for survival outcomes. As a result, there was limited information available regarding late relapse (beyond 5 years of treatment), particularly for those who had switched to an aromatase inhibitor. The committee stated that it was important to be able to advise people about the likelihood of late relapse to enable them to make an informed decision about their treatment as the benefits may not outweigh the harms for individuals with a low risk of relapse. Therefore, the committee made a research recommendation for the development and validation of a risk assessment tool to facilitate discussion of a patient's risk of late relapse.

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Review question 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Introduction

Adjuvant endocrine therapy for oestrogen positive (ER-positive) early breast cancer is well established. For premenopausal women, tamoxifen is the standard drug although the aromatase inhibitors can be given to premenopausal women if the ovaries are suppressed using gonadotropin-releasing hormone (GnRH) analogues or ablated by surgery or radiation.

Theoretically, the absence of circulating oestrogen with ovarian function suppression/ablation (OFS) in addition to tamoxifen or switching to aromatase inhibitors (which are more efficacious in postmenopausal women) should improve long term outcomes including local and distant relapse from breast cancer. However, OFS has additional side effects for young women including menopausal symptoms with the potential for additional adverse effects on bone and cardiovascular health.

International expert opinion (Burstein, 2016) suggests premenopausal women who receive chemotherapy or are considered high risk are offered OFS while the European Society for Medical Oncology (ESMO) Clinical Practice guidelines (Senkus, 2015) suggest a discussion with individual women based on risk and the potential side effect profile

This review aims to determine the effectiveness of OFS in addition to endocrine therapy in premenopausal women.

PICO table

See Table 4 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 4: Summary of the protocol (PICO table)

Population	Pre-menopausal adult women (18 or over) with oestrogen-receptor positive invasive breast cancer.
Intervention	Endocrine therapy with ovarian suppression: • Luteinizing-hormone releasing hormone (LHRH) agonists • Oophorectomy
Comparison	Endocrine therapy without ovarian suppression.
Outcome	**Critical** • Disease-free survival • Treatment-related morbidity • HRQoL **Important** • Local recurrence rate • Overall survival • Compliance • Treatment-related mortality

HRQoL, Health-related quality of life; LHRH, Luteinizing-hormone releasing hormone

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Six publications from four randomised trials (N=8762) were included in the review: Adjuvant Breast Cancer (ABC) Ovarian Ablation or Suppression Trial (k=1), E-3191 (k=1), Suppression of Ovarian Function Trial (SOFT; k=1), and Zoladex In Pre-menopausal Patients trial (ZIPP; k=3). The ABC Ovarian Ablation or Suppression Trial, E-3191 trial and the SOFT trial compare tamoxifen and ovarian suppression achieved by luteinizing-hormone releasing hormone (LHRH) agonists, oophorectomy, or radiation with tamoxifen alone, whereas the ZIPP trial compares tamoxifen and the LHRH agonist goserelin to tamoxifen alone.

All of the studies included some women with unknown, or negative oestrogen-receptor status. These studies were retained as their exclusion would have resulted in no clinical evidence for this review question. Furthermore, women in the ABC Ovarian Ablation or Suppression Trial and some women in the ZIPP trial were receiving concurrent chemotherapy. These studies were not excluded due to the small number of included studies but sensitivity analysis was planned to determine if the inclusion of such studies affects the overall estimate of effect. However, sensitivity analysis was not performed for survival outcomes as tests for heterogeneity were non-significant.

Only one study (Francis, 2015) reported data for subgroups of interest: Age (<35/35-39/40+), grade (1/2/3), human epidermal growth factor receptor 2 (HER2) status (+/-) and previous chemotherapy (Yes/No).

The clinical studies included in this evidence review are summarised in Table 5 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 6). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 5: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Adjuvant Breast Cancer Trials Collaborative Group 2007	ABC Ovarian Ablation or Suppression	No previous malignancy (except cervical cancer in situ or basal cell carcinoma) No previous systematic therapy for their current breast cancer	Intervention arm (TAM+OFS): 20 mg/day tamoxifen for 5 years and either oophorectomy, ovarian radiation, goserelin at 3.6 mg or leuprorelin acetate at 3.75 mg every 28 days for at least 2 years. Control arm (TAM): 20mg/day tamoxifen for 5 years

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		Included patients receiving chemotherapy	
Baum 2006	ZIPP	Normal liver function, renal function and full blood count No hormonal therapy in 6 weeks prior to joining trial No previous treatment for malignancies except for basal or squamous cell carcinoma of the skin or in situ carcinoma of the cervix. Excluded if unfit for surgery, severely limited life expectancy, primary carcinoma fixed to underlying muscle/chest wall or was ulcerated, had skin infiltration or axillary nodes that demonstrated deep fixity; unwilling/unable to attend treatment and long-term follow-up Included patients receiving chemotherapy	Intervention arm (TAM+GOS): Oral tamoxifen (20 or 40 mg daily) and goserelin 3.6 mg subcutaneous injection into abdominal wall. Control arm (TAM): Oral tamoxifen (20 or 40 mg daily
Francis 2015	SOFT	Patients had to have undergone either a total mastectomy with subsequent optional radiotherapy or breast-conserving surgery with subsequent radiotherapy. Either axillary dissection or a sentinel-node biopsy was required	Intervention arm (TAM + OFS): Oral tamoxifen at a dose of 20 mg daily and ovarian suppression by triptorelin at a dose of 3.75 mg administered by means of intramuscular injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation. Treatment duration 5 years. Control arm (TAM): Oral tamoxifen at a dose of 20 mg daily for five years.
Nystedt 2003	ZIPP	Post primary surgery Included patients receiving chemotherapy (but able to extract data separately for those not receiving chemotherapy)	2 years of endocrine therapy in both groups; details not reported (see Baum 2006)
Sverrisdottir 2004	ZIPP	Primary surgery consisting of a mastectomy or lumpectomy plus axillary node dissection Histopathologic tumour size greater than 10 mm Exclusion criteria: inoperable breast cancer, prior radiotherapy or neoadjuvant chemotherapy,	Intervention arm (TAM+GOS): tamoxifen 40 mg/d orally and goserelin 3.6 mg subcutaneously every 28 days. The treatment duration for both tamoxifen and goserelin was 2 years. Control arm (TAM): tamoxifen 40 mg/d orally for two years.

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		and prior or concurrent endocrine therapy	
Tevaarwerk 2014	E-3193	Node-negative Tumours ≤3 cm in diameter No prior systemic therapy (except ≤12 weeks of tamoxifen). No locally advanced disease. Other adjuvant systemic therapies including chemotherapy were not permitted.	Intervention arm (TAM +OFS): 20 mg oral tamoxifen per day for 5 years. OFS by LHRH analog goserelin 3.6 mg depot every 4 weeks for 5 years, LHRH analog leuprolide acetate 3.75 mg every 4 weeks for 5 years, surgical ablation, or 4) ovarian ablation radiation (20gy in 10 fractions). No dose reductions permitted Control arm (TAM): 20 mg oral tamoxifen per day for 5 years

ABC, adjuvant breast cancer; GOS, goserelin; LHRH, Luteinizing-hormone releasing hormone; OFS, ovarian function suppression; SOFT, suppression of ovarian function trial; TAM, tamoxifen; ZIPP, Zoladex in pre-menopausal patients trial

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (effectiveness of ovarian suppression in addition to endocrine therapy) is presented in Table 6.

Table 6: Summary clinical evidence profile: Comparison 1. Ovarian suppression plus tamoxifen versus tamoxifen alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Tamoxifen alone[6]	Corresponding risk: Tamoxifen + ovarian suppression			
Overall survival - Whole sample (5 to 9.9 year follow-up)	5 yr OS 95%	5 yr OS 96% [95% to 97%)	HR 0.81 (0.66 to 1)	4108 (4 studies)	Low[1,2,7]
Overall survival - Previous chemotherapy: yes (5 year follow-up)	5 yr OS 91%	5 yr OS 94% [91% to 96%)	HR 0.64 (0.42 to 0.97)	1084 (1 study)	Low[1,2]
Overall survival - Previous chemotherapy: no (5 year follow-up)	5 yr OS 100%	5 yr OS 99% [96% to 100%)	HR 3.84 (0.81 to 18.18)	949 (1 study)	Low[1,2]
Disease-free survival - Whole sample (5 to 9.9 year follow-up)	5 yr DFS 85%	5 yr DFS 87% [84% to 89%)	HR 0.83 (0.67 to 1.03)	2370 (2 studies)	Moderate[1]
Disease-free survival - Age: <35 (5 year follow-up)	5 yr DFS 67%	5 yr DFS 76% [64% to 85%)	HR 0.68 (0.42 to 1.11)	233 (1 study)	Low[1,2]
Disease-free survival - Age: 35-39 (5 year follow-up)	5 yr DFS 80%	5 yr DFS 84% [76% to 90%)	HR 0.78 (0.49 to 1.24)	387 (1 study)	Low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Tamoxifen alone[6]	Corresponding risk: Tamoxifen + ovarian suppression			
Disease-free survival - Age: 40+ (5 year follow-up)	5 yr DFS 92%	5 yr DFS 93% (91% to 95%)	HR 0.9 (0.66 to 1.22)	1413 (1 study)	Low[1,2]
Disease-free survival - Grade: 1 (5 year follow-up)	5 yr DFS 94%	5 yr DFS 92% (86% to 96%)	HR 1.23 (0.66 to 2.29)	540 (1 study)	Low[1,2]
Disease-free survival - Grade: 2 (5 year follow-up)	5 yr DFS 84%	5 yr DFS 89% (85% to 92%)	HR 0.67 (0.48 to 0.94)	1006 (1 study)	Low[1,2]
Disease-free survival - Grade: 3 (5 year follow-up)	5 yr DFS 74%	5 yr DFS 77% (68% to 83%)	HR 0.85 (0.59 to 1.23)	439 (1 study)	Low[1,2]
Disease-free survival - HER2: negative (5 year follow-up)	5 yr DFS 85%	5 yr DFS 87% (84% to 90%)	HR 0.88 (0.69 to 1.13)	1724 (1 study)	Low[2]
Disease-free survival - HER2: positive (5 year follow-up)	5 yr DFS 76%	5 yr DFS 89% (80% to 94%)	HR 0.42 (0.22 to 0.8)	236 (1 study)	Low[1,2]
Disease-free survival - Previous chemotherapy: yes (5 year follow-up)	5 yr DFS 77%	5 yr DFS 81% (76% to 85%)	HR 0.82 (0.63 to 1.06)	1084 (1 study)	Low[1,2]
Disease-free survival - Previous chemotherapy: no (5 year follow-up)	5 yr DFS 93%	5 yr DFS 94% (91% to 96%)	HR 0.83 (0.52 to 1.33)	949 (1 study)	Low[1,2]
Treatment-related morbidity: vasodilation (follow-up not-reported)	168 per 1000	438 per 1000 (349 to 549)	RR 2.6 (2.07 to 3.26)	920 (1 study)	Very low[1,2,7]
Treatment-related morbidity: weight gain (follow-up not reported)	57 per 1000	89 per 1000 (60 to 133)	RR 1.57 (1.05 to 2.35)	1265 (2 studies)	Very low[1,2,7]
Treatment-related morbidity: arthralgia (follow-up not-reported)	9 per 1000	24 per 1000 (8 to 75)	RR 2.79 (0.89 to 8.69)	920 (1 study)	Very low[1,2,7]
Treatment-related morbidity: anxiety/depression/irritability (follow-up not reported)	32 per 1000	48 per 1000 (26 to 87)	RR 1.5 (0.82 to 2.75)	3276 (3 studies)	Low[1,2]
Treatment-related morbidity: sweating (follow-up not reported)	8 per 1000	35 per 1000 (14 to 89)	RR 4.49 (1.79 to 11.24)	1265 (2 studies)	Low[1,2]
Treatment-related morbidity: hot flushes (grade 3+; 3 to 5.6 year follow-up)	71 per 1000	159 per 1000 (84 to 300)	RR 2.23 (1.18 to 4.21)	2356 (2 studies)	Low[1,2]
Treatment-related morbidity: hypertension (grade 3+; 5.6 year follow-up)	54 per 1000	75 per 1000 (53 to 105)	RR 1.39 (0.99 to 1.95)	2011 (1 study)	Low[1,2]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Tamoxifen alone[6]	Corresponding risk: Tamoxifen + ovarian suppression			
Treatment related morbidity: cardiac ischemia or infarction (grade 3+; 5.6 year follow-up)	4 per 1000	1 per 1000 (0 to 9)	RR 0.25 (0.03 to 2.24)	2011 (1 study)	Low[1,2]
Treatment related morbidity: thrombosis or embolism (grade 3+; 5.6 year follow-up)	17 per 1000	17 per 1000 (9 to 33)	RR 1 (0.51 to 1.95)	2011 (1 study)	Low[1,2]
Treatment related morbidity: musculoskeletal symptoms (grade 3+; 5.6 year follow-up)	63 per 1000	54 per 1000 (39 to 78)	RR 0.87 (0.62 to 1.24)	2011 (1 study)	Low[1,2]
Treatment related morbidity: osteoporosis (grade 3+; 5.6 year follow-up)	1 per 1000	3 per 1000 (0 to 29)	RR 3 (0.31 to 28.82)	2011 (1 study)	Low[1,2]
Treatment related morbidity: fractures (grade 3+; 5.6 year follow-up)	8 per 1000	8 per 1000 (3 to 21)	RR 1 (0.38 to 2.66)	2011 (1 study)	Low[1,2]
Treatment related morbidity: vaginal dryness (3 to 5.6 year follow-up)	358 per 1000	426 per 1000 (386 to 469)	RR 1.19 (1.08 to 1.31)	2356 (2 studies)	Moderate[1]
Treatment-related morbidity: changes in libido (3 to 5.6 year follow-up)	363 per 1000	406 per 1000 (370 to 446)	RR 1.12 (1.02 to 1.23)	2356 (2 studies)	Moderate[1]
Treatment related morbidity: CNS cerebrovascular ischemia (grade 3+; 5.6 year follow-up)	4 per 1000	1 per 1000 (0 to 9)	RR 0.25 (0.03 to 2.24)	2011 (1 study)	Low[1,2]
Treatment related morbidity: CNS haemorrhage (grade 3+; 5.6 year follow-up)	0 per 1000	0 per 1000 (0 to 0)	RR 3 (0.12 to 73.63)	2011 (1 study)	Low[2]
Treatment-related morbidity: vasomotor symptoms measured by Physical Symptoms and Problem List (3 year follow-up)		The mean treatment-related morbidity: vasomotor symptoms measured by Physical Symptoms and Problem List in the intervention groups was 0.1 higher (0.44 lower to 0.64 higher)		60 (1 study)	Very low[1,2,3,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: Tamoxifen alone[6]	Corresponding risk: Tamoxifen + ovarian suppression			
Treatment-related morbidity: vaginal dryness measured by Physical Symptoms and Problem List (3 year follow-up)		The mean treatment-related morbidity: vaginal dryness measured by Physical Symptoms and Problem List in the intervention groups was 0.17 lower (0.5 lower to 0.16 higher)		63 (1 study)	Very low[1,2,3,7]
Changes in total body bone density (g/cm2; 2 year follow-up)		The mean changes in total body bone density (g/cm2) in the intervention groups was 0 higher (0.01 lower to 0.02 higher)		32 (1 study)	Very low[1,2,3,7]
Compliance: treatment completed	407 per 1000	452 per 1000 (354 to 578)	RR 1.11 (0.87 to 1.42)	337 (1 study)	Moderate[2]
HRQoL: FACT-G		The mean HRQoL: FACT-G in the intervention groups was 1.42 lower (5.06 lower to 2.22 higher)		188 (1 study)	Very low[1,4]
HRQoL: FACT-B		The mean HRQoL: FACT-B in the intervention groups was 0.8 lower (5.66 lower to 4.06 higher)		177 (1 study)	Moderate[1,5]

Rates of disease-free survival and overall survival in the control group correspond to the trial with the shortest follow-up period

CNS, central nervous system; CI: Confidence interval; DFS, disease-free survival; FACT-B Functional assessment of cancer therapy – breast cancer; FACT-G Functional assessment of cancer therapy – general; HR: Hazard ratio; OS, overall survival; RR: Risk ratio;

[1] Unclear allocation concealment and/or randomisation sequence generation

[2] Optimal information size not met (Number of events=300 for dichotomous outcomes, N=400 for continuous outcomes [3] 29% of TAM+GOS arm and 11% of TAM arm were ER negative (Swedish subgroup of ZIPP trial)

[4] MID for FACT-G was 3 points; N<400

[5] MID for FACT-B total score was 7 points

[6] *Tamoxifen only group illustrative 5 year survival values come from the relevant subgroups in the SOFT trial*
[7] *Patients in the ZIPP and ABC trials received concurrent chemotherapy, at similar rates in both arms*

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1. Ovarian suppression plus tamoxifen versus tamoxifen alone

Critical outcomes

Disease-free survival

- There is moderate quality evidence from 2 RCTs (N=2370) that there is no effect of ovarian suppression on disease-free survival at 5 to 9.9 year follow-up in mixed populations of pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=233) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with ER positive invasive breast cancer aged <35 years.
- There is low quality evidence from 1 RCT (N=387) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with ER positive invasive breast cancer aged 35 to 39 years.
- There is low quality evidence from 1 RCT (N=1413) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with ER positive invasive breast cancer aged >40 years.
- There is low quality evidence from 1 RCT (N=540) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with grade 1, ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1006) that ovarian suppression plus tamoxifen produces a clinically meaningful improvement in disease-free at 5 year follow-up compared with tamoxifen alone for pre-menopausal women with grade 2, ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=439) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with grade 3, ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1724) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with HER2 negative, ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=236) that ovarian suppression plus tamoxifen produces a clinically meaningful improvement in disease-free at 5 year follow-up compared with tamoxifen alone for pre-menopausal women with HER2 positive, ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=1084) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with ER positive invasive breast cancer who have had chemotherapy.

- There is low quality evidence from 1 RCT (N=949) that there is no effect of ovarian suppression on disease-free survival at 5 year follow-up for pre-menopausal women with ER positive invasive breast cancer who have not had chemotherapy.

Treatment-related morbidity

- There is very low quality evidence from 1 RCT (N=920) that ovarian suppression plus tamoxifen produces clinically meaningful increases in vasodilation compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer.
- There is very low quality evidence from 2 RCTs (N=1265) that ovarian suppression plus tamoxifen produces clinically meaningful increases in weight gain compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=920) that ovarian suppression plus tamoxifen produces clinically meaningful increases in arthralgia compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 3 RCTs (N=3276) that ovarian suppression plus tamoxifen produces clinically meaningful increases in anxiety/depression/irritability compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 2 RCTs (N=1265) that ovarian suppression plus tamoxifen produces clinically meaningful increases in sweating compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from 2 RCTs (N=2356) that ovarian suppression plus tamoxifen produces clinically meaningful increases in grade 3+ hot flushes at 3 to 5.6 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=2011) that ovarian suppression plus tamoxifen produces clinically meaningful increases in grade 3+ hypertension at 5.6 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=2011) that ovarian suppression plus tamoxifen produces clinically meaningful reductions in grade 3+ cardiac ischemia or infarction at 5.6 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=2011) that there is no effect of ovarian suppression on grade 3+ thrombosis or embolism at 5.6 year follow-up for pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=2011) that there is no effect of ovarian suppression on grade 3+ musculoskeletal symptoms at 5.6 year follow-up for pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=2011) that ovarian suppression plus tamoxifen produces clinically meaningful increases in grade 3+ osteoporosis at 5.6 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=2011) that there is no effect of ovarian suppression on grade 3+ fractures at 5.6 year follow-up for pre-menopausal women with ER positive invasive breast cancer.
- There is moderate quality evidence from 2 RCTs (N=2356) that there is no effect of ovarian suppression on vaginal dryness at 3 to 5.6 year follow-up for pre-menopausal women with ER positive invasive breast cancer.

- There is moderate quality evidence from 2 RCTs (N=2356) that there is no effect of ovarian suppression on changes in libido at 3 to 5.6 year follow-up for pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from 1 RCT (N=2011) that ovarian suppression plus tamoxifen produces clinically meaningful reductions in grade 3+ CNS cerebrovascular ischemia at 5.6 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=2011) that ovarian suppression plus tamoxifen produces clinically meaningful increases in grade 3+ CNS haemorrhage at 5.6 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer. However, the effect was not statistically significant.
- There is very low quality evidence from 1 RCT (N=60) that there is no effect of ovarian suppression on vasomotor symptoms measured by Physical Symptoms and Problem List at 3 year follow-up for pre-menopausal women with ER positive invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=63) that there is no effect of ovarian suppression on vaginal dryness measured by Physical Symptoms and Problem List at 3 year follow-up for pre-menopausal women with ER positive invasive breast cancer.
- There is very low quality evidence from 1 RCT (N=32) that there is no effect of ovarian suppression on bone density at 2 year follow-up for pre-menopausal women with ER positive invasive breast cancer.

Health-related quality of life

- There is very low quality evidence from 1 RCT (N=188) that there is no effect of ovarian suppression on HRQoL measured by the FACT-G for pre-menopausal women with ER positive invasive breast cancer.
- There is moderate quality evidence from 1 RCT (N=177) that there is no effect of ovarian suppression on HRQoL measured by the FACT-B for pre-menopausal women with ER positive invasive breast cancer.

Important outcomes

Local recurrence rate

- No evidence was found for this outcome.

Overall survival

- There is low quality evidence from 4 RCTs (N=4108) that ovarian suppression plus tamoxifen produces a clinically meaningful improvement in overall survival at 5 to 9.9 year follow-up compared with tamoxifen alone for mixed populations of pre-menopausal women with ER positive invasive breast cancer.
- There is low quality evidence from one RCT (N=1084) that ovarian suppression plus tamoxifen produces a clinically meaningful improvement in overall survival at 5 year follow-up compared with tamoxifen alone for pre-menopausal women with ER positive invasive breast cancer who had received chemotherapy.
- There is low quality evidence from one RCT (N=949) that there is no effect of ovarian suppression on overall survival at 5 year follow-up for pre-menopausal women with ER positive invasive breast cancer who had not received chemotherapy.

Compliance

- There is moderate quality evidence from one RCT (N=227) that there is no effect of ovarian suppression on rates of treatment completion in pre-menopausal women with ER positive invasive breast cancer who had received chemotherapy.

Treatment-related mortality

- No evidence was found for this outcome.

Recommendations

D5. Consider ovarian function suppression in addition to endocrine therapy for premenopausal women with ER-positive invasive breast cancer.

D6. Discuss the benefits and risks of ovarian function suppression in addition to endocrine therapy with premenopausal women with ER-positive invasive breast cancer. Explain to women that ovarian function suppression may be most beneficial for those women who are at sufficient risk of disease recurrence to have been offered chemotherapy.

Rationale and impact

Why the committee made the recommendations

There was evidence that ovarian function suppression increased overall survival when combined with tamoxifen, and that women who have had chemotherapy benefited more. However, ovarian function suppression did not improve disease-free survival. In addition, it induces a temporary menopause and can worsen the menopausal symptoms seen with tamoxifen.

Given the limited evidence of benefits and the side effects of the treatment, the committee agreed that healthcare professionals should discuss the potential benefits and risks with women. This will help women to decide which treatment is right for them.

Impact of the recommendations on practice

There is variation among centres in the use of ovarian function suppression, so the recommendations should lead to greater consistency and improve access to the treatment, even though not all women will wish to have it. There will be an increase in required resources for centres that do not currently provide ovarian function suppression, because additional appointments will be needed to administer the medication and monitor side effects. However, this was not anticipated to be a substantial cost increase due to the number of centres already offering ovarian function suppression. Further, increased costs will be at least partially offset by improvements in survival outcomes.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised disease-free survival, treatment-related morbidity and health-related quality of life as critical outcomes; the latter outcomes were prioritised over overall survival due to the significant side-effect profile associated with ovarian suppression, including menopausal symptoms and the fact that conception is not possible or not advised for the duration of treatment. This meant that the disease-free survival benefits would need to be balanced against the side-effects. Overall survival, local recurrence rate, compliance with treatment, and treatment-related mortality were selected as important outcomes.

There was no evidence available for local recurrence rate or treatment-related mortality.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For disease-free survival the evidence was moderate quality for the sample as a whole, but low quality for all the subgroups due to small number of events of interest. The evidence was down-graded because of a risk of bias due to unclear randomisation and allocation concealment procedures.

For treatment-related morbidity the evidence quality ranged from very low to moderate, and was downgraded mainly due to uncertainty in the estimate due to the low number of events of interest, but also because of issues with risk of bias due to unclear randomisation and allocation concealment procedures, and indirectness due to concurrent chemotherapy administration in the ZIPP and ABC trials.

Health-related quality of life evidence was moderate for FACT-B and very low for FACT-G. This was because of risk of bias due to unclear randomisation and allocation concealment procedures for both scales. In addition, the evidence for FACT-G was downgraded because of imprecision due to a wide confidence interval and therefore uncertainty about the estimate.

Overall survival evidence was of low quality, and compliance evidence was also moderate due to a small number of events of interest.

Due to the quality of the evidence and the lack of benefit reported for the critical outcome of disease-free survival, the committee could only make a weak recommendation for the use of OFS. However, the evidence for the important outcome of overall survival was of moderate quality and showed benefit in the mixed population and those who had received chemotherapy so the committee also made a recommendation that this information should be taken into account.

Benefits and harms

The benefits of OFS in addition to endocrine therapy include improvements in disease-free and overall survival. There is a 1% improvement in overall survival at 5 years in the mixed population, and a 3% improvement in those who had received chemotherapy. There was also a 2% increase in disease-free survival but these results were not significant

It is accepted that OFS will lead to symptoms of early menopause. Whilst symptoms related to this were not all significantly increased in the current evidence review (based on very low to low quality evidence), there were increases in weight gain (number need to harm, NNH, 33), hot flushes (NNH=14), vasodilation (NNH=4) and sweating (NNH=33). In addition, women will be infertile for the duration of treatment, although women would normally be advised not to become pregnant while taking tamoxifen so the OFS may have limited additional impact in this respect.

The committee discussed the balance of benefits and harms, noting that menopausal symptoms and fertility will return after OFS treatment is ended (provided natural menopause has not been reached during this time), and that low to moderate quality evidence found that OFS had no effect on quality of life. In addition, the committee agreed that people tend to prioritise survival over side-effects, and that discussing the potential benefits/harms with women, and targeting those who are most likely to gain benefit (i.e. those who have had a risk deemed high enough to be offered chemotherapy) should help balance the acceptability of treatment side-effects in relation to the perceived risk to the patient.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee discussed the potential costs and savings of recommendations and thought that there could be additional costs associated with the use of ovarian suppression. As well as the costs of the ovarian suppression medication, there would also be costs associated with administration (monthly injections at GP surgery given by a practice nurse). There could also be additional appointments (and potentially procedures) required for the management of menopausal symptoms. For example, bone health monitoring using dual-energy X-ray absorptiometry may be required.

The committee thought that any additional costs associated with ovarian suppression would be offset, at least partially, by savings resulting from improvements in disease related outcomes (DFS and OS). These improvements should reduce the need (or at least delay the need) for future procedures, treatments and hospice care.

Overall, the committee did not anticipate that their recommendations would have a substantial resource impact. The committee noted that ovarian function suppression is already given in many centres and so the nationwide cost of implementing the recommendations is not anticipated to exceed £1 million per year. However there would be increased costs in those centres not currently offering ovarian function suppression.

Other factors the committee took into account

The committee gave greater weight to the SOFT and ECOG trial data from this evidence review as they identified three potential problems with the ABC and ZIPP studies that they believed reduced the applicability of this data to current practice. Firstly, in the ABC study women were given ovarian function suppression for 2 years and in the ZIPP study for 2-3 years. However, current standard practice is to give endocrine therapy (and therefore OFS) for at least 5 years. Secondly, the ZIPP and ABC studies both included chemotherapy administered concurrently with OFS and tamoxifen, and Albain (2009) showed that this combination is inferior. Thirdly, the SOFT trial confirmed that ovarian function had returned after chemotherapy whereas other trials did not confirm this; therefore it is possible that ovaries were not functioning in control arm.

In addition to the evidence presented in the evidence review the committee were aware of a combined analysis from two studies, SOFT and Tamoxifen and Exemestane Trial (TEXT; Pagani, 2014). This combined analysis showed greater benefit for OFS and AI whereas our current studies all used tamoxifen. Therefore, the committee have recommended considering OFS in addition to endocrine therapy despite the lack of significant disease-free survival benefit as a greater effect may have been observed if AIs had been used; a specific drug has not been recommended for endocrine therapy to allow clinician discretion to use AIs or tamoxifen as considered appropriate.

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Review question 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Introduction

Ductal carcinoma in situ (DCIS) is non-invasive and considered the earliest form of breast cancer. Abnormal cells are located inside milk ducts in the breast and have not spread or invaded other parts of the breast. Its detection has significantly increased since routine mammographic screening. The management of DCIS includes surgical intervention and with radiotherapy as appropriate.

Chemoprevention may be used in people who have been treated for DCIS to prevent the development of breast cancer. The most commonly used chemoprevention is with hormone therapy involving oestrogen receptor (ER) blockers (tamoxifen or raloxifene) or aromatase inhibitors (AIs; anastrozole, exemestane and letrozole). These hormone therapies are an established treatment for women with ER-positive invasive breast cancer. At the time of the previous guideline CG80 (NICE 2009), evidence was felt to be conflicting around use of hormonal therapies (chemoprevention) after adequate surgical treatment of DCIS.

The aim of this review is to assess the role of chemoprevention in women with DCIS, which will consider the benefits of reducing breast cancer recurrence and secondary breast cancers, compared to the side effects of increased risks of endometrial cancers and thromboembolic complications.

PICO table

See Table 7 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 7: Summary of the protocol (PICO table)

Population	Adults (18 or over) with DCIS who have undergone initial surgery
Intervention	• Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) • Tamoxifen • Raloxifene
Comparison	No treatment
Outcome	**Critical** • Disease-free survival • Local recurrence • Treatment-related morbidity **Important** • HRQoL • Overall survival • Treatment adherence

HRQoL, health-related quality of life

For full details see review protocol in appendix A.

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual; see the methods chapter for further information.

Declarations of interest were recorded according to NICE's 2014 conflicts of interest policy.

Clinical evidence

Included studies

Four studies (n=3,496) identified by the literature search were included in the review (Cuzick, 2011; Fisher, 1999, Guerrieri-Gonzaga, 2006; Wapnir, 2011), which report data from 3 trials: Guerrieri-Gonzaga, 2006 (k=1), National Surgical Adjuvant Breast and Bowel Project (NSAPB) B34 (k=2), and UK, Australia and New Zealand (UK/ANZ; k=1).

All included studies compared tamoxifen against no chemoprevention. Three studies reported data for critical outcomes for subgroups of interest: breast-conserving surgery (BCS) followed by radiotherapy (k=3) and BCS with no radiotherapy (k=1). No evidence was available for chemoprevention following mastectomy.

The clinical studies included in this evidence review are summarised in Table 8 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 9). See also the study selection flow chart in appendix C, forest plots in appendix E, and study evidence tables in appendix D.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

Table 8: Summary of included studies

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
Cuzick 2011	UK/ANZ	• Unilateral or bilateral DCIS that could be excised with clear margins by breast conserving surgery	• Intervention arm (TAM): 20mg tamoxifen daily for 5 years; radiotherapy was administered in 25 fractions over 5 weeks (2Gy given 5 times a week; total 50Gy) • Control arm (No chemoprevention): radiotherapy was administered in 25 fractions over 5 weeks (2Gy given 5 times a week; total 50Gy)
Fisher 1999	NSABP-B34	• Women with DCIS with a life expectancy of at least 10 years. Axillary dissection (if done) had to show negative lymph node involvement and time between surgery and randomisation ≤56 days. • Exclusion: previous diagnosis of cancer (except in situ carcinoma of the cervix or squamous cell or basal-cell carcinoma of the skin)	• Intervention arm (TAM): lumpectomy was performed within 56 days of randomisation. Radiation therapy total of 50 Gy. 10 mg tamoxifen was taken twice daily for 5 years. • Control arm (No chemoprevention): lumpectomy was performed within 56 days of randomisation. Radiation therapy total of 50 Gy. Placebo was taken twice daily for 5 years
Guerrieri-Gonzaga 2006		• Premenopausal women with: 1) in situ cancer or small invasive cancer of favourable prognosis within the last 3 years, or 2) Gail	• Intervention arm (TAM): 5 mg tamoxifen and fenretinide placebo capsules daily for 2 years

Study	Trial	Additional inclusion/exclusion criteria	Interventions/comparison
		5-year risk for breast cancer of 1.3%. • Exclusion: prior chemotherapy or hormonal therapy; malignancy other than carcinoma-in-situ and skin basal cell carcinoma; retinal/ocular disorders; photodermatitis; stage III or IV endometriosis; grade 2 alterations of hematologic, liver and renal function; hypertriglyceridemia; CNS diseases; major psychiatric diseases; history of venous thromboembolism; transient ischemic attack.	• Control arm (No chemoprevention): tamoxifen and fenretinide placebo capsules daily for 2 years
Wapnir 2011	NSAPB-B34	• Inclusion criteria • Women with DCIS with a life expectancy of at least 10 years. Axillary dissection (if done) had to show negative lymph node involvement and time between surgery and randomisation ≤56 days • Exclusion: previous diagnosis of cancer (except in situ carcinoma of the cervix or squamous cell or basal-cell carcinoma of the skin)	• Intervention arm (TAM): Radiation started within 8 weeks of surgery and was given at 10Gy per week over 5 weeks (total 50Gy); optional boost of 10Gy to lumpectomy cavity. 10mg tamoxifen taken twice daily for 5 years • Control arm (No chemoprevention): Radiation started within 8 weeks of surgery and was given at 10Gy per week over 5 weeks (total 50Gy); optional boost of 10Gy to lumpectomy cavity. Placebo was taken twice daily for 5 years

CNS, central nervous system; DCIS, ductal carcinoma in situ; Gy, gray; NSABP, National Surgical Adjuvant Breast and Bowel Project; TAM, tamoxifen; UK/ANZ, United Kingdom, Australia and New Zealand

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profile for this review question (chemoprevention in DCIS) is presented in Table 9. The quality of evidence ranges from very low to high. Main reasons for downgrading evidence was imprecision around the estimates due to a small number of events of interest and wide confidence intervals.

Table 9: Summary clinical evidence profile: Comparison 1. Tamoxifen versus no chemoprevention for people with excised DCIS

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: No chemoprevention	Corresponding risk: Tamoxifen			
Disease-free survival - Whole sample (10 year follow-up)	10yr DFS 74%	10yr DFS 81% (77% to 84%)	HR 0.71 (0.58 to 0.87)	1576 (1 study)	High

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: No chemopreventio n	Corresponding risk: Tamoxifen			
Disease-free survival - BCS+RT (10 year follow-up)	10yr DFS 87%	10yr DFS 87% (80% to 92%)	HR 0.99 (0.61 to 1.60)	523 (1 study)	Moderate [1]
Disease-free survival - BCS-RT (10 year follow-up)	10yr DFS 68%	10yr DFS 76% (71% to 80%)	HR 0.71 (0.57 to 0.88)	1053 (1 study)	Moderate [1]
Local recurrence – Mixed (10 year follow-up)	79% free from local recurrence at 10 yrs	83% free from local recurrence at 10 yrs (79% to 86%)	HR 0.78 (0.62 to 0.99)	1576 (1 study)	Moderate [1]
Local recurrence – Invasive (13.6 year follow-up)	91% free from local recurrence at 13.6 yrs	94% free from local recurrence at 13.6 yrs (91% to 96%)	HR 0.68 (0.49 to 0.95)	1799 (1 study)	Moderate [1]
Local recurrence – DCIS (13.6yr follow-up)	92% free from local recurrence at 13.6 yrs	93% free from local recurrence at 13.6 yrs (91% to 95%)	HR 0.84 (0.60 to 1.18)	1799 (1 study)	Moderate [1]
Local recurrence - BCS+RT (10 year follow-up)	91% free from local recurrence at 10 yrs	92% free from local recurrence at 10 yrs (85% to 95%)	HR 0.93 (0.50 to 1.74)	523 (1 study)	Moderate [1]
Local recurrence - BCS-RT (10 year follow-up)	74% free from local recurrence at 10 yrs	79% free from local recurrence at 10 yrs (74% to 84%)	HR 0.77 (0.60 to 0.99)	1053 (1 study)	Moderate [1]
Overall survival (13.6 year follow-up)	13.6yr OS 95%	13.6yr OS 96% (94% to 97%)	HR 0.86 (0.66 to 1.12)	1799 (1 study)	Moderate [1]
Treatment-related morbidity - vaginal dryness/discharge (3.3 to 6.2 year follow-up)	198 per 1000	321 per 1000 (274 to 375)	RR 1.62 (1.38 to 1.89)	1897 (2 studies)	High [2]
Treatment-related morbidity - grade 3+ toxicities (6.2 year follow-up)	43 per 1000	54 per 1000 (35 to 82)	RR 1.26 (0.83 to 1.91)	1781 (1 study)	Low [3]
Treatment-related morbidity - phlebitis/thromboembolism (6.2 year follow-up)	8 per 1000	18 per 1000 (7 to 43)	RR 2.28 (0.94 to 5.52)	1781 (1 study)	Low [3]
Treatment-related morbidity - mood	107 per 1000	106 per 1000 (80 to 138)	RR 0.99	1781 (1 study)	Low [4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk: No chemoprevention	Corresponding risk: Tamoxifen			
changes (6.2 year follow-up)			(0.75 to 1.29)		
Treatment-related morbidity - menstrual disorders (6.2 year follow-up)	160 per 1000	191 per 1000 (156 to 235)	RR 1.2 (0.98 to 1.47)	1781 (1 study)	Moderate [5]
Treatment-related morbidity - hot flashes (3.3 to 6.2 year follow-up)	568 per 1000	670 per 1000 (624 to 715)	RR 1.18 (1.1 to 1.26)	1897 (2 studies)	High[2]
Treatment-related morbidity - fluid retention (6.2 year follow-up)	279 per 1000	326 per 1000 (284 to 376)	RR 1.17 (1.02 to 1.35)	1781 (1 study)	High
Treatment-related morbidity - ocular/visual (3.3 year follow-up)	431 per 1000	328 per 1000 (203 to 526)	RR 0.76 (0.47 to 1.22)	116 (1 study)	Very low[6,7]
Treatment-related morbidity - dermatology/skin (3.3 year follow-up)	431 per 1000	293 per 1000 (177 to 483)	RR 0.68 (0.41 to 1.12)	116 (1 study)	Very low[6,7]
Treatment-related morbidity - dysuria/incontinence (3.3 year follow-up)	86 per 1000	86 per 1000 (27 to 282)	RR 1 (0.31 to 3.27)	116 (1 study)	Very low[4,6]
Treatment-related morbidity - vaginal bleeding (3.3 year follow-up)	69 per 1000	121 per 1000 (37 to 390)	RR 1.75 (0.54 to 5.66)	116 (1 study)	Very low[4,6]
Treatment-related morbidity - endometrial polyps (3.3 year follow-up)	52 per 1000	69 per 1000 (16 to 295)	RR 1.33 (0.31 to 5.7)	116 (1 study)	Very low[4,6]
Treatment-related morbidity - sweats/weight gain (3.3 year follow-up)	138 per 1000	156 per 1000 (65 to 374)	RR 1.13 (0.47 to 2.71)	116 (1 study)	Very low[4,6]

Rates of disease-free survival, local recurrence and overall survival in the control group correspond to the trial with the shortest follow-up period

BCS: breast-conserving surgery; CI: Confidence interval; DFS, disease-free survival; HR: hazards ratio; OS, overall survival; RR: Risk ratio; RT: radiotherapy

[1] <300 events

[2] Very serious indirectness in Guerrieri-Gonzaga 2006 due to population; evidence not downgraded as study only given 4.9% weight in analysis

[3] <300 events; 95% CI crosses boundary of no effect (1) and minimally important difference (1.25) based on GRADE default values

[4] <300 events; 95% CI crosses both boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values

[5] 95% CI crosses boundary of no effect (1) and minimally important difference (1.25) based on GRADE default values

[6] *Only 57% of population had excised DCIS*
[7] *<300 events; 95% CI crosses boundary of no effect (1) and minimally important difference (0.8) based on GRADE default values*

See appendix F for full GRADE tables.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Evidence statements

Comparison 1.Tamoxifen versus no chemoprevention for people with excised DCIS

Critical outcomes

Disease-free survival

- There is high quality evidence from 1 RCT (N=1576) that tamoxifen produces clinically meaningful increases in disease-free survival compared with no chemoprevention at 10 year follow-up for people with excised DCIS.
- There is moderate quality evidence from 1 RCT (N=523) that there is no clinically important effect of tamoxifen on disease-free survival at 10 year follow-up for people with excised DCIS following BCS and radiotherapy.
- There is moderate quality evidence from 1 RCT (N=1053) that tamoxifen produces clinically meaningful increases in disease-free survival compared with no chemoprevention at 10 year follow-up for people with excised DCIS following BCS alone.

Local recurrence

- There is moderate quality evidence from 1 RCT (N=1576) that tamoxifen produces clinically meaningful reductions in local recurrence compared with no chemoprevention at 10 year follow-up for people with excised DCIS.
- There is moderate quality evidence from 1 RCT (N=1799) that tamoxifen produces clinically meaningful reductions in invasive local recurrence compared with no chemoprevention at 13.6 year follow-up for people with excised DCIS following BCS and radiotherapy.
- There is moderate quality evidence from 1 RCT (N=1799) that there is no clinically important effect of tamoxifen on DCIS local recurrence at 13.6 year follow-up for people with excised DCIS following BCS and radiotherapy.
- There is moderate quality evidence from 1 RCT (N=523) that there is no clinically important effect of tamoxifen on local recurrence at 10 year follow-up for people with excised DCIS following BCS and radiotherapy.
- There is moderate quality evidence from 1 RCT (N=1053) that tamoxifen produces clinically meaningful reductions in local recurrence compared with no chemoprevention at 10 year follow-up for people with excised DCIS following BCS alone.

Treatment-related morbidity

- There is high quality evidence from 2 RCTs (N=1897) that tamoxifen produces clinically meaningful increases in vaginal dryness/discharge at 3.3 to 6.2 year follow-up compared with no chemoprevention for people with excised DCIS.

- There is low quality evidence from 1 RCT (N=1781) that tamoxifen produces clinically meaningful increases in grade 3+ toxicities at 6.2 year follow-up compared with no chemoprevention for people with excised DCIS. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1781) that tamoxifen produces clinically meaningful increases in phlebitis/thromboembolisms at 6.2 year follow-up compared with no chemoprevention for people with excised DCIS. However, the effect was not statistically significant.
- There is low quality evidence from 1 RCT (N=1781) that there is no clinically important effect of tamoxifen on mood changes at 6.2 year follow-up for people with excised DCIS.
- There is moderate quality evidence from 1 RCT (N=1781) that there is no clinically important effect of tamoxifen on menstrual disorders at 6.2 year follow-up for people with excised DCIS.
- There is high quality evidence from 2 RCTs (N=1897) that there is no clinically important effect of tamoxifen on hot flashes at 3.3 to 6.2 year follow-up for people with excised DCIS.
- There is high quality evidence from 1 RCT (N=1781) that there is no clinically important effect of tamoxifen on fluid retention at 6.2 year follow-up for people with excised DCIS.
- There is very low quality evidence from 1 RCT (N=116) that tamoxifen produces clinically meaningful reductions in ocular/visual treatment-related morbidities at 3.3 year follow-up compared with no chemoprevention for people with excised DCIS. However, the effect was not statistically significant.
- There is very low quality evidence from 1 RCT (N=116) that tamoxifen produces clinically meaningful reductions in dermatological treatment-related morbidities at 3.3 year follow-up compared with no chemoprevention for people with excised DCIS. However, the effect was not statistically significant.
- There is very low quality evidence from 1 RCT (N=116) that there is no clinically important effect of tamoxifen on dysuria/incontinence at 3.3 year follow-up for people with excised DCIS.
- There is very low quality evidence from 1 RCT (N=116) that tamoxifen produces clinically meaningful increases in vaginal bleeding at 3.3 year follow-up compared with no chemoprevention for people with excised DCIS. However, the effect was not statistically significant.
- There is very low quality evidence from 1 RCT (N=116) that tamoxifen produces clinically meaningful increases in endometrial polyps at 3.3 year follow-up compared with no chemoprevention for people with excised DCIS. However, the effect was not statistically significant.
- There is very low quality evidence from 1 RCT (N=116) that there is no clinically important effect of tamoxifen on sweats/weight gain at 3.3 year follow-up for people with excised DCIS.

Important outcomes

Health-related quality of life

- No evidence was found for this outcome.

Overall survival

- There is moderate quality evidence from 1 RCT (N=1799) that there is no clinically important effect of tamoxifen on overall survival at 13.6 year follow-up for people with excised DCIS following BCS and radiotherapy.

Treatment adherence

- No evidence was found for this outcome.

Economic evidence

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question. Economic modelling was not undertaken for this question because other topics were agreed as higher priorities for economic evaluation.

Recommendations

D7. Offer endocrine therapy after breast-conserving surgery for women with ER-positive DCIS if radiotherapy is recommended but not received.

D8. Consider endocrine therapy after breast-conserving surgery for women with ER-positive DCIS if radiotherapy is not recommended.

D9. Discuss the benefits and risks of endocrine therapy after breast-conserving surgery for women with ER-positive DCIS.

Rationale and impact

Why the committee made the recommendations

There was good evidence that endocrine therapy after breast-conserving surgery for ER-positive DCIS improved disease-free survival and reduced rates of local recurrence in women who did not have radiotherapy. Because of their concerns about overtreatment, the committee agreed that women who were at higher risk (those who should have had radiotherapy, but who did not receive it) would benefit more.

The committee agreed that the benefits and risks of endocrine therapy should be discussed with the woman because of the potential treatment-related complications such as menopausal symptoms, and the impact on family planning.

Impact of the recommendations on practice

Offering endocrine therapy after initial treatment of DCIS will be a change of practice because it is not currently routinely offered to these women. However, because of the small number of people with DCIS who will not receive radiotherapy, and the low cost of the medicines, the committee agreed that the impact will not be significant.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Disease-free survival, local recurrence and treatment related-morbidity were selected by the committee as the critical outcomes for this review. Local recurrence was prioritised over overall survival as this review question is examining whether chemoprevention is effective at preventing invasive cancer and return of DCIS in people following treatment of DCIS. DCIS itself does not usually have an impact on overall survival, except by increasing the chance of invasive cancer developing. Treatment-related morbidity also critical as it affects the tolerance of, and adherence to treatment, and quality of life.

Overall survival, HRQoL and treatment adherence were defined as the important outcomes, but no evidence for HRQoL or treatment adherence was identified.

The quality of the evidence

The quality of the evidence was assessed using GRADE. For disease-free survival the evidence was of a high-moderate quality, with the downgrading to moderate mainly due to a small number of events of interest.

For local recurrence and overall survival the evidence was of moderate quality, again downgraded due to small number of events of interest.

The quality of evidence for treatment-related morbidities ranged from high to very low. The main reason for downgrading here was a small number of events and a wide confidence interval.

The recommendations are based on the strong evidence of the benefits of chemoprevention in terms of disease-free survival and local recurrence for those people who do not have radiotherapy.

Benefits and harms

The evidence review identified specific benefits of chemoprevention for people with DCIS who do not have radiotherapy: there was an 8% improvements in DFS at 10 years (NNT 13) and 5% improvement in local recurrence at 10 years (NNT 10).

The main harm identified in the evidence review was a 12% increase in vaginal dryness in those women treated with tamoxifen compared with no chemoprevention (NNH 8). There was also an increased rate of endometrial polyps and thrombophlebitis in the tamoxifen arm but this was not statistically significant.

However, the committee knew from their clinical experience that the occurrence of menopausal symptoms with endocrine therapy is well established (despite lack of evidence in current review) and that this may lead to reduced adherence.

Pre-menopausal women who wish to have children may be less willing to take tamoxifen as, due to its potential teratogenic effects, conception is not recommended for the duration of the tamoxifen treatment.

The committee balanced the benefits and harms of chemoprevention in this population, and took into consideration the fact that the benefits relate to DFS and local recurrence rather than overall survival. There was no evidence available to stratify high and low risk populations in the current review; however, the committee felt there was a risk of over-treatment if chemoprevention was offered to everyone, and the potential amount of benefit would be proportional to the individual's risk level. The committee therefore chose to stratify the population for risk by assessing if they would have been offered radiotherapy.

Based on this stratification, the committee recommended chemoprevention is offered to those who are recommended radiotherapy but do not have it, and is considered for those who are not recommended radiotherapy, but that the benefits and risks are discussed with the woman.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The recommendation to offer endocrine therapy may require an increase in resources. However, the cost impact is likely to be minimal as DCIS affects a relatively small number of people in the UK and chemoprevention drugs are inexpensive. In addition to drug costs,

there may be some additional monitoring by GP required for people receiving chemoprevention but this would probably be limited to an annual check-up except in people experiencing side effects. The upfront costs associated with the use of chemoprevention are likely to be offset, at least partially, by downstream savings associated with preventing recurrences and future treatment.

Other factors the committee took into account

The only drug looked at in this evidence review was tamoxifen as trials of others were not available. However other drugs are available for endocrine chemoprevention and the committee agreed that benefits of other endocrine therapies were likely to be very similar in this population. The committee therefore recommended endocrine chemoprevention, rather than specifically tamoxifen.

The committee did not make a research recommendation to address the lack of data for other drugs in this situation as they were aware of other trials (e.g., International Breast Cancer Intervention Studies [IBIS]-II; Cuzick, 2014) comparing aromatase inhibitors with tamoxifen; this trial did not meet our inclusion criteria as it compared two different forms of endocrine chemoprevention rather than comparing endocrine chemoprevention with no chemoprevention.

The recommendations made are specific to ER-positive women. This was not specified in the protocol but it is well established that only those with ER-positive DCIS will benefit from endocrine therapy and therefore it would be inappropriate to offer endocrine chemoprevention to ER-negative women.

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Appendices

Appendix A – Review protocols

Review protocol for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Field (based on PRISMA-P)	Content
Review question	What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?
Type of review question	Intervention review
Objective of the review	The objective of this review is to review evidence regarding the optimal timing and duration of adjuvant endocrine therapy in relation to factors influencing risk. Recommendations will aim to cover which women with ER+ breast cancer will benefit from longer than 5 years of adjuvant endocrine therapy.
Eligibility criteria – population/disease/condition/issue/domain	Women (18 or over) with oestrogen-receptor positive invasive breast cancer (M0) after surgery and/or radiotherapy
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Continuous endocrine therapy for more than 5 years
Eligibility criteria – comparator(s)/control or reference (gold) standard	Continuous endocrine therapy for 5 years
Outcomes and prioritisation	• Critical (up to 3 outcomes) • Treatment-related morbidity (e.g., vasomotor symptoms [MID: GRADE default values], cardiovascular events [MID: any significant difference], endometrial cancer [MID: any significant difference], hypercholesterolemia [MID: GRADE default values], bone loss/fractures [MID: GRADE default values], thromboembolic clots [MID: GRADE default values]) • Disease free survival (MID: any significant difference) • Overall survival (MID: any significant difference) • Important but not critical

Field (based on PRISMA-P)	Content
	Compliance/ adherence (MID: GRADE default values) Treatment-related mortality (MID: any statistically significant difference) HRQoL (MID: values from the literature where available; GRADE default value for FACT-B endocrine scale) 15 year follow-up periods will be prioritised when multiple time points are reported. • MID values from the literature: • HRQoL: • 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
Eligibility criteria – study design	• Systematic reviews/meta-analyses of RCTs • RCTs
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (for critical outcomes only – excluding treatment-related morbidity: • Stage (1/2/3) • Grade (1/2/3
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this review question as it is a straightforward intervention review.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.

Field (based on PRISMA-P)	Content
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. The focus of this review question has changed since the previous technology appraisal. Therefore, searches will be undertaken from 1996 when the first studies on tamoxifen were published. A general exclusions filter and methodological filters (RCT and systematic review) will be used as it is an intervention question.
Identify if an update	Previous topics/question: TA112: Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer Date of TA112: 22/11/0 Relevant recommendation(s) from previous guidelines: 1) The aromatase inhibitors anastrozole, exemestane and letrozole, within their licensed indications, are recommended as options for the adjuvant treatment of early oestrogen-receptor-positive invasive breast cancer in postmenopausal women. 2) The choice of treatment should be made after discussion between the responsible clinician and the woman about the risks and benefits of each option. Factors to consider when making the choice include whether the woman has received tamoxifen before, the licensed indications and side-effect profiles of the individual drugs and, in particular, the assessed risk of recurrence.
Author contacts	Please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).

Field (based on PRISMA-P)	Content
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; ER, oestrogen receptor; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Review protocol for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Field (based on PRISMA-P)	Content
Review question	What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?
Type of review question	Intervention review
Objective of the review	The objective of this review is to determine whether endocrine therapy with the addition of ovarian suppression is more clinically and cost effective than endocrine therapy alone. Recommendations will cover whether, and for which groups, there is an additional benefit and ovarian suppression should be discussed with the patient.
Eligibility criteria – population/disease/condition/issue/domain	Pre-menopausal adult women (18 or over) with oestrogen-receptor positive invasive breast cancer.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Endocrine therapy with ovarian suppression: Luteinizing-hormone releasing hormone (LHRH) agonists Oophorectomy
Eligibility criteria – comparator(s)/control or reference (gold) standard	Endocrine therapy without ovarian suppression.
Outcomes and prioritisation	Critical (up to 3 outcomes) Disease-free survival (MID: any statistically significant difference) Treatment-related morbidity (e.g., bone health [MID: GRADE default values], cardiovascular [MID: GRADE default values]) HRQoL (MID: values from the literature) Important but not critical Local recurrence rate (MID: any statistically significant difference) Overall survival (MID: any statistically significant difference) Compliance (MID: GRADE default values) Treatment-related mortality (MID: any statistically significant difference) 5 year follow-ups will be prioritised if multiple time points are reported. MID values from the literature: HRQoL: FACT-G total: 3-7 points FACT-B total: 7-8 points

Field (based on PRISMA-P)	Content
	TOI (trial outcome index) of FACT-B: 5-6 points BCS of FACT-B: 2-3 points WHOQOL-100: 1 point
Eligibility criteria – **study design**	Systematic reviews/meta-analyses of RCTs RCTs
Other inclusion **exclusion criteria**	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/**sub-group analysis**, or meta-regression	Subgroups: Age (<35, 35 - 40, ≥40) Stage Grade HER2 status Previous chemotherapy (yes/no)
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will be performed on at least 10% of records and where possible all records as this is the first research question examined for this guideline and not all reviewers have previous experience of cancer guidelines; 90% agreement is required and any discussions will be resolved through discussion and consultation with senior staff where necessary.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. The focus of this review question has changed since the previous guideline. Therefore searches will be undertaken from 1992 onwards as this when tamoxifen became the standard of care, rather than from 2008 when the previous

Field (based on PRISMA-P)	Content
	search was undertaken. A general exclusions filter and methodological filters (RCT and systematic review) will also be used as it is an intervention question.
Identify if an update	Previous question: In premenopausal breast cancer patients, what are the benefits of ovarian suppression versus tamoxifen? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Do not offer adjuvant ovarian ablation/suppression to premenopausal women with ER-positive early invasive breast cancer who are being treated with tamoxifen and, if indicated, chemotherapy. 2) Offer adjuvant ovarian ablation/suppression in addition to tamoxifen to premenopausal women with ER-positive early invasive breast cancer who have been offered chemotherapy but have chosen not to have it.
Author contacts	Please see the guideline in development web page.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/

Field (based on PRISMA-P)	Content
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; ER, oestrogen receptor; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; LHRH, Luteinizing-hormone releasing hormone; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Review protocol for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Field (based on PRISMA-P)	Content
Review question	What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?
Type of review question	Intervention review
Objective of the review	The aim of this review is to assess the role of chemoprevention in women with DCIS which will also consider the benefits; reducing breast cancer recurrence and secondary breast cancers, against the side effects; increased risks of endometrial cancers and thromboembolic complications. Recommendations will aim to cover whether, and for which groups, chemoprevention should be offered.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with DCIS who have undergone initial surgery
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	• Aromatase inhibitors (e.g., anastrozole, exemestane, letrozole) • Tamoxifen • Raloxifene
Eligibility criteria – comparator(s)/control or reference (gold) standard	No treatment
Outcomes and prioritisation	• Critical (up to 3 outcomes) • Disease free survival (MID: any statistically significant difference) • Local recurrence • Treatment related morbidity (MID: GRADE default values) • Important but not critical • HRQoL (MID: values from the literature where available, otherwise GRADE default values) • Overall survival (MID: any statistically significant difference) • Treatment adherence (MID: GRADE default values) • Longest follow-up periods will be prioritised where multiple time points are reported. • HRQoL MID values from the literature: • FACT-G total: 3-7 points

Field (based on PRISMA-P)	Content
	• 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
Eligibility criteria – study design	Systematic reviews/meta-analyses of RCTs RCTs
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (for critical outcomes only – excluding treatment-related morbidity: • Breast conservation - radiotherapy • Breast conservation + radiotherapy • Mastectomy
Selection process – duplicate screening/selection/analysis	Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the reviewing team. Quality control will be performed by the senior systematic reviewer. Dual sifting will not be performed for this review question as it is a straightforward intervention review limited to RCTs.
Data management (software)	Study sifting and data extraction will be undertaken in STAR. Pairwise meta-analyses will be performed using Cochrane Reviewer Manager (RevMan 5). GRADEpro will be used to assess the quality of evidence for each outcome.
Information sources – databases and dates	The following key databases will be searched: Cochrane Library (CDSR, DARE, CENTRAL, HTA) through Wiley, Medline & Medline in Process and Embase through OVID. Additionally Web of Science may be searched and consideration will be given to subject-specific databases and used as appropriate. Searches will be undertaken from 1990, when the first RCT using chemoprevention in DCIS was published. A general exclusions filter and methodological filters (RCT and systematic review) will be used as it is an intervention question.

Field (based on PRISMA-P)	Content
Identify if an update	N/A
Author contacts	Please see the guideline in development web page.
Highlight if amendment to previous protocol	For details please see Section 4.5 of Developing NICE guidelines: the manual
Search strategy	For details please see appendix B.
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or appendix H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see Section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis	For details please see Section 6.4 of Developing NICE guidelines: the manual
Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the methods chapter.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.
Confidence in cumulative evidence	For details please see Sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – what is known	For details please see the introduction to the evidence review.

Field (based on PRISMA-P)	Content
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by the NGA and chaired by Dr Jane Barrett in line with section 3 of Developing NICE guidelines: the manual. Staff from NGA undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
Sources of funding/support	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Name of sponsor	NGA is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists.
Roles of sponsor	NICE funds NGA to develop guidelines for the NHS in England.
PROSPERO registration number	N/A

BCS, breast cancer subscale; DCIS, ductal carcinoma in situ; FACT-B, Functional assessment of cancer therapy – Breast cancer; FACT-G, Functional assessment of cancer therapy – General; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HRQoL, health-related quality of life; MID, minimally important difference; N/A, not applicable; NHS, National Health Service, NICE, National Institute of Health and Care Excellence; NGA, National Guideline Alliance; RCT, randomised controlled trial; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Literature search strategies for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Database: Medline

Last searched on **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present**.

Date of last search: 27 September 2017

#	Searches
1	exp Breast Neoplasms/
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/
3	Carcinoma, Intraductal, Noninfiltrating/
4	Carcinoma, Lobular/
5	Carcinoma, Medullary/
6	1 or 2 or 3 or 4 or 5
7	exp Breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp Neoplasms/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
18	Paget's Disease, Mammary/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp Aromatase Inhibitors/
23	aromatase inhibitor$.mp.
24	anastrazole.mp.
25	arimidex.mp.
26	letrozole.mp.
27	femara.mp.
28	exemestane.mp.
29	aromasin.mp.
30	Tamoxifen/
31	(Nolvadex or tamoxifen$).mp.

#	Searches
32	or/22-31
33	21 and 32
34	Time Factors/
35	(duration$ or timing).tw.
36	(sequenc$ or sequential).tw.
37	extended.tw.
38	(continu$ or stop$).tw.
39	((optimal or different) adj (regimen$ or treatment or therapy or course)).tw.
40	(length adj2 (regimen$ or treatment or therapy or course)).tw.
41	or/34-40
42	33 and 41
43	("MA.17" or MA17 or ATTOM or ATLAS).tw.
44	21 and 43
45	42 or 44
46	limit 45 to yr="1996 -Current"
47	Limit 46 to RCTs and SRs, and general exclusions filter applied

Database: Embase

Last searched on **Embase Classic+Embase** 1947 to 2017 September 26.

Date of last search: 27 September 2017

#	Searches
1	exp breast cancer/
2	exp breast carcinoma/
3	exp medullary carcinoma/
4	exp intraductal carcinoma/
5	exp breast tumor/
6	1 or 2 or 3 or 4 or 5
7	exp breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp neoplasm/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
18	exp Paget nipple disease/
19	(paget$ and (breast$ or mammary or nipple$)).tw.

#	Searches
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp aromatase inhibitor/
23	aromatase inhibitor$.mp.
24	anastrazole.mp.
25	arimidex.mp.
26	letrozole.mp.
27	femara.mp.
28	exemestane.mp.
29	aromasin.mp.
30	tamoxifen/
31	(Nolvadex or tamoxifen$).mp.
32	or/22-31
33	21 and 32
34	time factor/
35	(duration$ or timing).tw.
36	(sequenc$ or sequential).tw.
37	extended.tw.
38	(continu$ or stop$).tw.
39	((optimal or different) adj (regimen$ or treatment or therapy or course)).tw.
40	(length adj2 (regimen$ or treatment or therapy or course)).tw.
41	or/34-40
42	33 and 41
43	("MA.17" or MA17 or ATTOM or ATLAS).tw.
44	21 and 43
45	42 or 44
46	limit 45 to yr="1996 -Current"
47	Limit 46 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 27 September 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11

#	Searches
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#23	aromatase inhibitor*:ti,ab,kw (Word variations have been searched)
#24	(anastrazole or arimidex or letrozole or femara or exemestane or aromasin):ti,ab,kw (Word variations have been searched)
#25	MeSH descriptor: [Tamoxifen] this term only
#26	(Nolvadex or tamoxifen*):ti,ab,kw (Word variations have been searched)
#27	#22 or #23 or #24 or #25 or #26
#28	#21 and #27
#29	MeSH descriptor: [Time Factors] this term only
#30	(duration* or timing):ti,ab,kw (Word variations have been searched)
#31	(sequenc* or sequential):ti,ab,kw (Word variations have been searched)
#32	extended:ti,ab,kw (Word variations have been searched)
#33	(continu* or stop*):ti,ab,kw (Word variations have been searched)
#34	((optimal or different) next (regimen* or treatment or therapy or course)):ti,ab,kw (Word variations have been searched)
#35	(length near/2 (regimen* or treatment or therapy or course)):ti,ab,kw (Word variations have been searched)
#36	#29 or #30 or #31 or #32 or #33 or #34 or #35
#37	#28 and #36
#38	(MA.17 or MA17 or ATTOM or ATLAS):ti,ab,kw (Word variations have been searched)
#39	#21 and #38
#40	#37 or #39 Publication Year from 1996 to 2017

Literature search strategies for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Database: Medline

Last searched on **Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present.**

Date of last search: 28 September 2017

#	Searches
1	exp Breast Neoplasms/
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/
3	Carcinoma, Intraductal, Noninfiltrating/
4	Carcinoma, Lobular/
5	Carcinoma, Medullary/
6	1 or 2 or 3 or 4 or 5
7	exp Breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp Neoplasms/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp.
18	Paget's Disease, Mammary/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp Ovariectomy/
23	(ovariectom$ or oophorectom$).ti,ab.
24	(removal adj3 ovar$).ti,ab.
25	((radiation or irradiation or radiotherap$) adj3 ovar$).ti,ab.
26	exp Ovary/
27	exp Radiation/
28	(ovar$ adj3 (suppress$ or ablat$)).ti,ab.
29	26 and 27
30	22 or 23 or 24 or 25 or 28 or 29
31	21 and 30
32	Luteinizing Hormone/
33	lutein$ hormon$ releas$.mp.

#	Searches
34	(LHRH$ or LH-RH$).mp.
35	exp Gonadotropin-Releasing Hormone/
36	gonadotrop$ releas$ hormon$.mp.
37	(GnRH$ or GnRHA$).mp.
38	(goserelin$ or zolade$ or novgos or buserelin$ or suprefact or suprecur or leuprolid$ or leuprorelin$ or lupron or nafarelin$ or synarel or triptorelin$ or decapeptyl or gonapeptyl).mp.
39	(hormon$ adj3 (suppress$ or ablat$)).mp.
40	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	21 and 40
42	31 or 41
43	limit 42 to yr="1992 -Current"
44	Limit 43 to RCTs and SRs, and general exclusions filter applied

Database: Embase

Last searched on **Embase Classic+Embase** 1947 to 2017 September 27.

Date of last search: 28 September 2017

#	Searches
1	exp breast cancer/
2	exp breast carcinoma/
3	exp medullary carcinoma/
4	exp intraductal carcinoma/
5	exp breast tumor/
6	1 or 2 or 3 or 4 or 5
7	exp breast/
8	breast.tw.
9	7 or 8
10	(breast adj milk).tw.
11	(breast adj tender$).tw.
12	10 or 11
13	9 not 12
14	exp neoplasm/
15	13 and 14
16	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
17	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
18	exp Paget nipple disease/
19	(paget$ and (breast$ or mammary or nipple$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp ovariectomy/
23	(ovariectom$ or oophorectom$).ti,ab.
24	(removal adj3 ovar$).ti,ab.

#	Searches
25	((radiation or irradiation or radiotherap$) adj3 ovar$).ti,ab.
26	exp ovary/
27	exp radiation/
28	(ovar$ adj3 (suppress$ or ablat$)).ti,ab.
29	26 and 27
30	22 or 23 or 24 or 25 or 28 or 29
31	21 and 30
32	exp gonadorelin/
33	lutein$ hormon$ releas$.mp.
34	(LHRH$ or LH-RH$).mp.
35	exp growth hormone releasing factor/
36	gonadotrop$ releas$ hormon$.mp.
37	(GnRH$ or GnRHA$).mp.
38	(goserelin$ or zolade$ or novgos or buserelin$ or suprefact or suprecur or leuprolid$ or leuprorelin$ or lupron or nafarelin$ or synarel or triptorelin$ or decapeptyl or gonapeptyl).mp.
39	(hormon$ adj3 (suppress$ or ablat$)).mp.
40	32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
41	21 and 40
42	31 or 41
43	limit 42 to yr="1992 -Current"
44	Limit 43 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 28 September 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)

#	Searches
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Ovariectomy] explode all trees
#23	(ovariectom* or oophorectom*):ti,ab,kw (Word variations have been searched)
#24	(removal near/3 ovar*):ti,ab,kw (Word variations have been searched)
#25	((radiation or irradiation or radiotherap*) near/3 ovar*):ti,ab,kw (Word variations have been searched)
#26	MeSH descriptor: [Ovary] explode all trees
#27	MeSH descriptor: [Radiation] explode all trees
#28	(ovar* near/3 (suppress* or ablat*)):ti,ab,kw (Word variations have been searched)
#29	#26 and #27
#30	#22 or #23 or #24 or #25 or #28 or #29
#31	#21 and #30
#32	MeSH descriptor: [Luteinizing Hormone] explode all trees
#33	lutein* hormon* releas*:ti,ab,kw (Word variations have been searched)
#34	(LHRH* or LH-RH*):ti,ab,kw (Word variations have been searched)
#35	MeSH descriptor: [Gonadotropin-Releasing Hormone] explode all trees
#36	gonadotrop* releas* hormon*:ti,ab,kw (Word variations have been searched)
#37	(GnRH* or GnRHA*):ti,ab,kw (Word variations have been searched)
#38	(goserelin* or zolade* or novgos or buserelin* or suprefact or suprecur or leuprolid* or leuprorelin* or lupron or nafarelin* or synarel or triptorelin* or decapeptyl or gonapeptyl):ti,ab,kw (Word variations have been searched)
#39	(hormon* near/3 (suppress* or ablat*)):ti,ab,kw (Word variations have been searched)
#40	#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39
#41	#21 and #40
#42	#31 or #41 Publication Year from 1992 to 2016

Literature search strategies for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 March 28**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 29 March 2017.

#	Searches
1	exp breast cancer/ use oemezd
2	exp breast carcinoma/ use oemezd
3	exp medullary carcinoma/ use oemezd
4	exp intraductal carcinoma/ use oemezd
5	exp breast tumor/ use oemezd
6	exp Breast Neoplasms/ use prmz
7	exp "Neoplasms, Ductal, Lobular, and Medullary"/ use prmz
8	Carcinoma, Intraductal, Noninfiltrating/ use prmz
9	Carcinoma, Lobular/ use prmz
10	Carcinoma, Medullary/ use prmz
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12	exp breast/ use oemezd
13	exp Breast/ use prmz
14	breast.tw.
15	12 or 13 or 14
16	(breast adj milk).tw.
17	(breast adj tender$).tw.
18	16 or 17
19	15 not 18
20	exp neoplasm/ use oemezd
21	exp Neoplasms/ use prmz
22	20 or 21
23	19 and 22
24	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
25	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw. use oemezd
26	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
27	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).mp. use prmz
28	exp Paget nipple disease/ use oemezd
29	Paget's Disease, Mammary/ use prmz
30	(paget$ and (breast$ or mammary or nipple$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30

#	Searches
32	11 or 31
33	Tamoxifen/ use prmz
34	tamoxifen/ use oemezd
35	(Nolvadex$ or tamoxifen$).mp.
36	exp Aromatase Inhibitors/ use prmz
37	exp aromatase inhibitor/ use oemezd
38	aromatase inhibitor$.mp.
39	(anastrazol$ or arimidex$ or letrozol$ or femara$ or exemestan$ or aromasin$).mp.
40	exp Selective Estrogen Receptor Modulators/ use prmz
41	Raloxifene Hydrochloride/ use prmz
42	exp selective estrogen receptor modulator/ use oemezd
43	raloxifene/ use oemezd
44	(raloxifen$ or evista$).mp.
45	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44
46	32 and 45
47	exp Primary Prevention/ use prmz
48	exp Chemoprevention/ use prmz
49	exp primary prevention/ use oemezd
50	exp chemoprophylaxis/ use oemezd
51	(chemoprevent$ or chemoprophylax$).tw.
52	(prevent$ adj3 (breast$ adj2 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular))).tw.
53	(prevent$ adj3 (mammar$ adj2 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular))).tw.
54	47 or 48 or 49 or 50 or 51 or 52 or 53
55	46 and 54
56	remove duplicates from 55
57	prevent$.m_titl.
58	46 and 57
59	56 or 58
60	remove duplicates from 59
61	Limit 60 to RCTs and SRs, and general exclusions filter applied

Database: Cochrane Library via Wiley Online

Date of last search: 29 March 2017.

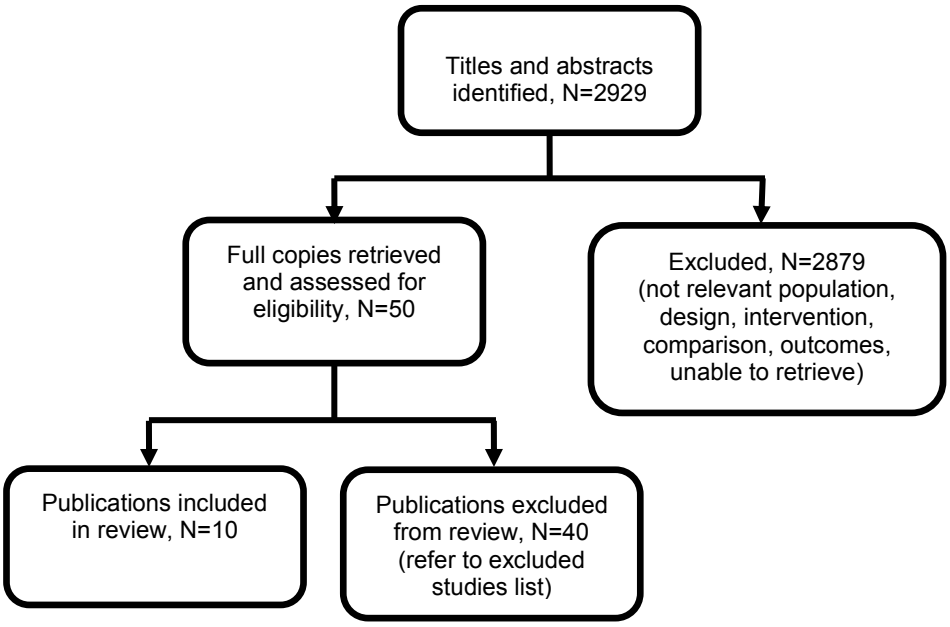
#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	MeSH descriptor: [Neoplasms, Ductal, Lobular, and Medullary] explode all trees
#3	MeSH descriptor: [Carcinoma, Intraductal, Noninfiltrating] explode all trees
#4	MeSH descriptor: [Carcinoma, Lobular] this term only
#5	MeSH descriptor: [Carcinoma, Medullary] this term only
#6	#1 or #2 or #3 or #4 or #5
#7	MeSH descriptor: [Breast] explode all trees

#	Searches
#8	breast:ti,ab,kw (Word variations have been searched)
#9	#7 or #8
#10	(breast next milk):ti,ab,kw (Word variations have been searched)
#11	(breast next tender*):ti,ab,kw (Word variations have been searched)
#12	#10 or #11
#13	#9 not #12
#14	MeSH descriptor: [Neoplasms] explode all trees
#15	#13 and #14
#16	(breast* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#17	(mammar* near/5 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular)):ti,ab,kw (Word variations have been searched)
#18	MeSH descriptor: [Paget's Disease, Mammary] this term only
#19	(paget* and (breast* or mammary or nipple*)):ti,ab,kw (Word variations have been searched)
#20	#15 or #16 or #17 or #18 or #19
#21	#6 or #20
#22	MeSH descriptor: [Aromatase Inhibitors] explode all trees
#23	aromatase inhibitor*:ti,ab,kw (Word variations have been searched)
#24	(anastrazol* or arimidex* or letrozol* or femara* or exemestan* or aromasin*):ti,ab,kw (Word variations have been searched)
#25	MeSH descriptor: [Tamoxifen] this term only
#26	(Nolvadex* or tamoxifen*):ti,ab,kw (Word variations have been searched)
#27	MeSH descriptor: [Selective Estrogen Receptor Modulators] explode all trees
#28	MeSH descriptor: [Raloxifene Hydrochloride] explode all trees
#29	(raloxifen* or evista*):ti,ab,kw (Word variations have been searched)
#30	#22 or #23 or #24 or #25 or #26 or #27 or #28 or #29
#31	#21 and #30
#32	MeSH descriptor: [Primary Prevention] explode all trees
#33	MeSH descriptor: [Chemoprevention] explode all trees
#34	(chemoprevent* or chemoprophylax*):ti,ab,kw (Word variations have been searched)
#35	(prevent* near/3 (breast* near/2 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular))):ti,ab,kw (Word variations have been searched)
#36	(prevent* near/3 (mammar* near/2 (neoplasm* or cancer* or tumo?r* or carcinoma* or adenocarcinoma* or sarcoma* or leiomyosarcoma* or dcis or duct* or infiltrat* or intraduct* or lobul* or medullary or tubular))):ti,ab,kw (Word variations have been searched)
#37	prevent*:ti (Word variations have been searched)
#38	#32 or #33 or #34 or #35 or #36 or #37
#39	#31 and #38

Appendix C – Clinical evidence study selection

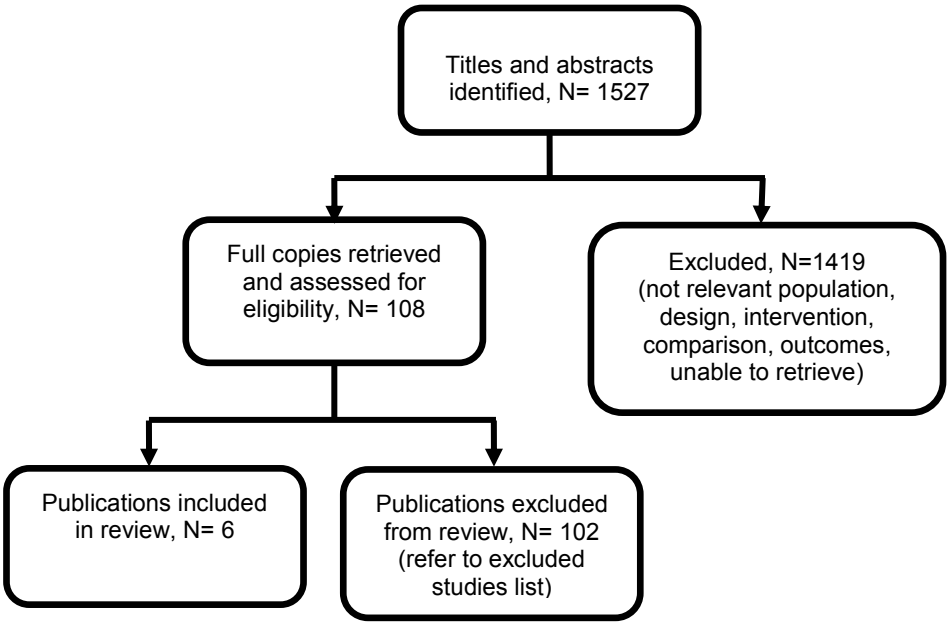
Clinical evidence study selection for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Figure 1: Flow diagram of clinical article selection for duration of endocrine therapy



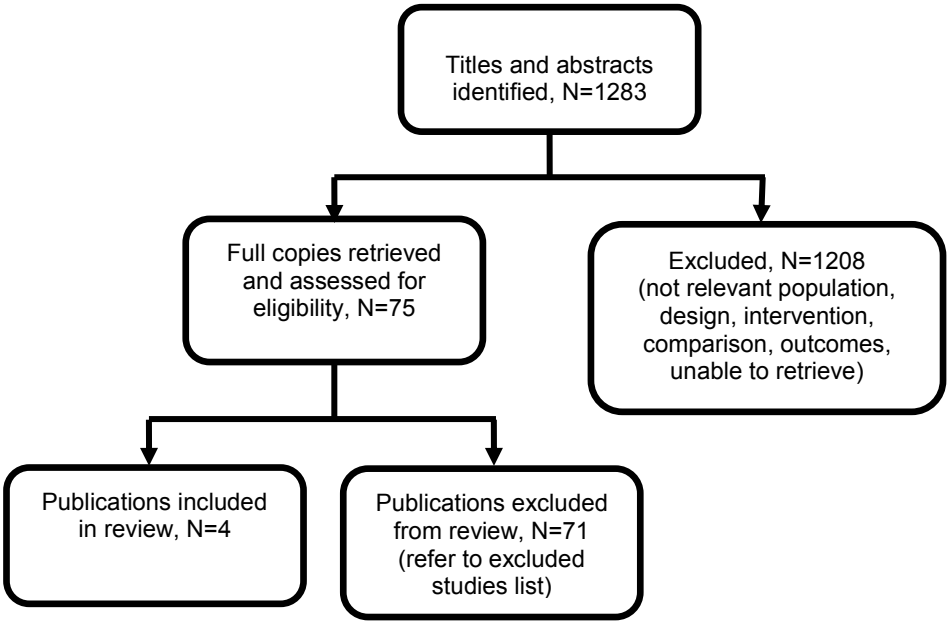
Clinical evidence study selection for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Figure 2: Flow diagram of clinical article selection for ovarian suppression review



Clinical evidence study selection for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Figure 3: Flow diagram of clinical article selection for chemoprevention in DCIS



Appendix D – Clinical evidence tables

Clinical evidence tables for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Table 10: Studies included in the evidence review for duration of endocrine therapy

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Stewart, H. J., Prescott, R. J., Forrest, A. P., Scottish adjuvant tamoxifen trial: a randomized study updated to 15 years, Journal of the National Cancer Institute, 93, 456-62, 2001 **Ref Id** 571870 **Country/ies where the study was carried out** Scotland **Study type** RCT **Aim of the study** To determine if there is a benefit of continuing adjuvant tamoxifen beyond 5 years of treatment. **Study dates**	**Sample size** 342 **Characteristics** Gender: 100% women (taken from Stewart 1996) Age: TAM=5yrs Median 63, Range 36-81; TAM>5yrs Median 64, Range 39-82 (taken from Stewart 1996) Ethnicity: NR **Inclusion criteria** Disease-free after 5 years of continuous tamoxifen therapy. No additional criteria reported but patients in the original trial received a mastectomy and had axillary lymph node clearance (levels I–III) or a lower axillary lymph node sample by which three or four lymph nodes were removed for histologic examination. If sampling indicated involved lymph nodes, patients also had received radiotherapy to the chest wall and to the regional lymph node sites. **Exclusion criteria**	**Interventions** **Intervention arm:** tamoxifen to be taken indefinitely **Control arm:** no endocrine therapy	**Details** **Intervention arm (TAM>5yrs):** 20mg tamoxifen daily to be taken indefinitely (following 5 years of tamoxifen taken during parent trial) **Control arm (TAM=5yrs):** no endocrine therapy (following 5 years of tamoxifen taken during parent trial)	**Results** **DFS (median follow-up 15 years):** O-E: 9.14; V: 29.71 **OS (median follow-up 15 years):** O-E: 8.61; V: 31.02 **Compliance - did not comply with assigned treatment:** TAM>5yrs 2/173; TAM=5yrs 15/169	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Sealed envelopes: Low **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have significant impact: Low **Detection bias** Low **Attrition bias** Missing data for 21 patients - treatment arm not reported: Unclear **Selective reporting** Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Initially recruited to parent trial (to receive tamoxifen immediately or await until disease recurs) April 1978 to September 1984. Disease-free patients were re-randomised to continue or stop tamoxifen after 5 years of treatment between February 1985 and September 1989. **Source of funding** Cancer Research Campaign, the Medical Research Council, ICI Ltd., and the Hartwell Trust Fund	Women entering the parent trial before March 1980 were ineligible, as most had already stopped tamoxifen (taken from Stewart 1996) **Reported subgroups** None of interest				**Indirectness** 39% unknown ER status: serious **Limitations** **Other information** Scottish Adjuvant Tamoxifen Trial
Full citation Goss, P. E., Ingle, J. N., Martino, S., Robert, N. J., Muss, H. B., Piccart, M. J., Castiglione, M., Tu, D., Shepherd, L. E., Pritchard, K. I., Livingston, R. B., Davidson, N. E., Norton, L., Perez, E. A., Abrams, J. S., Cameron, D. A., Palmer, M. J., Pater, J. L., Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17, Journal of the National Cancer Institute, 97, 1262-71, 2005	**Sample size** 5187 randomised - 17 excluded due to non-compliance leaving 5170 **Characteristics** Gender: 100% women Age: Median 62 Ethnicity: 91% Caucasian; 3% Black **Inclusion criteria** Patients must have received prior adjuvant tamoxifen therapy for 4.5–6 years for a histologically confirmed breast cancer that was oestrogen receptor and/or progesterone receptor positive defined as ≥10	**Interventions** **Intervention arm:** letrozole for 5 years **Control arm:** placebo for 5 years	**Details** **Intervention arm (ET>5yrs):** 2.5mg oral letrozole daily for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy) **Control arm (ET=5yrs):** placebo for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy)	**Results** **DFS (4 year follow-up):** O-E: -30.48; V: 55.95 **OS (4 year follow-up):** O-E: -5.63; V: 28.36 **Treatment-related morbidity - hot flashes/flushes (4 year-follow-up):** ET>5yrs 1486/2572; ET=5yrs 1383/2577 **Treatment-related morbidity - hypertension (4 year-follow-**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Double-blind: Low **Detection bias** Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 571978 **Country/ies where the study was carried out** North America and Europe (countries not reported) **Study type** RCT **Aim of the study** To determine whether the aromatase inhibitor letrozole, given after 5 years of tamoxifen, could further decrease the risk of late relapse and improve survival **Study dates** Recruited August 1998 to September 2002 **Source of funding** Canadian Cancer Society through National Cancer Institute of Canada Grant 10362, grants from the National Cancer Institute of the United States (CA31946, CA21115, CA25224, CA38926 and CA32102), and Novartis Pharmaceuticals.	fmol/mg protein by a biochemical assay or positive by immunohistochemical stain or hormone receptor unknown provided an effort was made to determine the receptor status of the primary tumour. **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest			**up):** ET>5yrs 130/2572; ET=5yrs 129/2577 **Treatment-related morbidity - vaginal bleeding (4 year-follow-up):** ET>5yrs 145/2572; ET=5yrs 196/2577 **Treatment-related morbidity - arthralgia (4 year-follow-up):** ET>5yrs 651/2572; ET=5yrs 532/2577 **Treatment-related morbidity - myalgia (4 year-follow-up):** ET>5yrs 380/2572; ET=5yrs 310/2577 **Treatment-related morbidity - vaginal dryness (4 year-follow-up):** ET>5yrs 147/2572; ET=5yrs 129/2577 **Treatment-related morbidity - osteoporosis (4 year-follow-up):** ET>5yrs 209/2561; ET=5yrs 155/2565 **Treatment-related morbidity - bone fracture (4 year-follow-up):** ET>5yrs 137/2561; ET=5yrs 119/2565	**Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information** MA.17

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Treatment-related morbidity - cardiovascular disease (4 year-follow-up): ET>5yrs 149/2561; ET=5yrs 144/2565 **Compliance (discontinued treatment):** ET>5yrs 519/2583; ET=5yrs 502/2587	
Full citation Stewart, H. J., Forrest, A. P., Everington, D., McDonald, C. C., Dewar, J. A., Hawkins, R. A., Prescott, R. J., George, W. D., Randomised comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer. The Scottish Cancer Trials Breast Group, British Journal of Cancer, 74, 297-9, 1996 **Ref Id** 572034 **Country/ies where the study was carried out** Scotland **Study type** RCT	**Sample size** 342 **Characteristics** Gender: 100% women Age: TAM=5yrs Median 63, Range 36-81; TAM>5yrs Median 64, Range 39-82 Ethnicity: NR **Inclusion criteria** Disease-free after 5 years of continuous tamoxifen therapy. No additional criteria reported but patients in the original trial received a mastectomy and had axillary lymph node clearance (levels I–III) or a lower axillary lymph node sample by which three or four lymph nodes were removed for histologic examination. If sampling indicated involved lymph nodes, patients also had received	**Interventions** **Intervention arm:** tamoxifen to be taken indefinitely **Control arm:** no endocrine therapy	**Details** **Intervention arm (TAM>5yrs):** 20mg tamoxifen daily to be taken indefinitely (following 5 years of tamoxifen taken during parent trial) **Control arm (TAM=5yrs):** no endocrine therapy (following 5 years of tamoxifen taken during parent trial)	**Results** **Treatment-related morbidity - any secondary cancer (median 6 year follow-up): TAM>5yrs 18/173; TAM=5yrs 13/169** **Treatment-related morbidity - contralateral breast cancer (median 6 year follow-up): TAM>5yrs 5/173; TAM=5yrs 3/169** **Treatment-related morbidity - endometrial cancer (median 6 year follow-up): TAM>5yrs 4/173; TAM=5yrs 1/169**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Sealed envelopes: Low **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have significant impact: Low **Detection bias** Low **Attrition bias** Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Aim of the study To determine if there is a benefit of continuing adjuvant tamoxifen beyond 5 years of treatment. **Study dates** Initially recruited to parent trial (to receive tamoxifen immediately or await until disease recurs) April 1978 to September 1984. Disease-free patients were re-randomised to continue or stop tamoxifen after 5 years of treatment between February 1985 and September 1989. **Source of funding** Cancer Research Campaign, the Medical Research Council, ICI Ltd., and the Hartwell Trust Fund	radiotherapy to the chest wall and to the regional lymph node sites. **Exclusion criteria** Women entering the parent trial before March 1980 were ineligible, as most had already stopped tamoxifen. **Reported subgroups** None of interest				**Selective reporting** Low **Indirectness** 39% unknown ER status: serious **Limitations** Sample size not adequate to detect small differences between treatment groups. **Other information** Scottish Adjuvant Tamoxifen Trial
Full citation Tormey,D.C., Gray,R., Falkson,H.C., Postchemotherapy adjuvant tamoxifen therapy beyond five years in patients with lymph node-positive breast cancer. Eastern Cooperative Oncology Group, Journal of the National Cancer Institute, 88, 1828-1833, 1996	**Sample size** 194 randomly assigned - 1 subsequently excluded due to recurrence of cancer before randomisation leaving final sample of 193 **Characteristics** Gender: 100% women	**Interventions** **Intervention arm:** tamoxifen continued until relapse **Control arm:** no endocrine therapy	**Details** **Intervention arm (TAM>5yrs):** 10mg tamoxifen twice daily until relapse (following 5 years of 10mg tamoxifen twice daily and 1 year of chemotherapy [at the beginning of tamoxifen treatment]	**Results** **DFS (median follow-up 5.6 years):** O-E: -6.85; V: 7.76 **OS (median follow-up 5.6 years):** O-E: -1.55; V: 5.83	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Telephone calls to central office and sealed envelopes: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 282950 **Country/ies where the study was carried out** North America and South Africa **Study type** RCT **Aim of the study** To investigate the potential benefit of continuing tamoxifen beyond 5 years of treatment **Study dates** Not reported - parent trials initiated in 1982 **Source of funding** Public Health Service grants CA21076, CA21692, CA23318, CA66636, and CA21115 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services	Age: NR Ethnicity: NR **Inclusion criteria** Women who were disease free after treatment with 1 year of chemotherapy plus tamoxifen and 4 additional years of tamoxifen on ECOG protocols E4181 and E5181 were eligible for random assignment. Criteria for entry into the parent E4181 and E5181 studies were: infiltrating carcinomas pathologically less than or equal to 5 cm in diameter, one or more histopathologically involved ipsilateral axillary lymph nodes; a known estrogen receptor (ER) assay; normal hematologic function and biochemical profiles; a normal bone scan; and definitive surgery performed within the preceding 6 weeks. **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest		during the parent trials) **Control arm (TAM=5yrs):** no endocrine therapy (following 5 years of 10mg tamoxifen twice daily and 1 year of chemotherapy [at the beginning of tamoxifen treatment] during the parent trials)	**Treatment related morbidity - any secondary cancer (median follow-up 5.6 years):** TAM>5yrs 3/100; TAM=5yrs 4/93 **Treatment related morbidity - any severe toxicity (median follow-up 5.6 years):** TAM>5yrs 4/100; TAM=5yrs 4/93	**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have significant impact: Low **Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** 27% ER-: serious (none for DFS as this reported separately by ER status) **Limitations** Underpowered - small sample size would not allow detection of therapeutic effect unless there was a major difference **Other information** Parent trials E4181/E5181

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Davies, C., Pan, H., Godwin, J., Gray, R., Arriagada, R., Raina, V., Abraham, M., Medeiros Alencar, V. H., Badran, A., Bonfill, X., Bradbury, J., Clarke, M., Collins, R., Davis, S. R., Delmestri, A., Forbes, J. F., Haddad, P., Hou, M. F., Inbar, M., Khaled, H., Kielanowska, J., Kwan, W. H., Mathew, B. S., Mittra, I., Muller, B., Nicolucci, A., Peralta, O., Pernas, F., Petruzelka, L., Pienkowski, T., Radhika, R., Rajan, B., Rubach, M. T., Tort, S., Urrutia, G., Valentini, M., Wang, Y., Peto, R., Adjuvant Tamoxifen: Longer Against Shorter Collaborative, Group, Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial.[Erratum appears in Lancet. 2013 Mar 9;381(9869):804], Lancet, 381, 805-16, 2013 **Ref Id** 572426 **Country/ies where the study was carried out**	**Sample size** 15,244 randomised - 18 excluded who were entered into the trial in error and 2350 women were excluded who had only completed a median of 2.4 years of adjuvant tamoxifen. This left 12,894 for analysis of side effects - survival outcomes reported for only those patients that were confirmed ER+ (n=6846). **Characteristics** Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria** Women who had had early breast cancer (in which all detected disease could be removed) who had subsequently received tamoxifen and were still on it, or had stopped in the past year, and were clinically free of disease (with any local recurrence removed and no distant recurrence detected). **Exclusion criteria** Any contraindications to continuation of tamoxifen (e.g., pregnancy, breast-feeding, serious toxicity attributed to tamoxifen, life-threatening co-morbidities). **Reported subgroups** None of interest	**Interventions** **Intervention arm:** 5 years of tamoxifen **Control arm:** no endocrine therapy	**Details** **Intervention arm (TAM=10yrs):** 20mg of Nolvadex (tamoxifen) daily for a further 5 years (after a median of 5 years of tamoxifen prior to entry into the trial) resulting in 10 years of tamoxifen treatment. **Control arm (TAM=5yrs):** no endocrine therapy (after a median of 5 years of tamoxifen prior to entry into the trial).	**Results** **DFS (median 7.6 years follow-up):** O-E: -55.27; V: 340.08 **OS (median 7.6 years follow-up):** O-E: -47.7; V: 340.2 **Treatment-related morbidity - any secondary cancer (median 7.6 years follow-up):** TAM=10yrs 838/6454; TAM=5yrs 836/6440 **Treatment-related morbidity - contralateral breast cancer (median 7.6 years follow-up):** TAM=10yrs 419/6454; TAM=5yrs 467/6440 **Treatment-related morbidity - endometrial cancer (median 7.6 years follow-up):** TAM=10yrs 116/6454; TAM=5yrs 63/6440 **Treatment-related morbidity - stroke (median 7.6 years follow-up):** TAM=10yrs 130/6454; TAM=5yrs 119/6440	**Selection bias: random sequence generation** Unclear **Selection bias: allocation concealment** Allocated at regional/national centres: Low **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Rates of loss to follow-up comparable in each arm: Low **Selective reporting** Low **Indirectness** 47% ER-/unknown: serious (none for survival outcomes as this reported separately by ER status)

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
International (36 countries/regions) **Study type** RCT **Aim of the study** To assess the further effects of continuing tamoxifen to 10 years instead of stopping at 5 years. **Study dates** Recruited 1996 to 2005 **Source of funding** Cancer Research UK, UK Medical Research Council, AstraZeneca UK, US Army, EU-Biomed				**Treatment-related morbidity - pulmonary embolus (median 7.6 years follow-up):** TAM=10yrs 41/6454; TAM=5yrs 21/6440 **Treatment-related morbidity - ischemic heart disease (median 7.6 years follow-up):** TAM=10yrs 127/6454; TAM=5yrs 163/6440 **Treatment-related morbidity - bone fracture (median 7.6 years follow-up):** TAM=10yrs 62/6454; TAM=5yrs 70/6440 **Compliance - took allocated treatment for first two years:** TAM=10yrs 5421/6454; TAM=5yrs 6182/6440	**Limitations** **Other information** ATLAS trial
Full citation Fisher,B., Dignam,J., Bryant,J., DeCillis,A., Wickerham,D.L., Wolmark,N., Costantino,J., Redmond,C., Fisher,E.R., Bowman,D.M., Deschenes,L., Dimitrov,N.V., Margolese,R.G., Robidoux,A., Shibata,H., Terz,J., Paterson,A.H.,	**Sample size** 1172 **Characteristics** Gender: 100% women Age: Mean 56 SD 9.5 Ethnicity: 92% white; 4% black	**Interventions** **Intervention arm:** tamoxifen for 5 years **Control arm:** placebo for 5 years	**Details** **Intervention arm (TAM=10yrs):** 10mg of tamoxifen orally twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial)	**Results** **Treatment-related morbidity - hot flashes (4 year follow-up):** TAM=10yrs 222/583; TAM=5yrs 228/569 **Treatment-related morbidity - vaginal discharge (4 year**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Feldman,M.I., Farrar,W., Evans,J., Lickley,H.L., Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors, Journal of the National Cancer Institute, 88, 1529-1542, 1996 **Ref Id** 300619 **Country/ies where the study was carried out** USA and Canada **Study type** RCT **Aim of the study** To determine whether more than 5 years of tamoxifen administration would provide an advantage greater than that observed when administration of the drug was limited to 5 years **Study dates** Recruited to initial trial January 1982 to October 1988 - re-randomised to duration trial between April 1987 and March 1994 **Source of funding**	**Inclusion criteria** Women aged 70 years or younger with ER positive primary operable breast cancer whose axillary lymph nodes were negative on histologic examination. **Exclusion criteria** Discontinued therapy because of side effects of other reasons. Breast tumour recurrence or second primary cancer. **Reported subgroups** None of interest		**Control arm (TAM=5yrs):** placebo twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial)	**follow-up):** TAM=10yrs 82/583; TAM=5yrs 102/569 **Treatment-related morbidity - irregular menstruation (4 year follow-up):** TAM=10yrs 146/583; TAM=5yrs 154/569 **Treatment-related morbidity - phlebitis/thromboembolic events (4 year follow-up):** TAM=10yrs 8/583; TAM=5yrs 1/569	Unclear **Performance bias** Double blind: Low **Detection bias** Low **Attrition bias** 98% had follow-up data available, same number (n=10) without follow-up in both arms: Low **Selective reporting** Low **Indirectness** None **Limitations** Limited to N0 patients - cannot generalise results to those that are node positive **Other information** BA-14 trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Supported by Public Health Service grants U10CA12027, U10CA37377, and U1OCA39O86 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by grant ACS-R-13 from the American Cancer Society.					
Full citation Fisher, B., Dignam, J., Bryant, J., Wolmark, N., Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial, Journal of the National Cancer Institute, 93, 684-90, 2001 **Ref Id** 572675 **Country/ies where the study was carried out** USA and Canada (taken from Fisher 1996) **Study type** RCT **Aim of the study**	**Sample size** 1172 **Characteristics** Gender: 100% women Age: Mean 56 SD 9.5 Ethnicity: 92% white; 4% black **Inclusion criteria** Women with ER positive operable breast cancer and axillary lymph nodes that were determined to be negative on histologic examination. **Exclusion criteria** Discontinued therapy because of side effects of other reasons. Breast tumour recurrence or second primary cancer. **Reported subgroups** None of interest	**Interventions** **Intervention arm:** tamoxifen for 5 years **Control arm:** placebo for 5 years	**Details** **Intervention arm (TAM=10yrs):** 10mg of tamoxifen orally twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial) **Control arm (TAM=5yrs):** placebo twice a day for 5 years (following 10mg of tamoxifen orally twice a day for 5 years during initial trial)	**Results** **DFS (7 year follow-up):** O-E: 16.78; V: 59.76 **OS (7 year follow-up):** O-E: 8.72; V: 23.16 **Treatment-related morbidity - any secondary cancer (7 year follow-up) -** TAM=10yrs 63/583; TAM=5yrs 54/569 **Treatment-related morbidity - contralateral breast cancer (7 year follow-up) -** TAM=10yrs 17/583; TAM=5yrs 20/569 **Treatment-related morbidity - endometrial cancer (7 year**	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Double blind: Low **Detection bias** Low **Attrition bias** 98% had follow-up data available, same number (n=10) without follow-up in both arms: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
To determine whether more than 5 years of tamoxifen administration would provide an advantage greater than that observed when administration of the drug was limited to 5 years **Study dates** Recruited to initial trial January 1982 to October 1988 - re-randomised to duration trial between April 1987 and March 1994 **Source of funding** Public Health Service grants U10CA12027, U10CA69651, U10CA37377, and U10CA69974 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services				**follow-up) -** TAM=10yrs 12/583; TAM=5yrs 6/569 **Compliance - did not complete treatment:** TAM=10yrs 95/583; TAM=5yrs 77/569	**Selective reporting** Low **Indirectness** None **Limitations** **Other information** B-14 trial
Full citation Jakesz, R., Greil, R., Gnant, M., Schmid, M., Kwasny, W., Kubista, E., Mlineritsch, B., Tausch, C., Stierer, M., Hofbauer, F., Renner, K., Dadak, C., Rucklinger, E., Samonigg, H., Austrian, Breast, Colorectal Cancer Study, Group, Extended adjuvant therapy with anastrozole among	**Sample size** 1135 were randomised but informed consent was only obtained for 860, of which 4 were ineligible, leaving final sample of 856 **Characteristics** Gender: 100% women Age: ET=8yrs Median 67.8; ET=5yrs Median 68.5; Range 518-85.5	**Interventions** **Intervention arm:** anastrozole for 3 years **Control arm:** no endocrine therapy	**Details** **Intervention arm (ET=8yrs):** 1mg anastrozole daily for 3 years (commencing within 6 weeks of completing 5 years of adjuvant tamoxifen [40mg daily for 2 years followed by 20mg daily for 3	**Results** **Whole sample:** **DFS (median follow-up 62 months):** O-E: -9.58; V: 20.05 **OS (median follow-up 62 months):** O-E: -2.66; V: 22.84	**Selection bias: random sequence generation** Computer-assisted minimisation: Low **Selection bias: allocation concealment** Randomisation occurred before informed consent was obtained: High

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
postmenopausal breast cancer patients: results from the randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a.[Erratum appears in J Natl Cancer Inst. 2008 Feb 6;100(3):226], Journal of the National Cancer Institute, 99, 1845-53, 2007 **Ref Id** 572716 **Country/ies where the study was carried out** Austria **Study type** RCT **Aim of the study** To investigate the efficacy of extended adjuvant therapy with anastrozole in breast cancer patients who remain recurrence free after 5 years of adjuvant tamoxifen **Study dates** Not reported **Source of funding** AstraZeneca.	Ethnicity: NR **Inclusion criteria** Post-menopausal women who had had surgical treatment (BCS or modified radical mastectomy with negative margins + ANC) for histologically confirmed ER and/or PR positive stage I or stage II breast cancer. **Exclusion criteria** Excluded if an evidence of metastatic disease or had previous malignant disease (except cured squamous cell skin carcinoma and early-stage cervical cancer). Other exclusion criteria included preoperative antineoplastic treatment and irradiation, general contraindications including hypersensitivity to tamoxifen or aminoglutethimide, more than 4 weeks between randomization and start of treatment, inflammatory breast cancer, serious comorbid disease rendering treatment impossible as per protocol, Karnofsky Index greater than 3, aged greater than 80 years and bilateral oophorectomy/radiotherapy to ovaries. **Reported subgroups** Grade 3		years] during original trial ABCSG6) **Control arm (ET=5yrs):** no further treatment (following 5 years of adjuvant tamoxifen [40mg daily for 2 years followed by 20mg daily for 3 years] during original trial ABCSG6)	**Treatment-related morbidity - fracture (median follow-up 2 months):** ET=8yrs 3/387; ET=5yrs 5/469 **Treatment-related morbidity - myocardial infarction (median follow-up 2 months):** ET=8yrs 1/387; ET=5yrs 0/469 **Treatment-related morbidity - thrombosis/embolism (median follow-up 2 months):** ET=8yrs 3/387; ET=5yrs 1/469 **Treatment-related morbidity - hot flushes (median follow-up 2 months):** ET=8yrs 151/387; ET=5yrs 105/469 **Treatment-related morbidity - vaginal bleeding (median follow-up 2 months):** ET=8yrs 3/387; ET=5yrs 1/469 **Treatment-related morbidity - vaginal dryness (median follow-up 2 months):** ET=8yrs 45/387; ET=5yrs 32/469	**Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** Follow-up data was missing for 1 patient in the intervention arm and 3 in the control arm: Low **Selective reporting** Low **Indirectness** Roughly 6% were ER- or unknown ER status: Low **Limitations** A prerandomization procedure was used to randomly assign all eligible patients in ABCSG Trial 6 (i.e., all those who remained in the trial and disease free) to an arm of Trial 6a to ensure that there would be no gap in treatment between completion of 5 years of

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Treatment-related morbidity - vaginal discharge (median follow-up 2 months): ET=8yrs 23/387; ET=5yrs 13/469 **Treatment-related morbidity - bone pain/arthralgia (median follow-up 2 months):** ET=8yrs 95/387; ET=5yrs 86/469 **Grade 3:** **DFS (median follow-up 62 months):** O-E: -1.41; V: 4.47	primary adjuvant therapy and commencement of the extended study. Limited to post-menopausal so cannot draw conclusions about benefit of extended adjuvant endocrine therapy in premenopausal patients. **Other information** ABCSG Trial 6a
Full citation Muss, H. B., Tu, D., Ingle, J. N., Martino, S., Robert, N. J., Pater, J. L., Whelan, T. J., Palmer, M. J., Piccart, M. J., Shepherd, L. E., Pritchard, K. I., He, Z., Goss, P. E., Efficacy, toxicity, and quality of life in older women with early-stage breast cancer treated with letrozole or placebo after 5 years of tamoxifen: NCIC CTG intergroup trial MA.17, Journal of clinical oncology, 26, 1956-64, 2008	**Sample size** 5187 randomised - 17 excluded due to non-compliance leaving 5170. HRQoL data limited to those aged 70 years or older - 24 month data available for 413 **Characteristics** Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm:** letrozole for 5 years **Control arm:** placebo for 5 years	**Details** **Intervention arm (ET>5yrs):** 2.5mg oral letrozole daily for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy) **Control arm (ET=5yrs):** placebo for 5 years (following 4.5-6 years of adjuvant tamoxifen therapy)	**Results** **HRQoL - change in SF-36 physical health scores from baseline (2 year follow-up):** ET>5yrs N=211, M=-1.5, SD=8; ET=5yrs N=171, M=-2.5, SD=9 **HRQoL - change in SF-36 mental health scores from baseline (2 year follow-up):** ET>5yrs N=211, M=-2.8, SD=9; ET=5yrs N=171, M=-2.2, SD=9	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Double blind: Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Ref Id 572803 **Country/ies where the study was carried out** North America and Europe (countries not reported) **Study type** RCT **Aim of the study** Main trial: to determine the efficacy of letrozole in preventing disease recurrence in postmenopausal women with primary breast cancer who had completed about 5 years (range, 4.5 to 6 years) of adjuvant tamoxifen. HRQoL study: to conduct an extensive quality-of-life (QOL) assessment to further explored the effects of AI therapy on other important survivorship domains in addition to standard toxicity grading. **Study dates** Recruited August 1998 to September 2002	Patients must have received prior adjuvant tamoxifen therapy for 4.5–6 years for a histologically confirmed breast cancer that was oestrogen receptor and/or progesterone receptor positive defined as ≥10 fmol/mg protein by a biochemical assay or positive by immunohistochemical stain or hormone receptor unknown provided an effort was made to determine the receptor status of the primary tumour. Eligibility for the QOL substudy included willingness to complete QOL questionnaires before randomization and fluency in English or French. **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest			**HRQoL - change in MENQOL vasomotor scores from baseline (2 year follow-up):** ET>5yrs N=209, M=0.1, SD=1.3; ET=5yrs N=177, M=-0.3, SD=1.2 **HRQoL - change in MENQOL psychosocial scores from baseline (2 year follow-up):** ET>5yrs N=209, M=0.1, SD=1.0; ET=5yrs N=170, M=0.2, SD=1.1 **HRQoL - change in MENQOL physical scores from baseline (2 year follow-up):** ET>5yrs N=208, M=0.1, SD=1.0; ET=5yrs N=178, M=0.1, SD=1.1 **HRQoL - change in MENQOL sexual scores from baseline (2 year follow-up):** ET>5yrs N=152, M=0.0, SD=1.3; ET=5yrs N=111, M=-0.2, SD=1.0	**Detection bias** Low **Attrition bias** Low **Selective reporting** Low **Indirectness** None **Limitations** Limited to those aged over 70 years - cannot draw conclusions about HRQoL in younger populations, which may be expected to differ. **Other information** MA.17

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding Canadian Cancer Society through National Cancer Institute of Canada Grant 10362, grants from the National Cancer Institute of the United States (CA31946, CA21115, CA25224, CA38926 and CA32102), and Novartis Pharmaceuticals. (taken from Goss 2005)					
Full citation Mamounas, E. P., Jeong, J. H., Wickerham, D. L., Smith, R. E., Ganz, P. A., Land, S. R., Eisen, A., Fehrenbacher, L., Farrar, W. B., Atkins, J. N., Pajon, E. R., Vogel, V. G., Kroener, J. F., Hutchins, L. F., Robidoux, A., Hoehn, J. L., Ingle, J. N., Geyer, C. E., Jr., Costantino, J. P., Wolmark, N., Benefit from exemestane as extended adjuvant therapy after 5 years of adjuvant tamoxifen: intention-to-treat analysis of the National Surgical Adjuvant Breast And Bowel Project B-33 trial, Journal of clinical oncology, 26, 1965-71, 2008 **Ref Id** 573204	**Sample size** 1,598 randomly assigned - 1,577 were eligible **Characteristics** Gender: 100% women Age: NR Ethnicity: NR **Inclusion criteria** Post-menopausal women who had received tamoxifen for 57-66 months for T1-3, N0-1, M0 ER and/or PR positive invasive breast cancer. Had to be disease-free at random assignment and the interval between tamoxifen completion and random assignment had to be less than 180 days. Original surgical treatment	**Interventions** **Intervention arm:** exemestane for 5 years **Control arm:** placebo for 5 years	**Details** **Intervention arm (ET=10yrs):** no further details reported (following approximately 5 years of tamoxifen) **Control arm (ET=5yrs):** no further details reported (following approximately 5 years of tamoxifen)	**Results** **DFS (median follow-up 30 months):** O-E: -8.34; V: 21.62 **Treatment-related morbidity - any grade 3+ toxicity (median follow-up 30 months):** ET=10yrs 78/783; ET=5yrs 55/779 **Treatment-related morbidity - grade 3+ arthralgia (median follow-up 30 months):** ET=10yrs 8/783; ET=5yrs 4/779 **Treatment-related morbidity - fractures (median follow-up 30 months):** ET=10yrs 28/783; ET=5yrs 20/779	**Selection bias: random sequence generation** biased-coin minimisation: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Initially double blinded, but knowing condition is unlikely to have a significant impact: Low **Detection bias** Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Not reported **Study type** RCT **Aim of the study** The primary aim of the trial was to determine whether adjuvant exemestane after 5 years of tamoxifen would prolong disease-free survival (DFS). Secondary aims were to determine whether adjuvant exemestane would prolong overall survival (OS) and relapse-free survival (RFS) and to evaluate the effect of exemestane and of tamoxifen withdrawal on bone mineral density, blood lipid profile, and quality of life (QOL). **Study dates** Recruited May 2001 to October 2003 **Source of funding** Public Health Service Grants No. U10CA-12027, U10CA-69974, U10CA-37377, and U10CA-69651 from the	could have been lumpectomy or mastectomy with either axillary dissection or sentinel node biopsy. Prior adjuvant or neoadjuvant chemotherapy was allowed. Post lumpectomy breast radiotherapy was required but other types of locoregional radiotherapy were optional. **Exclusion criteria** Inadequate hematologic, hepatic and/or renal function **Reported subgroups** None of interest				**Attrition bias** Follow-up data was missing for 15 people - treatment arms not reported: Low **Selective reporting** Bone mineral density and blood lipid data not reported. HRQoL data not reported in sufficient detail: High **Indirectness** Roughly 6% were ER- or unknown ER status: Low **Limitations** In response to interim results from MA.17, accrual to the trial was stopped, treatment was unblended and patients in the placebo group were offered exemestane - 44% of those in the placebo condition swapped arms. Limited to post-menopausal patients so results do not generalise to those pre-menopausal. Stopping accrual early meant that the study was underpowered to detect the expected reduction in DFS. **Other information** B-33 trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
National Cancer Institute, Department of Health and Human Services; and by the Pharmacia Corporation, a Pfizer Company, New York, NY.					

ABCSG, Austrian Breast and Colorectal Cancer Study Group; ANC, axillary node clearance; ATLAS, Adjuvant Tamoxifen Longer Against Shorter; BCS, breast conserving surgery; DFS, disease-free survival; ER, oestrogen receptor; ET, endocrine therapy; HRQoL, health-related quality of life; NR, not reported; OS, overall survival; PR, progesterone receptor; QoL, quality of life; RCT, randomised controlled trial; TAM, tamoxifen

Clinical evidence tables for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Table 11: Studies included in the evidence review for ovarian suppression

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Adjuvant Breast Cancer Trials Collaborative, Group, Ovarian ablation or suppression in premenopausal early breast cancer: results from the international adjuvant breast cancer ovarian ablation or suppression randomized trial, Journal of the National Cancer Institute, 99, 516-25, 2007 **Ref Id** 537805 **Country/ies where the study was carried out** UK, India, Iran, Sri Lanka, Egypt, Malta, Saudi Arabia, New Zealand, Pakistan, Singapore **Study type** RCT **Aim of the study** To identify the added benefits of prescribing ovarian ablation or suppression in addition to	**Sample size** 2144 randomised - 10 subsequently deemed ineligible (7 in OFS+TAM arm and 3 in TAM arm) Only interest in ER+ (N=838) group **Characteristics** Whole sample (NR separately for ER+): Gender: 100% women Age: range NR; mean 43.2 SD 5.7 Ethnicity: NR **Inclusion criteria** Eligible patients were women who were pre- or peri-menopausal with histologically confirmed early-stage operable (T1-3a N0-1 M0) invasive breast cancer. **Exclusion criteria** Patients could have had no previous malignancy (except cervical cancer in situ or basal	**Interventions** Intervention arm: tamoxifen + ovarian suppression (with or without chemotherapy) Control arm: tamoxifen (with or without chemotherapy)	**Details** **Intervention arm (TAM+OFS):** Tamoxifen (20 mg/day) was prescribed for a minimum of 5 years in all patients starting within 4 weeks of primary surgery and concurrently with chemotherapy, if given. The method of achieving ovarian ablation or suppression was at the clinician's discretion but was to be according to center policy and declared before randomization. For radiation-induced menopause, 1600 cGy in four fractions was to be delivered to the midplane by the anteroposterior fields of the pelvis after ultrasound localization of the ovaries. If LH-RH agonists were to be used, goserelin (Zoladex) at 3.6 mg or leuprorelin acetate (Prostap SR) at 3.75 mg was recommended every 28 days for at least 2 years. **Control arm (TAM):** Tamoxifen (20 mg/day) was prescribed for a minimum of 5 years in all	**Results** **OS - ER+ patients [N=838] (Median follow-up 5.9 years; interquartile range 4.2 - 7.7):** O-E: -5.32; V: 30.49	**Selection bias: random sequence generation** Permuted blocks: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low **Attrition bias** High: 122 deviated from treatment in TAM+OFS arm compared with 22 in TAM arm

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
prolonged tamoxifen or prolonged tamoxifen accompanied by chemotherapy in pre- and peri-menopausal women with early breast cancer. **Study dates** Recruited 1993 - 2000 **Source of funding** Supported by grants from Cancer Research UK and the Medical Research Council, which played no role in the study design, analysis or interpretation of the data, writing of the manuscript, or the decision to submit the manuscript for publication.	cell carcinoma) and no previous systemic therapy for their current breast cancer and had to be available for follow-up. **Reported subgroups** None of interest		patients starting within 4 weeks of primary surgery and concurrently with chemotherapy, if given.		**Selective reporting** Low **Indirectness** Population: 39% confirmed ER+; 80% receiving chemotherapy (although comparable levels in each arm): very serious **Limitations** Probability of chemotherapy-induced castration in a majority of patients, which may have precluded the identification of an ovarian ablation or suppression associated benefit. 11% of patients did not receive ovarian ablation as allocated may result in slight underestimate of effect. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					ABC Ovarian Ablation or Suppression Trial
Full citation Baum, M., Hackshaw, A., Houghton, J., Rutqvist,, Fornander, T., Nordenskjold, B., Nicolucci, A., Sainsbury, R., Zipp International Collaborators Group, Adjuvant goserelin in pre-menopausal patients with early breast cancer: Results from the ZIPP study, European journal of cancer, 42, 895-904, 2006 **Ref Id** 537868 **Country/ies where the study was carried out** UK, Italy, Sweden **Study type** RCT **Aim of the study** To determine whether goserelin with or without tamoxifen offered any additional benefit to standard therapy in the management of premenopausal breast cancer.	**Sample size** Total sample size 2710 Only interested in those that are ER+ in the tamoxifen only (N=467) and tamoxifen + goserelin (N=433) arms. **Characteristics** Whole sample (NR separately for groups of interest): Gender: 100% women Age: range <50 (lower limit NR); mean NR Ethnicity: NR **Inclusion criteria** Pre-menopausal women with invasive operable stage I or stage II breast cancer confined to one breast, regardless of ER status. No evidence of distant metastases and normal liver function, renal function and full blood count. **Exclusion criteria** Received hormonal therapy in the 6 weeks prior to joining the trial; unfit for surgery; severely	**Interventions** Intervention arm: tamoxifen + goserelin (with or without chemotherapy) Control arm: tamoxifen (with or without chemotherapy)	**Details** **Intervention arm (TAM+GOS):** Oral tamoxifen (20 or 40mg daily) and goserelin 3.6mg subcutaneous injection into abdominal wall - 2 year duration in Italian and Swedish trial, duration NR in UK trials. **Control arm (TAM):** Oral tamoxifen (20 or 40mg daily - 2 year duration in Italian and Swedish trial, duration NR in UK trials)	**Results** **OS - ER+ patients [N=900] (Median follow-up 5.5 years):** O-E: -4.38; V: 26.97 **Treatment-related morbidity from CRUK trial only (not limited to ER+)** **Treatment-related morbidity - vasodilation (measurement NR; follow-up NR):** TAM+GOS: 200/457; TAM: 78/463 **Treatment-related morbidity - weight gain (measurement NR; follow-up NR):** TAM+GOS: 50/457; TAM: 32/463 **Treatment-related morbidity - arthralgia (measurement NR; follow-up NR):** TAM+GOS: 11/457; TAM: 4/463 **Treatment-related morbidity - anxiety/depression/irritability (measurement NR; follow-up NR):** 26/457; 10/463	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low for OS; High for PROs **Attrition bias** Not reported: Unclear **Selective reporting**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study dates Recruited August 1987 - March 1999 **Source of funding** UK: grant from CRUK Italy: grant from AstraZeneca Sweden: King Gustaf V Jubilee Fund and AstraZeneca	limited life expectancy as a result of intercurrent illness; previously received treatment for other malignancies (with the exception of basal or squamous cell carcinoma of the skin or adequately biopsied in situ carcinoma of the cervix); primary carcinoma fixed to underlying muscle/chest wall or was ulcerated, had skin infiltration or axillary nodes that demonstrated deep fixity; unwilling/unable to attend treatment and long-term follow-up. **Reported subgroups** None of interest			**Treatment-related morbidity - sweating (measurement NR; follow-up NR):** 23/457; 5/463	Low **Indirectness** Population: unclear what proportion of patients in groups of interest were also receiving chemotherapy: serious **Limitations** Lack of information regarding study procedure due to combination of four trials. **Other information** ZIPP trial
Full citation Francis, P. A., Regan, M. M., Fleming, G. F., Lang, I., Ciruelos, E., Bellet, M., Bonnefoi, H. R., Climent, M. A., Da Prada, G. A., Burstein, H. J., Martino, S., Davidson, N. E., Geyer, C. E., Jr., Walley, B. A., Coleman, R., Kerbrat, P., Buchholz, S., Ingle, J. N., Winer, E. P., Rabaglio-Poretti, M., Maibach, R., Ruepp, B., Giobbie-Hurder, A., Price, K. N., Colleoni, M., Viale, G., Coates, A. S., Goldhirsch, A., Gelber, R.	**Sample size** 3066 randomised - 19 subsequently withdrew consent (3 in TAM, 9 in TAM+OFS, 7 in EXE+OFS) Only interested in TAM (N=1021) and TAM+OFS (N=1024) arms **Characteristics** Gender: 100% women Age: Median 43; range NR Ethnicity: NR	**Interventions** **Intervention arm:** tamoxifen + ovarian suppression **Control arm:** tamoxifen only	**Details** **Intervention arm (TAM + OFS):** Oral tamoxifen at a dose of 20 mg daily and ovarian suppression by triptorelin (Decapeptyl Depot [triptorelin acetate], Ipsen; or Trelstar Depot [triptorelin pamoate], Debio) at a dose of 3.75 mg administered by means of intramuscular injection every 28 days, bilateral oophorectomy, or bilateral ovarian irradiation. Patients receiving triptorelin could subsequently opt to undergo	**Results** **Whole sample:** **DFS (5 year follow-up):** O-E: -13.85 ; V: 74.31 **OS (5 year follow-up):** O-E: -8.02; V: 26.64 **Treatment related morbidity - hot flushes (grade 3+ on Common Terminology Criteria for Adverse**	**Selection bias: random sequence generation** IBCSG Internet-based system - cannot find details of this: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
D., Soft Investigators, International Breast Cancer Study, Group, Adjuvant ovarian suppression in premenopausal breast cancer, New England Journal of MedicineN Engl J Med, 372, 436-46, 2015 **Ref Id** 538140 **Country/ies where the study was carried out** International (27 countries) **Study type** RCT **Aim of the study** Evaluate adjuvant endocrine therapy in women who remained premenopausal after the completion of adjuvant or neoadjuvant chemotherapy and for whom adjuvant tamoxifen alone was considered suitable treatment **Study dates** Recruited December 2003 - January 2011 **Source of funding** Funded by Pfizer and others	**Inclusion criteria** Eligibility criteria included documented premenopausal status, operable breast cancer, and tumor that expressed estrogen or progesterone receptors in at least 10% of the cells. Patients had to have undergone either a total mastectomy with subsequent optional radiotherapy or breast-conserving surgery with subsequent radiotherapy. Either axillary dissection or a sentinel-node biopsy was required **Exclusion criteria** No additional criteria reported **Reported subgroups** Age (<35/35-39/40+ [40-44, 45-49 & 50+ subgroups combined]) Grade (1/2/3) HER2 status (+/-) Previous chemotherapy (Yes/No)		oophorectomy or irradiation. Treatment duration 5 years. **Control arm (TAM):** Oral tamoxifen at a dose of 20 mg daily for five years.	**Events, version 3.0; median follow-up 67 months):** TAM+OFS: 133/1005; TAM: 76/1006 **Treatment related morbidity - depression (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 44/1005; TAM: 38/1006 **Treatment related morbidity - hypertension (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 75/1005; TAM: 54/1006 **Treatment related morbidity - cardiac ischemia or infarction (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 1/1005; TAM: 4/1006 **Treatment related morbidity - thrombosis or embolism (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 17/1005; TAM: 17/1006 **Treatment related morbidity - musculoskeletal symptoms (grade 3+ on**	Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low for survival outcomes; high for PROs **Attrition bias** Similar rates of participants never started treatment & withdrew consent but higher loss to follow-up in TAM+OFS (N=32) compared with TAM only (N=52): High **Selective reporting** Low **Indirectness** Population: 98% were ER+: not serious **Limitations** Longer follow-up is required, because SOFT is currently

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months): TAM+OFS: 55/1005; TAM: 63/1006 **Treatment related morbidity - osteoporosis (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 3/1005; TAM: 1/1006 **Treatment related morbidity - fractures (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 8/1005; TAM: 8/1006 **Treatment related morbidity - vaginal dryness (measured using Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 500/1005; TAM: 421/1006 **Treatment related morbidity - libido decrease (measured using Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 477/1005; TAM: 427/1006 **Treatment related morbidity - CNS cerebrovascular ischemia (grade 3+ on Common Terminology Criteria for**	underpowered, and the overall survival analysis is premature after 5% of patients have died. **Other information** SOFT trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				Adverse Events, version 3.0; median follow-up 67 months): TAM+OFS: 1/1005; TAM: 4/1006 **Treatment related morbidity - CNS hemorrhage (grade 3+ on Common Terminology Criteria for Adverse Events, version 3.0; median follow-up 67 months):** TAM+OFS: 1/1005; TAM: 0/1006 **Age - <35:** **DFS (5 year follow-up):** O-E: -6.08; V: 15.78 **Age - 35-39:** **DFS (5 year follow-up):** O-E: -4.43; V: 17.82 **Age - 40+ (calculated using fixed effects meta-analysis of 40-44, 45-49 and 50+ groups):**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				DFS (5 year follow-up): O-E: -4.29; V: 40.71 **Grade - 1:** **DFS (5 year follow-up):** O-E: 2.06; V: 9.93 **Grade - 2:** **DFS (5 year follow-up):** O-E: -13.20; V: 32.97 **Grade - 3:** **DFS (5 year follow-up):** O-E: -4.63; V: 28.47 **HER-2 status - positive:**	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
				DFS (5 year follow-up): O-E: -8.00; V: 9.22 **HER-2 status - negative:** **DFS (5 year follow-up):** O-E: -8.07; V: 63.15 **Previous chemotherapy - yes:** **DFS (5 year follow-up):** O-E: -11.54; V: 58.17 **OS (5 year follow-up):** O-E: -10.03; V: 22.48 **Previous chemotherapy - no:** **DFS (5 year follow-up):** O-E: -3.20; V: 17.15 **OS (5 year follow-up):** O-E: 2.14; V: 1.59	

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Nystedt,M., Berglund,G., Bolund,C., Fornander,T., Rutqvist,L.E., Side effects of adjuvant endocrine treatment in premenopausal breast cancer patients: a prospective randomized study, Journal of Clinical Oncology, 21, 1836-1844, 2003 **Ref Id** 254564 **Country/ies where the study was carried out** Sweden **Study type** RCT **Aim of the study** To compare the effect of adjuvant endocrine therapies with and without chemotherapy on physical symptoms, anxiety, and depressive symptoms in premenopausal women with breast cancer in a randomized clinical trial (the Zoladex in Premenopausal Patients trial). **Study dates**	**Sample size** Total sample size 408 Only interested in those that did not have concurrent chemotherapy in the tamoxifen only (N=35) and tamoxifen + goserelin (N=39) arms. **Characteristics** Whole sample (NR separately for groups of interest) Gender: 100% women Age: Mean NR; Range 29-55 Ethnicity: NR **Inclusion criteria** Premenopausal women (last menstruation 6 months from the start of the study) with invasive breast cancer, post primary surgery. **Exclusion criteria** No additional criteria reported **Reported subgroups** None of interest	**Interventions** Intervention arm: Tamoxifen + goserelin Control arm: Tamoxifen only	**Details** 2 years of endocrine therapy in both groups; details not reported (see Baum 2006)	**Results** **Treatment-related morbidity - vasomotor symptoms (measured by modified version of Physical Symptoms and Problem List; follow-up 36 months):** TAM+GOS N=32, M=0.68, SD=1.23; TAM N=28, M=0.58, SD=0.91 **Treatment-related morbidity - vaginal dryness (measured by modified version of Physical Symptoms and Problem List; follow-up 36 months):** TAM+GOS N=33, M=0.45, SD=0.87; TAM N=30, M=0.40, SD=0.62	**Selection bias: random sequence generation** Permuted blocks: Low **Selection bias: allocation concealment** Patient identifiers were recorded before the allocated treatment was revealed to the responsible physician: Low **Selection bias: overall judgement** Low **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** High **Attrition bias** Overall rates of attrition reported but not differences between groups: Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
October 1990 - June 1994 **Source of funding** Supported by the Cancer Society of Stockholm and the King Gustav V Jubilee Fund					**Selective reporting** Unclear: anxiety & depression outcomes not reported in sufficient detail for analysis **Indirectness** Population: unclear what proportion are ER+: serious **Limitations** Those that did not have chemotherapy were node-negative, so may be lower risk than some patient groups. At the time of the initiation of the trial, 2 years of adjuvant tamoxifen was a standard duration at most centers in Europe. However, 5 years of tamoxifen therapy has now become the accepted standard worldwide. This change may impact the duration of symptoms among patients receiving tamoxifen, particularly because

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					the recommended duration of goserelin treatment ranges between 2 and 5 years. This might change the relative impact of the two treatments on physical symptoms in those not receiving chemotherapy, so the current result should be evaluated against this background. **Other information** Subset of patients included in ZIPP trial (Baum 2006) - Stockholm patients only
Full citation Sverrisdottir, A., Fornander, T., Jacobsson, H., von Schoultz, E., Rutqvist, L. E., Bone mineral density among premenopausal women with early breast cancer in a randomized trial of adjuvant endocrine therapy, Journal of clinical oncology, 22, 3694-9, 2004 **Ref Id** 538771	**Sample size** 89 but only interested in TAM+GOS (N=14) and TAM (N=18) arms **Characteristics** Gender: 100% women Age: Mean 45, Range NR Ethnicity: NR **Inclusion criteria** Invasive breast cancer, premenopausal menstrual	**Interventions** Intervention arm: tamoxifen + goserelin Control arm: tamoxifen only	**Details** **Intervention arm (TAM+GOS):** The dose of tamoxifen was 40 mg/d orally and the dose of goserelin was 3.6 mg subcutaneously every 28 days. The treatment duration for both tamoxifen and goserelin was 2 years. **Control arm (TAM):** The dose of tamoxifen was	**Results** **Change in TBBD between 24 months and baseline (g/cm^2):** TAM+GOS N=14, M=-0.015, LCI=-0.027, UCI=-0.003, p=0.02; TAM N=18, M=-0.018, LCI=-0.026, UCI=-0.010, p<0.001	**Selection bias: random sequence generation** Permuted blocks: Low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out Sweden **Study type** RCT **Aim of the study** Sub-protocol of ZIPP study to detect changes in bone mass of clinical significance for long-term survivors **Study dates** October 1990 - June 1994 **Source of funding** King Gustaf V Jubilee Fund and AstraZeneca	status, primary surgery consisting of a mastectomy or lumpectomy plus axillary node dissection, histopathologic tumor size greater than 10 mm, and no clinical evidence of distant metastases. Only patients from the strata not receiving chemotherapy were eligible for the bone mineral study. **Exclusion criteria** The exclusion criteria were inoperable breast cancer, prior radiotherapy or neoadjuvant chemotherapy, and prior or concurrent endocrine therapy. **Reported subgroups** None of interest		40mg/d orally and treatment lasted 2 years. **Bone densitrometry:** carried out before initiation of treatment and at 12, 24, and 36 months later. Total-body bone density (TBBD) measured by dual-energy x-ray absorptiometry using a Lunar DPX-L device (Luncar Corporation, Madison, WI).		**Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low risk **Attrition bias** Overall attrition high but numbers in each group not reported: Unclear **Selective reporting** Low **Indirectness** Population: 29% of TAM+GOS arm and 11% of TAM arm ER-: very serious **Limitations** Data on possible confounders such as smoking, calcium intake, and physical exercise were unavailable. Short follow-up period in comparison to

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
					current endocrine therapy standards. **Other information** ZIPP trial
Full citation Tevaarwerk, A. J., Wang, M., Zhao, F., Fetting, J. H., Cella, D., Wagner, L. I., Martino, S., Ingle, J. N., Sparano, J. A., Solin, L. J., Wood, W. C., Robert, N. J., Phase III comparison of tamoxifen versus tamoxifen plus ovarian function suppression in premenopausal women with node-negative, hormone receptor-positive breast cancer (E-3193, INT-0142): A trial of the eastern cooperative oncology group, Journal of Clinical Oncology, 32, 3948-3958, 2014 **Ref Id** 404986 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study**	**Sample size** 345 randomised - 8 subsequently deemed ineligible (4 in each arm) **Characteristics** Gender: 100% women Age: range 26-55; mean NR Ethnicity: 91% Caucasian; 5% Black **Inclusion criteria** Eligible patients were premenopausal women with node-negative, ER+ and/or PR+ primary invasive breast cancer (tumours had to be ≤3cm in diameter) **Exclusion criteria** Patients could not have received prior systemic therapy (except ≤12 weeks of tamoxifen).	**Interventions** Intervention arm: tamoxifen + ovarian suppression Control arm: tamoxifen only	**Details** **Intervention arm (TAM +OFS):** 20mg oral tamoxifen per day for 5 years. OFS was according to patient/physician choice between: 1) LHRH analog goserelin 3.6 mg depot every 4 weeks for 5 years (within 4 weeks of random assignment), 2) LHRH analog leuprolide acetate 3.75mg every 4 weeks for 5 years (within 4 weeks of random assignment), 3) surgical ablation (within 12 weeks of random assignment), or 4) ovarian ablation radiation (20gy in 10 fractions within 12 weeks of random assignment). No dose reductions permitted **Control arm (TAM):** 20mg oral tamoxifen per day for 5 years Other adjuvant systemic therapies including chemotherapy were not permitted.	**Results** **DFS (median follow-up 9.9 years; range 0.2 - 12.3 years):** O-E: -1.64; V: 11.06 **Treatment-related morbidity - hot flashes (grade 3+ on National Cancer Institute Common Toxicity Criteria, version 1; follow-up NR):** TAM+OFS: 28/174; TAM: 8/171 **Treatment-related morbidity - neuropsychiatric inc. anxiety & depresison (grade 3+ on National Cancer Institute Common Toxicity Criteria, version 1; follow-up NR):** TAM+OFS: 4/174; TAM: 4/171 **Treatment-related morbidity - weight gain (grade 3+ on National Cancer Institute Common Toxicity Criteria, version 1; follow-up NR):** TAM+OFS: 6/174; TAM: 4/171 **Treatment-related morbidity - vaginal dryness (grade 3+ on National Cancer Institute Common Toxicity Criteria,**	**Selection bias: random sequence generation** Permuted blocks: low **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have a significant impact: Low **Detection bias** Low for survival outcomes; high for PROs **Attrition bias** Attrition high, but similar in both arms: Unclear

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Phase III trial comparing tamoxifen versus tamoxifen plus OFS in premenopausal women with node-negative, hormone receptor–positive primary invasive breast cancers who did not receive adjuvant chemotherapy. Primary objectives - comparing OS and DFS between the two arms. **Study dates** Recruited September 1994 - November 1997 **Source of funding** Supported in part by Public Health Service Grants No. CA23318, CA66636, CA21115, CA21076, CA16116, CA17145, CA14958, CA32102, and CA25224 from the National Cancer Institute, National Institutes of Health (NIH), Department of Health and Human Services, and by Grant No. UL1TR000427 from the Clinical and Translational Science Award program through the NIH National Center for Advancing Translational Sciences (A.J.T.).	Ineligible if they had locally advanced or metastatic disease. Other adjuvant systemic therapies including chemotherapy were not permitted. **Reported subgroups** None of interest			**version 1; follow-up NR):** TAM+OFS: 1/174; TAM: 0/171 **Treatment-related morbidity - changes in libido (grade 3+ on National Cancer Institute Common Toxicity Criteria, version 1; follow-up NR):** TAM+OFS: 1/174; TAM: 0/171 **Treatment-related morbidity - night sweats (grade 3+ on National Cancer Institute Common Toxicity Criteria, version 1; follow-up NR):** TAM+OFS: 1/174; TAM: 0/171 **HRQoL - FACT-G scale (5 year follow-up):** TAM+OFS N:91, M:89.88, SD:12.62; TAM N:97, M:91.30, SD:12.87 **HRQoL - FACT B scale (5 year follow-up):** TAM+OFS N:84, M:116.24, SD:15.49; TAM N:93, M:117.04, SD:17.51 **OS (median follow-up 9.9 years; range 0.2 - 12.3 years):** O-E: -0.99; V: 5.67 **Compliance - treatment completed:** TAM+OFS: 77/170; TAM: 68/167	**Selective reporting** Low **Indirectness** Population: 97% ER+; not serious **Limitations** The trial closed because of slow accrual prior to meeting enrollment goal for survival endpoints - DFS/OS therefore underpowered. **Other information** E-3193, INT-0142 trial

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments

ABC, adjuvant breast cancer; DFS, disease-free survival; ER, oestrogen receptor; GOS, goserelin; Gy, gray; HER2, human epidermal growth factor receptor 2; LHRH, Luteinizing-hormone releasing hormone; NR, not reported; OFS, ovarian function suppression; RCT, randomised controlled trial; SD, standard deviation; SOFT, suppression of ovarian function trial; TAM, tamoxifen; ZIPP, Zoladex in pre-menopausal patients trial

Clinical evidence tables for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Table 12: studies included in the evidence review for chemoprevention in DCIS

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Full citation Cuzick, J., Sestak, I., Pinder, S. E., Ellis, I. O., Forsyth, S., Bundred, N. J., Forbes, J. F., Bishop, H., Fentiman, I. S., George, W. D., Effect of tamoxifen and radiotherapy in women with locally excised ductal carcinoma in situ: Long-term results from the UK/ANZ DCIS trial, The Lancet Oncology, 12, 21-29, 2011 **Ref Id** 660989 **Country/ies where the study was carried out** UK, Australia, New Zealand **Study type** RCT **Aim of the study** To assess the role of radiotherapy and tamoxifen in people with excised DCIS **Study dates**	**Sample size** Total sample 1701, randomised to ± tamoxifen 1576 **Characteristics** Gender: 100% female Age: NR Ethnicity: NR **Inclusion criteria** Unilateral or bilateral DCIS that could be excised with clear margins by breast conserving surgery - confirmed by histological examination after surgery **Exclusion criteria** No additional criteria reported **Reported subgroups** BCS+RT; BCS-RT	**Interventions** **Intervention arm:** breast conserving surgery followed by tamoxifen (± radiotherapy) **Control arm:** breast conserving surgery followed by no endocrine treatment (± radiotherapy)	**Details** **Intervention arm (TAM):** 20mg tamoxifen daily for 5 years; radiotherapy was administered in 25 fractions over 5 weeks (2Gy given 5 times a week; total 50Gy) **Control arm (No chemoprevention):** radiotherapy was administered in 25 fractions over 5 weeks (2Gy given 5 times a week; total 50Gy)	**Results** **Whole sample:** **DFS (10 year follow-up):** O-E: -30.28; V: 88.41 **Local recurrence (10 year follow-up):** O-E: -17.43; V: 70.16 **BCS+RT:** **DFS (10 year follow-up):** O-E: -0.17; V: 16.74 **Local recurrence (10 year follow-up):** O-E: -0.71; V: 9.79 **BCS-RT:** **DFS (10 year follow-up):** O-E: -29.43; V: 85.93 **Local recurrence (10 year follow-up):** O-E: -15.60; V: 59.68	**Selection bias: random sequence generation** Insufficient information: Unclear **Selection bias: allocation concealment** Unclear **Selection bias: overall judgement** Unclear **Performance bias** No blinding but unlikely to have significant impact **Detection bias** Low due to objective nature of outcomes **Attrition bias** Low

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Randomised May 1990 to August 1998 **Source of funding** Cancer Research UK; Australian National Health and Medical Research Council					**Selective reporting** Low **Indirectness** None **Limitations** **Other information** UK/ANZ trial
Full citation Fisher, B., Dignam, J., Wolmark, N., Wickerham, D. L., Fisher, E. R., Mamounas, E., Smith, R., Begovic, M., Dimitrov, N. V., Margolese, R. G., Kardinal, C. G., Kavanah, M. T., Fehrenbacher, L., Oishi, R. H., Tamoxifen in treatment of intraductal breast cancer: National surgical adjuvant breast and bowel project B-24 randomised controlled trial, Lancet, 353, 1993-2000, 1999 **Ref Id** 649412	**Sample size** 1804 **Characteristics** Gender: 100% female Age: NR Ethnicity: 86% white, 7% black **Inclusion criteria** Women with DCIS with a life expectancy of at least 10 years. Axillary dissection (if done) had to show negative lymph node involvement and time between surgery and randomisation ≤56 days. **Exclusion criteria**	**Interventions** **Intervention arm:** lumpectomy + radiotherapy + tamoxifen **Control arm:** lumpectomy + radiotherapy + placebo	**Details** **Intervention arm (TAM):** Lumpectomy was performed within 56 days of randomisation. Radiation therapy total of 50Gy. 10mg tamoxifen was taken twice daily for 5 years. **Control arm (No chemoprevention):** Lumpectomy was performed within 56 days of randomisation. Radiation therapy total of 50Gy. Placebo was taken twice daily for 5 years	**Results** **Treatment-related morbidity - grade 3+ toxicities:** Tam 48/891; No chemoprevention 38/890 **Treatment-related morbidity - phlebitis/thromboembolism:** Tam 16/891; No chemoprevention 7/890 **Treatment-related morbidity - mood changes:** Tam 94/891; No chemoprevention 95/890 **Treatment-related morbidity - menstrual disorders:** Tam 171/891; No chemoprevention 142/890 **Treatment-related morbidity - hot flashes:** Tam 620/891; No chemoprevention 525/890	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** RCT **Aim of the study** To investigate if lumpectomy, radiotherapy and tamoxifen has greater benefits for people with DCIS compared with lumpectomy and radiotherapy alone **Study dates** Randomly assigned between May 1991 and April 1994 **Source of funding** National Cancer Institute, National Institutes of Health, and Department of Health and Human Services	Previous diagnosis of cancer (except in situ carcinoma of the cervix or squamous cell or basal-cell carcinoma of the skin) **Reported subgroups** All patients BCS+RT			**Treatment-related morbidity - fluid retention:** Tam 291/891; No chemoprevention 248/890 **Treatment-related morbidity - vaginal discharge:** Tam 289/891; No chemoprevention 178/890	Double blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** No follow-up for 3 individuals in both arms: Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information** NSABP-B24 trial
Full citation Guerrieri-Gonzaga, A., Robertson, C., Bonanni, B., Serrano, D., Cazzaniga, M.,	**Sample size** Total 235 - only interested in tamoxifen + placebo and placebo + placebo arms (n=116)	**Interventions** **Intervention arm:** tamoxifen + placebo (fenretinide)	**Details** **Intervention arm (TAM):** 5mg tamoxifen and fenretinide placebo capsules daily for 2 years	**Results** **Treatment-related morbidity - ocular/visual:** Tam 19/58; no chemoprevention 25/58	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Mora, S., Gulisano, M., Johansson, H., Intra, M., Latronico, A., Franchi, D., Pelosi, G., Johnson, K., Decensi, A., Preliminary results on safety and activity of a randomized, double-blind, 2 X 2 trial of low-dose tamoxifen and fenretinide for breast cancer prevention in premenopausal women [Erratum: 2006; 24(19): 3321], Journal of clinical oncology, 24, 129-135, 2006 **Ref Id** 661105 **Country/ies where the study was carried out** Italy **Study type** RCT **Aim of the study** To determine the effect of tamoxifen and fenretinide on surrogate biomarkers for premenopausal women at risk for breast cancer. **Study dates** Randomised prior to February 2005	**Characteristics** Gender: 100% female Age: mean 46; range 32-57 Ethnicity: NR **Inclusion criteria** Premenopausal women with: 1) in situ cancer or small invasive cancer of favourable prognosis within the last 3 years, or 2) Gail 5-year risk for breast cancer of 1.3%. Had to be willing to forgo pregnancy and use of oral contraceptives **Exclusion criteria** Prior chemotherapy or hormonal therapy for breast cancer; malignancy other than carcinoma-in-situ and skin basal cell carcinoma; retinal/ocular disorders; photodermatitis; stage III or IV endometriosis; grade 2 alterations of hematologic, liver and renal function; hypertriglyceridemia; CNS diseases; major psychiatric diseases; history of venous thromboembolism; transient ischemic attack. **Reported subgroups** None of interest	**Control arm:** placebo + placebo	**Control arm (No chemoprevention):** **T**amoxifen and fenretinide placebo capsules daily for 2 years	**Treatment-related morbidity - dermatology/skin:** Tam 17/58; no chemoprevention 25/58 **Treatment-related morbidity - hot flashes:** Tam 15/58; no chemoprevention 13/58 **Treatment-related morbidity - vaginal dryness/discharge:** Tam 15/58; no chemoprevention 10/58 **Treatment-related morbidity - Dysuria/incontinence:** Tam 5/58; no chemoprevention 5/58 **Treatment-related morbidity - vaginal bleeding:** Tam 7/58; no chemoprevention 4/58 **Treatment-related morbidity - endometrial polyps:** Tam 4/58; no chemoprevention 3/58 **Treatment-related morbidity - sweats/weight gain:** Tam 9/58; no chemoprevention 8/58	Permuted blocks: Low **Selection bias: allocation concealment** Centralised allocation - personnel and participants blinded: Low **Selection bias: overall judgement** Low **Performance bias** Double-blind: Low **Detection bias** Low due to objective nature of outcomes **Attrition bias** Low **Selective reporting** Low **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Source of funding National Cancer Institute, Italian Foundation for Cancer Research, Associazione Italiana per la Ricerca sul Cancro					Population - only 57% excised DCIS: very serious **Limitations** **Other information**
Full citation Wapnir, I. L., Dignam, J. J., Fisher, B., Mamounas, E. P., Anderson, S. J., Julian, T. B., Land, S. R., Margolese, R. G., Swain, S. M., Costantino, J. P., Wolmark, N., Long-term outcomes of invasive ipsilateral breast tumor recurrences after lumpectomy in NSABP B-17 and B-24 randomized clinical trials for DCIS, Journal of the National Cancer InstituteJ Natl Cancer Inst, 103, 478-88, 2011 **Ref Id** 540955 **Country/ies where the study was carried out** USA	**Sample size** 1804 **Characteristics** Gender: 100% female Age: NR Ethnicity: 86% white, 7% black **Inclusion criteria** Women with DCIS with a life expectancy of at least 10 years. Axillary dissection (if done) had to show negative lymph node involvement and time between surgery and randomisation ≤56 days (taken from Fisher 1999) **Exclusion criteria** Previous diagnosis of cancer (except in situ carcinoma of the cervix or squamous cell or basal-cell carcinoma of the skin) (taken from Fisher 1999)	**Interventions** **Intervention arm:** lumpectomy + radiotherapy + tamoxifen **Control arm:** lumpectomy + radiotherapy + placebo	**Details** **Intervention arm (TAM):** Details of lumpectomy not reported. Radiation started within 8 weeks of surgery and was given at 10Gy per week over 5 weeks (total 50Gy); optional boost of 10Gy to lumpectomy cavity. 10mg tamoxifen taken twice daily for 5 years (taken from Fisher 1999) **Control arm (No chemoprevention):** Details of lumpectomy not reported. Radiation started within 8 weeks of surgery and was given at 10Gy per week over 5 weeks (total 50Gy); optional boost of 10Gy to lumpectomy cavity. Placebo was taken twice daily for 5 years (taken from Fisher 1999)	**Results** **Local recurrence - invasive (median follow-up 13.6 year)s:** O-E: -13.52; V: 35.06 **Local recurrence - DCIS (median follow-up 13.6 years):** O-E: -5.71; V: 32.77 **OS (median follow-up 13.6 years):** O-E: -8.57; V: 56.85	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Double-blind: Low **Detection bias**

Study details	Participants	Interventions	Methods	Outcomes and Results	Comments
Study type RCT **Aim of the study** To investigate the addition of tamoxifen to lumpectomy and radiotherapy for people with DCIS **Study dates** Randomised May 1991 to April 1994 **Source of funding** U.S. National Cancer Institute, AstraZeneca	**Reported subgroups** All patients BCS+RT				Low due to objective nature of outcomes **Attrition bias** 2 with no follow-up in control arm and 3 with no follow-up in intervention arm: Low **Selective reporting** Low **Indirectness** None **Limitations** **Other information** NSABP B-24 trial

BCS, breast conserving surgery; CNS, central nervous system; DCIS, ductal carcinoma in situ; DFS, disease-free survival; Gy, gray; NSABP, National Surgical Adjuvant Breast and Bowel Project; RCT, randomised controlled trial; RT, radiotherapy; TAM, tamoxifen; UK/ANZ, United Kingdom, Australia and New Zealand

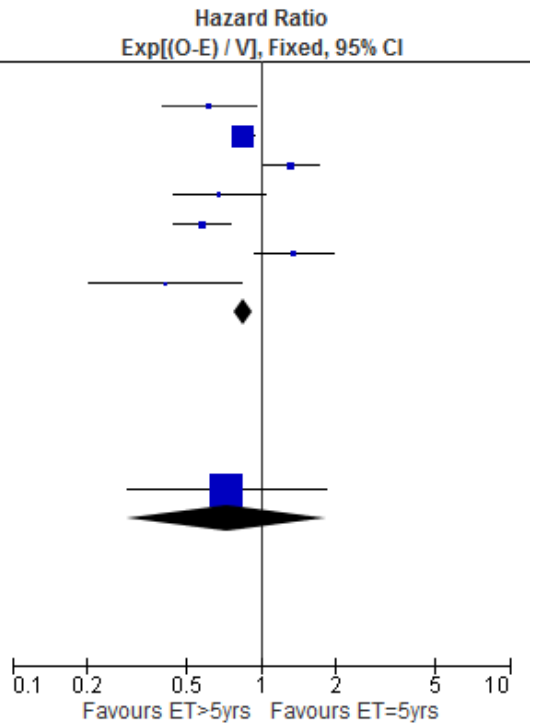
Appendix E – Forest plots

Forest plots for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Comparison 1. Endocrine therapy for greater than 5 years versus endocrine therapy for 5 years only

Figure 4: Disease free survival at 2.5 to 15 year follow-up

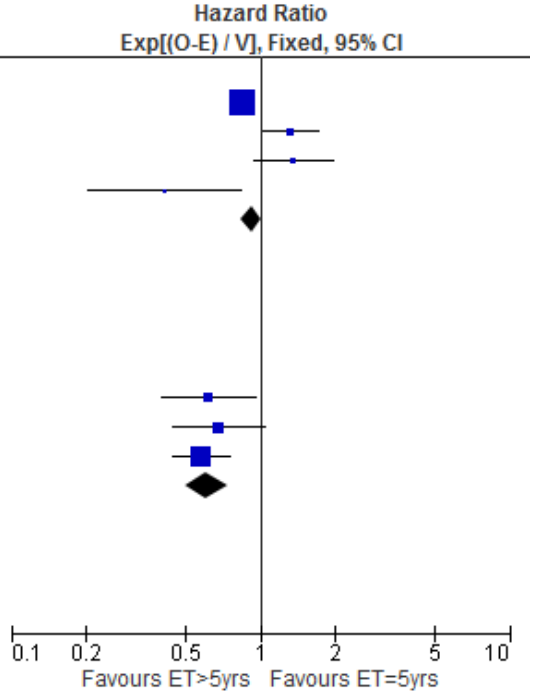
Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.1.1 Whole sample								
ABCSG 6a	30	386	57	466	-9.58	20.05	3.7%	0.62 [0.40, 0.96]
ATLAS	617	3428	711	3418	-55.27	340.08	63.6%	0.85 [0.76, 0.95]
B-14	137	583	106	569	16.78	59.76	11.2%	1.32 [1.03, 1.71]
B-33	37	783	52	770	-8.34	21.62	4.0%	0.68 [0.45, 1.04]
MA.17	92	2583	155	2587	-30.48	55.95	10.5%	0.58 [0.45, 0.75]
Scottish Adjuvant Tamoxifen Trial	0	173	0	169	9.14	29.71	5.6%	1.36 [0.95, 1.95]
Tormey 1996 (Parent trials E4181/E5181)	12	73	22	67	-6.85	7.76	1.5%	0.41 [0.20, 0.84]
Subtotal (95% CI)		**8009**		**8046**			**100.0%**	**0.85 [0.78, 0.93]**
Total events	925		1103					
Heterogeneity: Chi² = 33.57, df = 6 (P < 0.00001); I² = 82%								
Test for overall effect: Z = 3.66 (P = 0.0003)								
1.1.2 Grade 3								
ABCSG 6a	0	79	0	92	-1.41	4.47	100.0%	0.73 [0.29, 1.84]
Subtotal (95% CI)		**79**		**92**			**100.0%**	**0.73 [0.29, 1.84]**
Total events	0		0					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.67 (P = 0.50)								



Note. Number of events in each arm not reported for Scottish Adjuvant Tamoxifen Trial

Figure 5: Disease free survival at 2.5 to 15 year follow-up: tamoxifen and aromatase inhibitor subgroups

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.2.2 Continued tamoxifen - whole sample								
ATLAS	617	3428	711	3418	-55.27	340.08	77.8%	0.85 [0.76, 0.95]
B-14	137	583	106	569	16.78	59.76	13.7%	1.32 [1.03, 1.71]
Scottish Adjuvant Tamoxifen Trial	0	173	0	169	9.14	29.71	6.8%	1.36 [0.95, 1.95]
Tormey 1996 (Parent trials E4181/E5181)	12	73	22	67	-6.85	7.76	1.8%	0.41 [0.20, 0.84]
Subtotal (95% CI)		**4257**		**4223**			**100.0%**	**0.92 [0.84, 1.01]**
Total events	766		839					
Heterogeneity: Chi² = 19.56, df = 3 (P = 0.0002); I² = 85%								
Test for overall effect: Z = 1.73 (P = 0.08)								
1.2.4 Swtiched to AI								
ABCSG 6a	30	386	57	466	-9.58	20.05	20.5%	0.62 [0.40, 0.96]
B-33	37	783	52	770	-8.34	21.62	22.1%	0.68 [0.45, 1.04]
MA.17	92	2583	155	2587	-30.48	55.95	57.3%	0.58 [0.45, 0.75]
Subtotal (95% CI)		**3752**		**3823**			**100.0%**	**0.61 [0.50, 0.74]**
Total events	159		264					
Heterogeneity: Chi² = 0.40, df = 2 (P = 0.82); I² = 0%								
Test for overall effect: Z = 4.90 (P < 0.00001)								

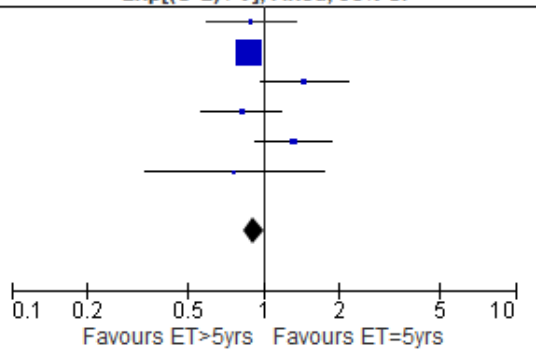


Note. Number of events in each arm not reported for Scottish Adjuvant Tamoxifen Trial

Figure 6: Overall survival at 4 to 15 year follow-up

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
ABCSG 6a	40	386	55	466	-2.66	22.84	5.1%	0.89 [0.59, 1.34]
ATLAS	639	3428	722	3418	-47.7	340.2	75.4%	0.87 [0.78, 0.97]
B-14	57	583	39	569	8.72	23.16	5.1%	1.46 [0.97, 2.19]
MA.17	51	2583	62	2587	-5.63	28.36	6.3%	0.82 [0.57, 1.18]
Scottish Adjuvant Tamoxifen Trial	0	173	0	169	8.61	31.02	6.9%	1.32 [0.93, 1.88]
Tormey 1996 (Parent trials E4181/E5181)	14	100	10	93	-1.55	5.83	1.3%	0.77 [0.34, 1.73]
Total (95% CI)		**7253**		**7302**			**100.0%**	**0.91 [0.83, 1.00]**
Total events	801		888					

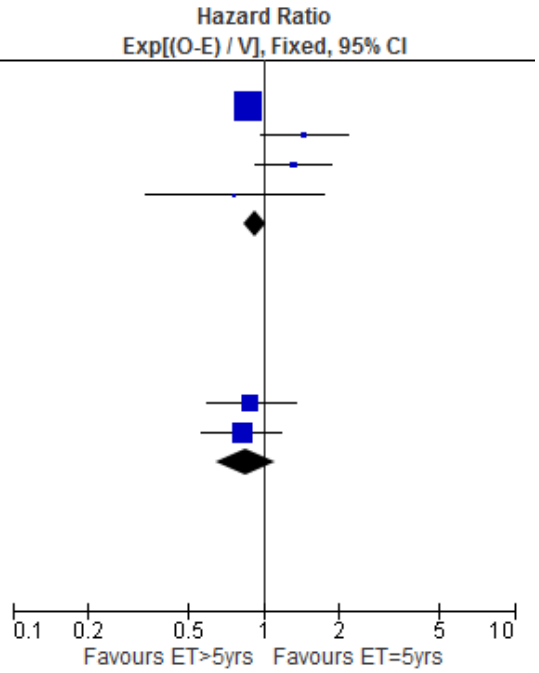
Heterogeneity: Chi² = 10.62, df = 5 (P = 0.06); I² = 53%
Test for overall effect: Z = 1.89 (P = 0.06)



Note. Number of events in each arm not reported for Scottish Adjuvant Tamoxifen Trial

Figure 7: Overall survival at 4 to 15 year follow-up: tamoxifen and aromatase inhibitor subgroups

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	O-E	Variance	Weight	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
1.4.1 Continued tamoxifen								
ATLAS	639	3428	722	3418	-47.7	340.2	85.0%	0.87 [0.78, 0.97]
B-14	57	583	39	569	8.72	23.16	5.8%	1.46 [0.97, 2.19]
Scottish Adjuvant Tamoxifen Trial	0	173	0	169	8.61	31.02	7.8%	1.32 [0.93, 1.88]
Tormey 1996 (Parent trials E4181/E5181)	14	100	10	93	-1.55	5.83	1.5%	0.77 [0.34, 1.73]
Subtotal (95% CI)		**4284**		**4249**			**100.0%**	**0.92 [0.84, 1.02]**
Total events	710		771					
Heterogeneity: Chi² = 10.23, df = 3 (P = 0.02); I² = 71%								
Test for overall effect: Z = 1.60 (P = 0.11)								
1.4.2 Switched to AI								
ABCSG 6a	40	386	55	466	-2.66	22.84	44.6%	0.89 [0.59, 1.34]
MA.17	51	2583	62	2587	-5.63	28.36	55.4%	0.82 [0.57, 1.18]
Subtotal (95% CI)		**2969**		**3053**			**100.0%**	**0.85 [0.65, 1.12]**
Total events	91		117					
Heterogeneity: Chi² = 0.09, df = 1 (P = 0.77); I² = 0%								
Test for overall effect: Z = 1.16 (P = 0.25)								



Note. Number of events in each arm not reported for Scottish Adjuvant Tamoxifen Trial

Figure 8: Compliance: did not comply with assigned treatment

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	Weight	Risk Ratio M-H, Random, 95% CI
ATLAS	1033	6454	258	6440	28.0%	4.00 [3.50, 4.56]
B-14	95	583	77	569	27.5%	1.20 [0.91, 1.59]
MA.17	519	2583	502	2587	28.0%	1.04 [0.93, 1.16]
Scottish Adjuvant Tamoxifen Trial	2	173	15	169	16.5%	0.13 [0.03, 0.56]
Total (95% CI)		**9793**		**9765**	**100.0%**	**1.12 [0.44, 2.81]**
Total events	1649		852			
Heterogeneity: Tau² = 0.79; Chi² = 264.30, df = 3 (P < 0.00001); I² = 99%						
Test for overall effect: Z = 0.24 (P = 0.81)						

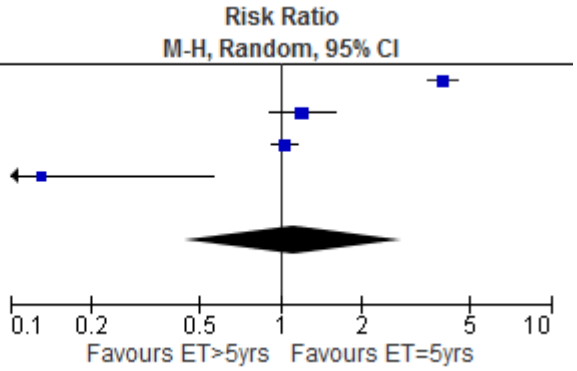


Figure 9: Treatment-related morbidity: hot flushes at 2 month to 4 year follow-up

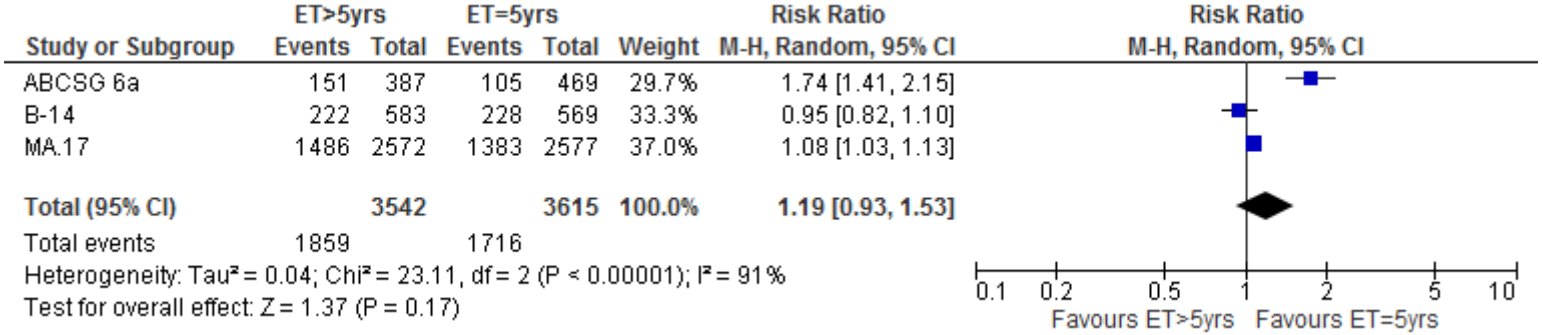


Figure 10: Treatment-related morbidity: secondary cancer at 5.6 to 7.6 year follow-up

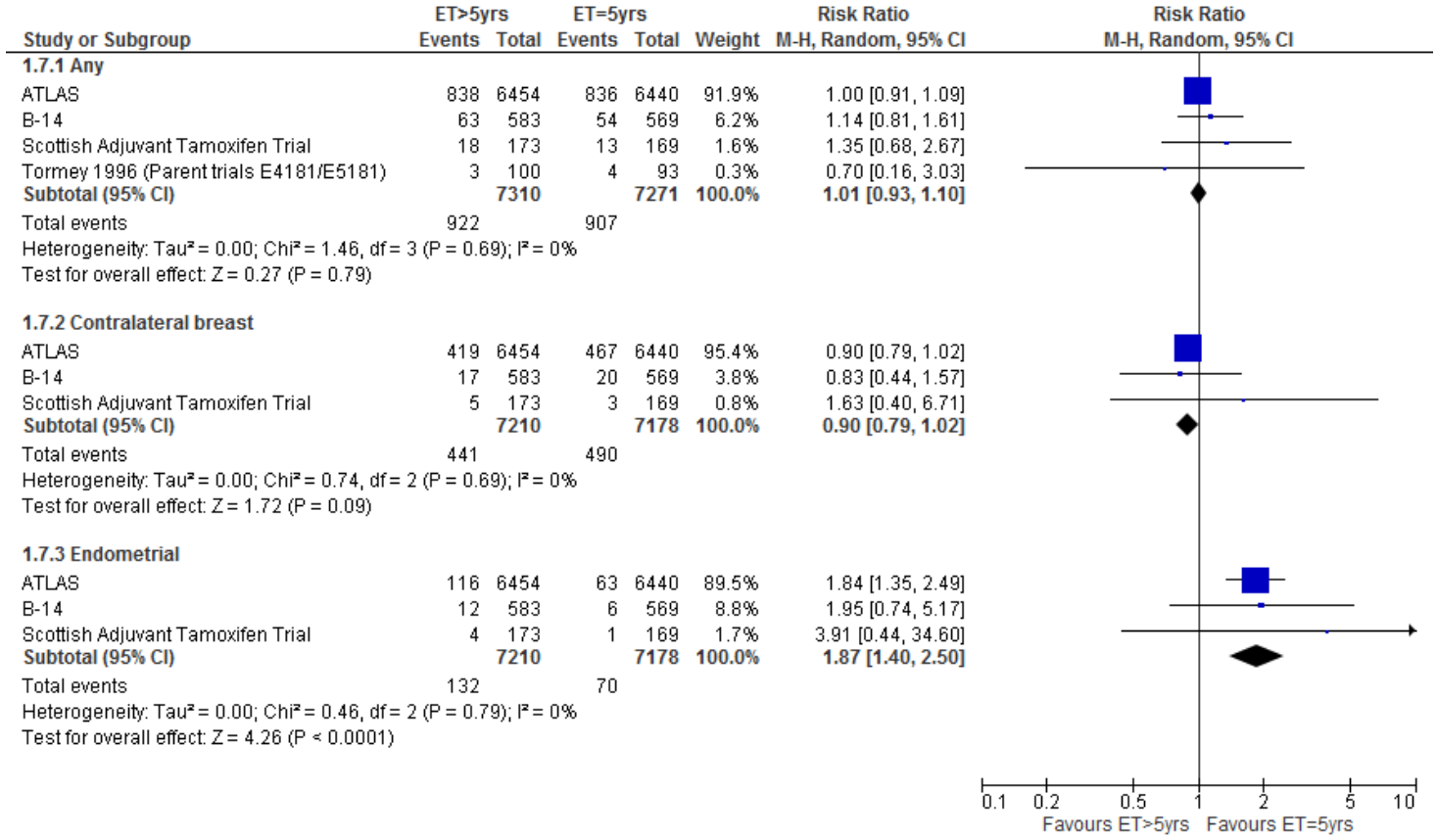


Figure 11: Treatment-related morbidity: bone fractures at 2 month to 7.6 year follow-up

Study or Subgroup	ET>5yrs Events	Total	ET=5yrs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ABCSG 6a	3	387	5	469	1.7%	0.73 [0.17, 3.02]
ATLAS	62	6454	70	6440	29.1%	0.88 [0.63, 1.24]
B-33	28	783	20	779	10.5%	1.39 [0.79, 2.45]
MA.17	137	2561	119	2565	58.7%	1.15 [0.91, 1.46]
Total (95% CI)		**10185**		**10253**	**100.0%**	**1.08 [0.90, 1.30]**
Total events	230		214			

Heterogeneity: Tau² = 0.00; Chi² = 2.70, df = 3 (P = 0.44); I² = 0%
Test for overall effect: Z = 0.83 (P = 0.41)

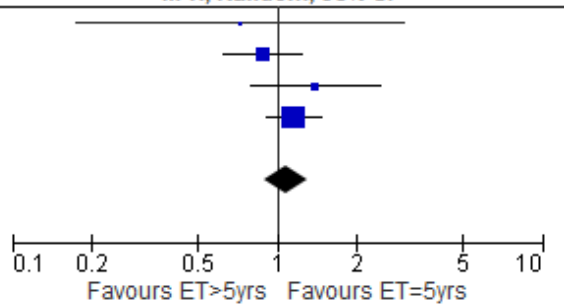


Figure 12: Treatment-related morbidity: arthralgia at 2 month to 4 year follow-up

Study or Subgroup	ET>5yrs Events	Total	ET=5yrs Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
ABCSG 6a	95	387	86	469	13.1%	1.34 [1.03, 1.73]
B-33	8	783	4	779	0.6%	1.99 [0.60, 6.58]
MA.17	651	2572	532	2577	86.3%	1.23 [1.11, 1.36]
Total (95% CI)		**3742**		**3825**	**100.0%**	**1.24 [1.13, 1.37]**
Total events	754		622			

Heterogeneity: Tau² = 0.00; Chi² = 0.98, df = 2 (P = 0.61); I² = 0%
Test for overall effect: Z = 4.57 (P < 0.00001)

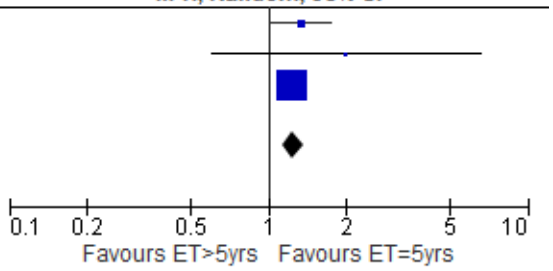


Figure 13: Treatment-related morbidity: cardiac disease/event at 2 month to 7.6 year follow-up

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	Weight	Risk Ratio M-H, Random, 95% CI
ABCSG 6a	1	387	0	469	0.7%	3.63 [0.15, 88.95]
ATLAS	127	6454	163	6440	49.1%	0.78 [0.62, 0.98]
MA.17	149	2561	144	2565	50.2%	1.04 [0.83, 1.29]
Total (95% CI)		**9402**		**9474**	**100.0%**	**0.91 [0.69, 1.19]**
Total events	277		307			

Heterogeneity: Tau² = 0.02; Chi² = 3.84, df = 2 (P = 0.15); I² = 48%
Test for overall effect: Z = 0.71 (P = 0.48)

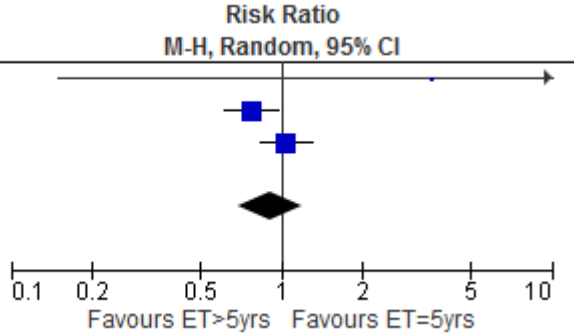


Figure 14: Treatment-related morbidity: hypertension at 4 year follow-up

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	Risk Ratio M-H, Random, 95% CI
MA.17	130	2572	129	2577	1.01 [0.80, 1.28]

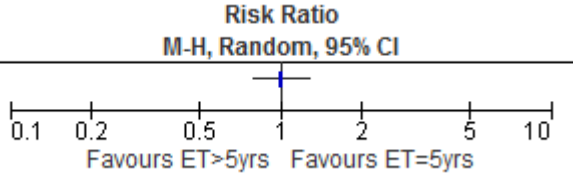


Figure 15: Treatment-related morbidity: osteoporosis at 4 year follow-up

Study or Subgroup	ET>5yrs Events	ET>5yrs Total	ET=5yrs Events	ET=5yrs Total	Risk Ratio M-H, Random, 95% CI
MA.17	209	2561	155	2565	1.35 [1.11, 1.65]

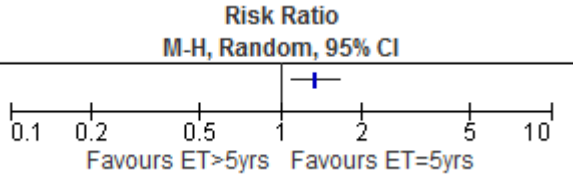


Figure 16: Treatment-related morbidity: myalgia at 4 year follow-up

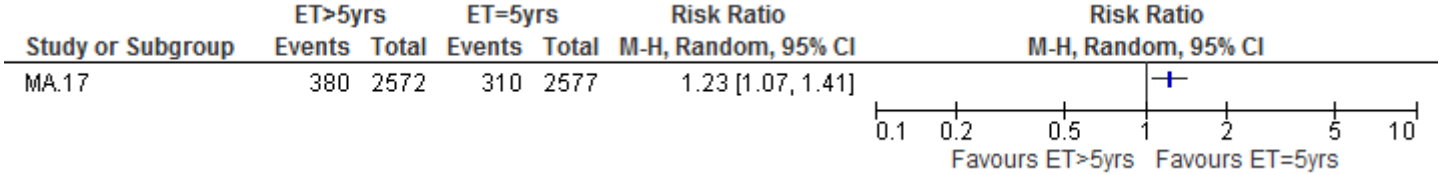


Figure 17: Treatment-related morbidity: any grade 3+ toxicity at 2.5 to 5.6 year follow-up

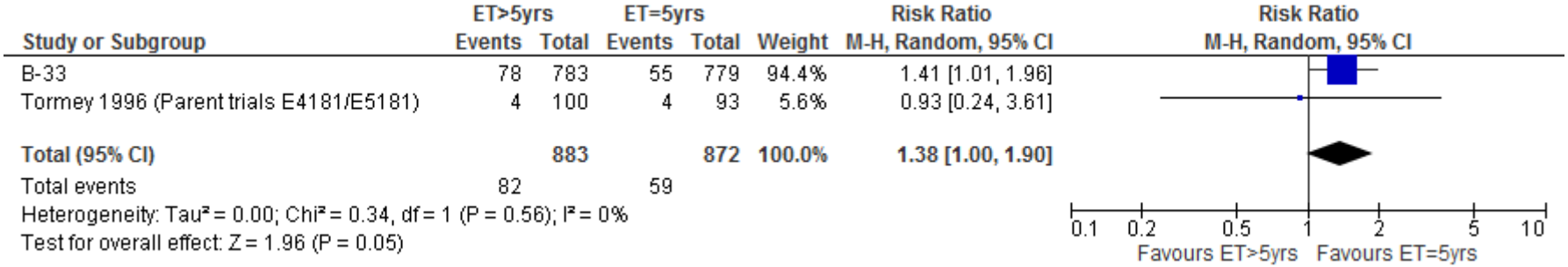


Figure 18: Treatment-related morbidity: vaginal dryness at 2 month to 4 year follow-up

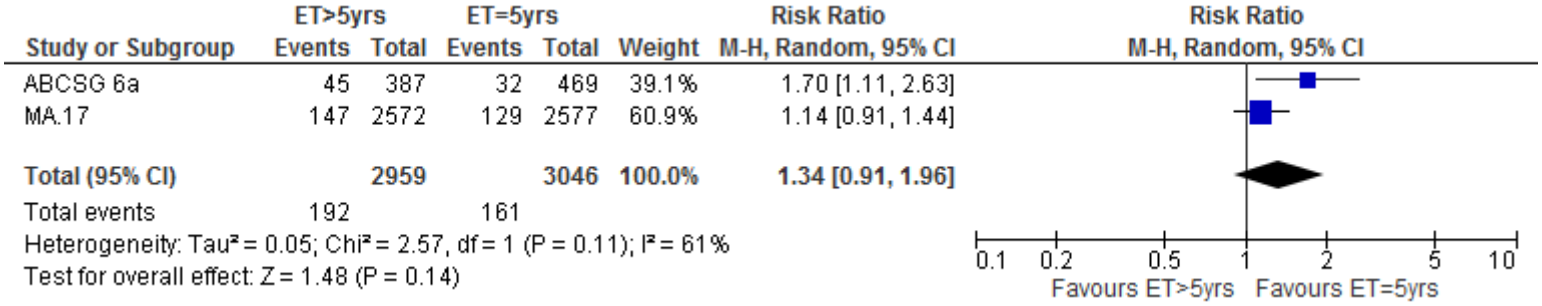


Figure 19: Treatment-related morbidity: vaginal bleeding at 2 month to 4 year follow-up

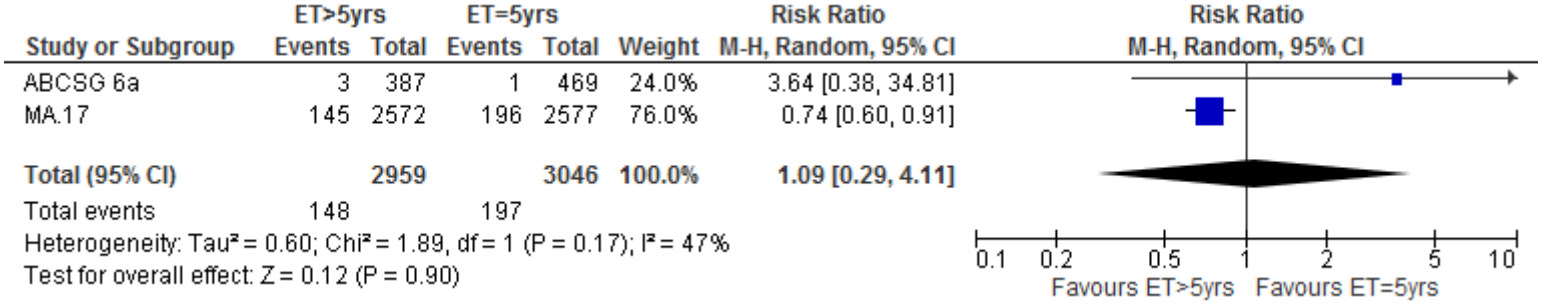


Figure 20: Treatment-related morbidity: vaginal discharge at 2 month to 4 year follow-up

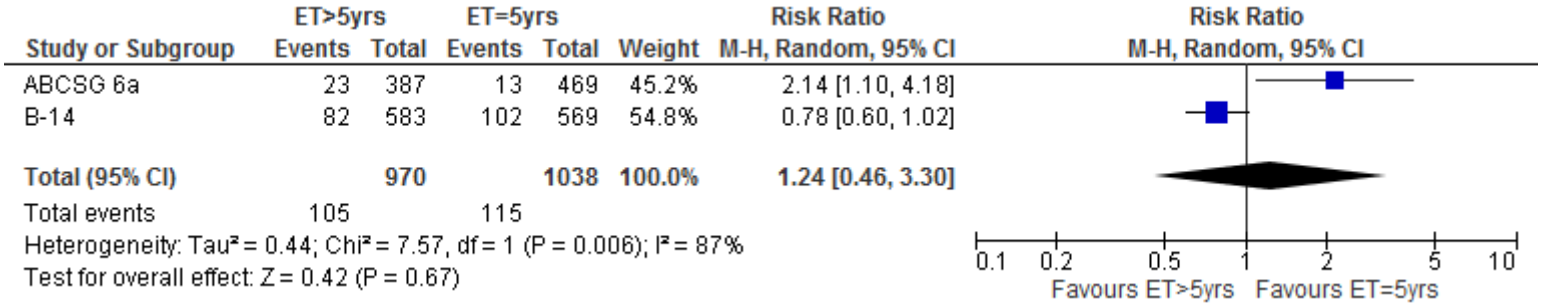


Figure 21: Treatment-related morbidity: stroke at 7.6 year follow-up

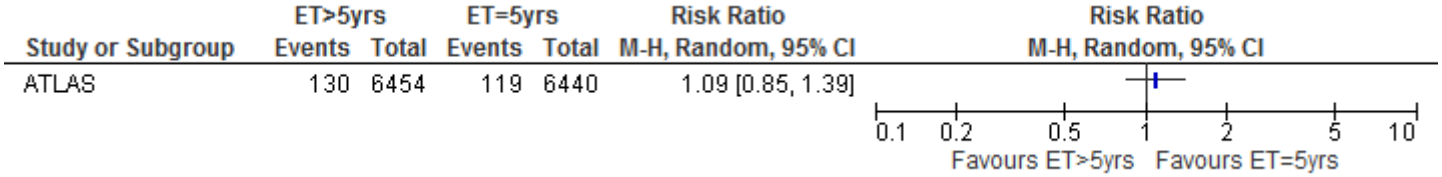


Figure 22: Treatment-related morbidity: irregular menstruation at 4 year follow-up

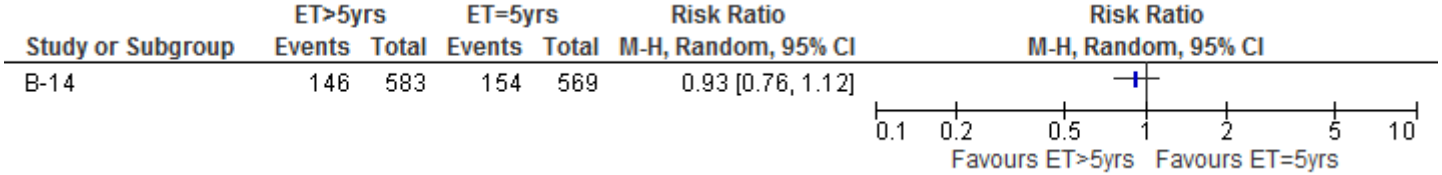


Figure 23: Treatment-related morbidity: phlebitis/thromboembolic events at 2 month to 7.6 year follow-up

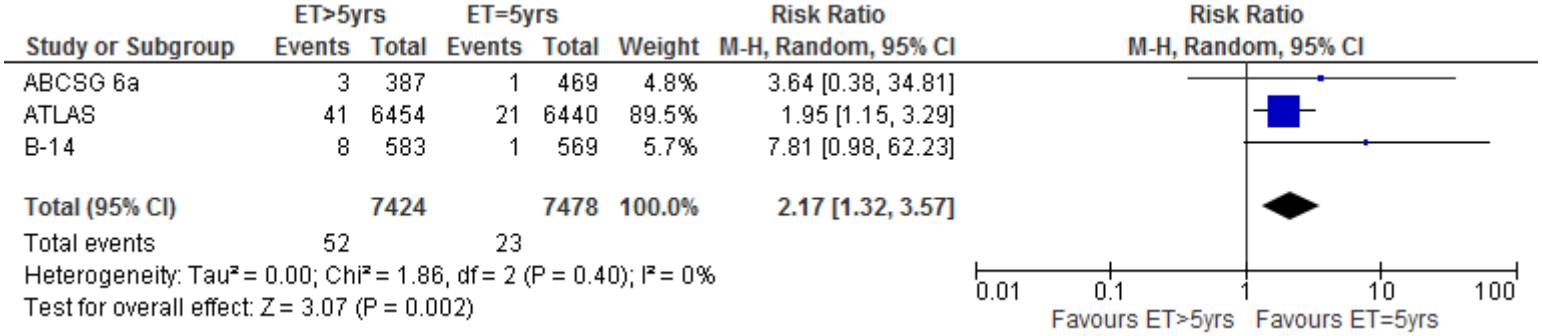
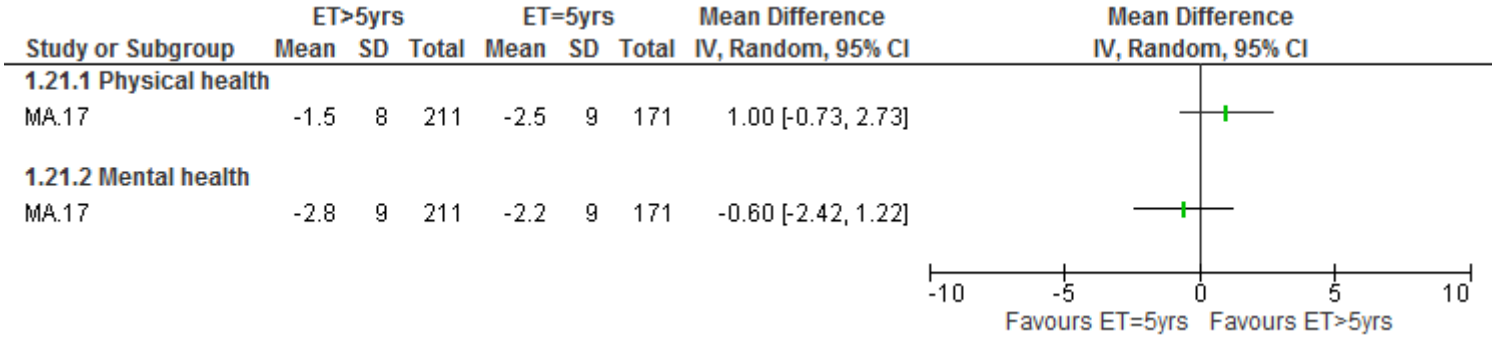
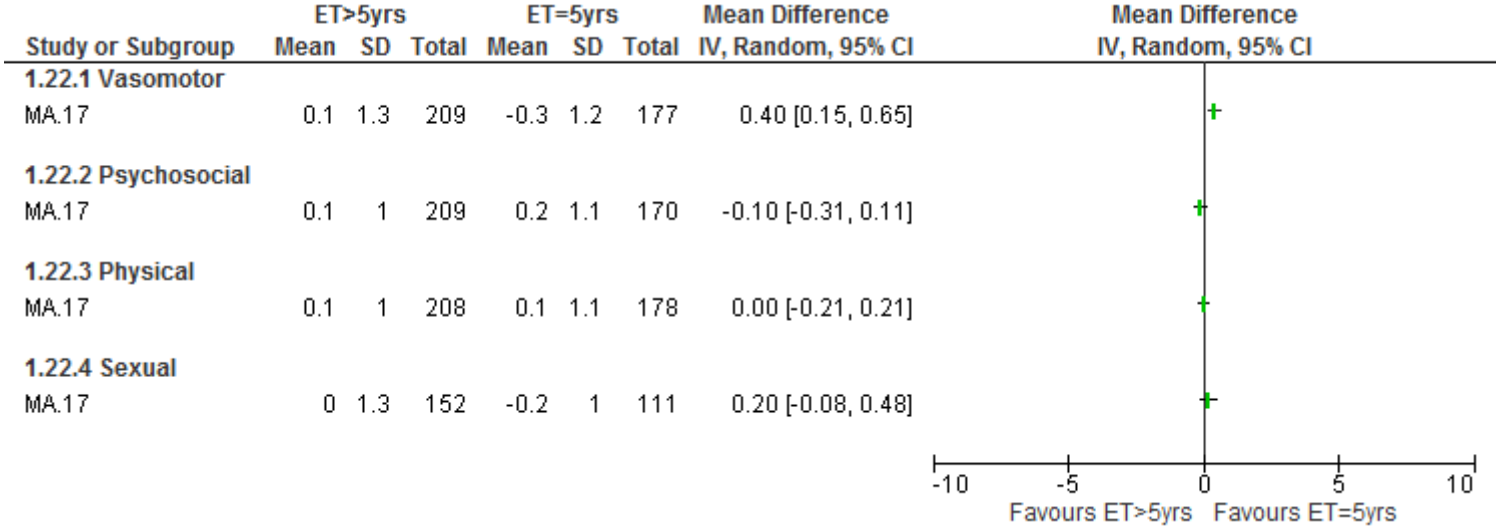


Figure 24: HRQoL: change in SF-36 scores from baseline (2 year follow-up)



Better indicated by higher values

Figure 25: HRQoL: change in MENQOL scores from baseline (2 year follow-up)

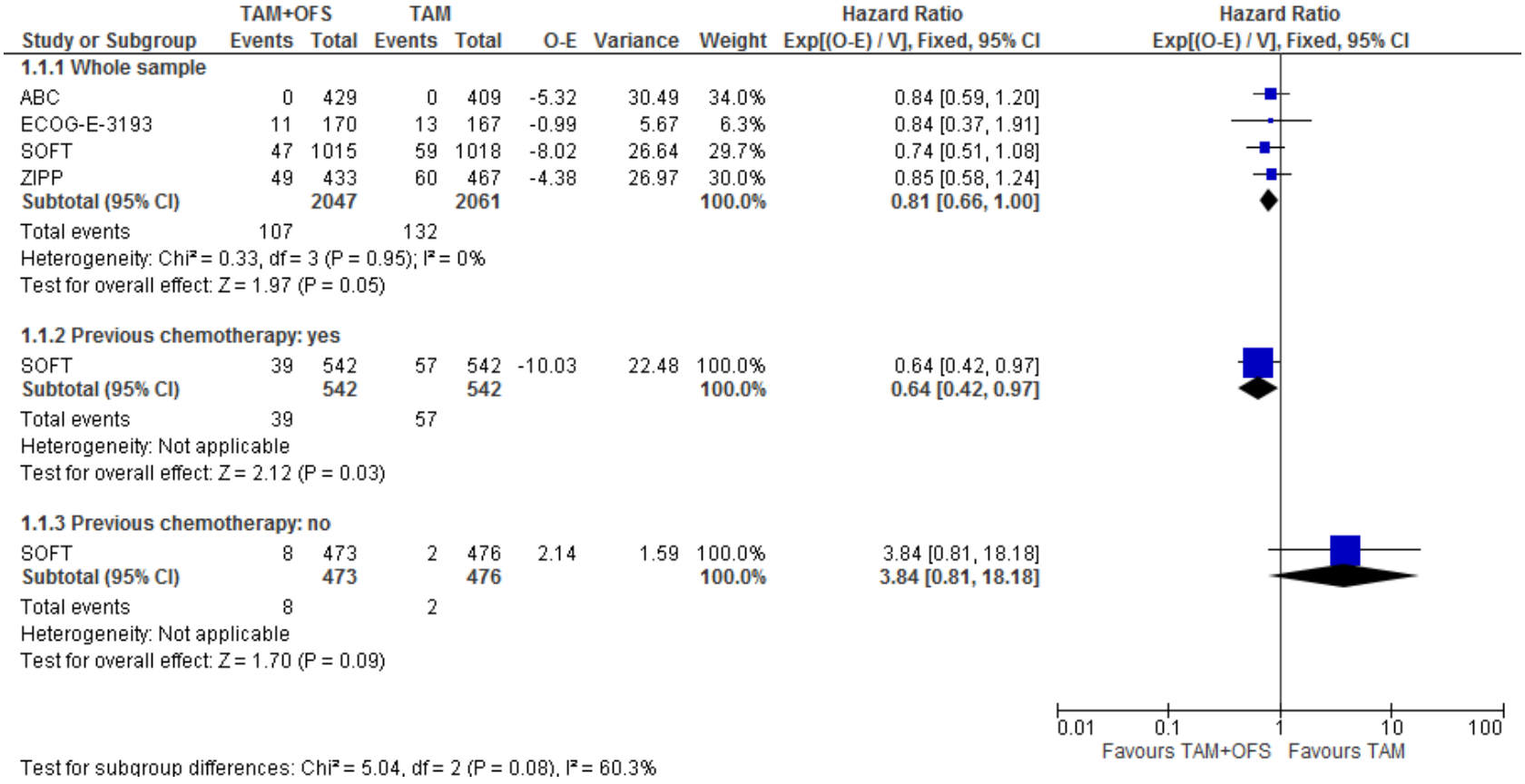


Better indicated by lower values

Forest plots for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Comparison 1. Ovarian suppression plus tamoxifen versus tamoxifen alone

Figure 26: Overall survival at 5 to 9.9 year follow-up



Note. Number of events in each arm not reported for ABC trial

Figure 27: Disease-free survival at 5 to 9.9 year follow-up

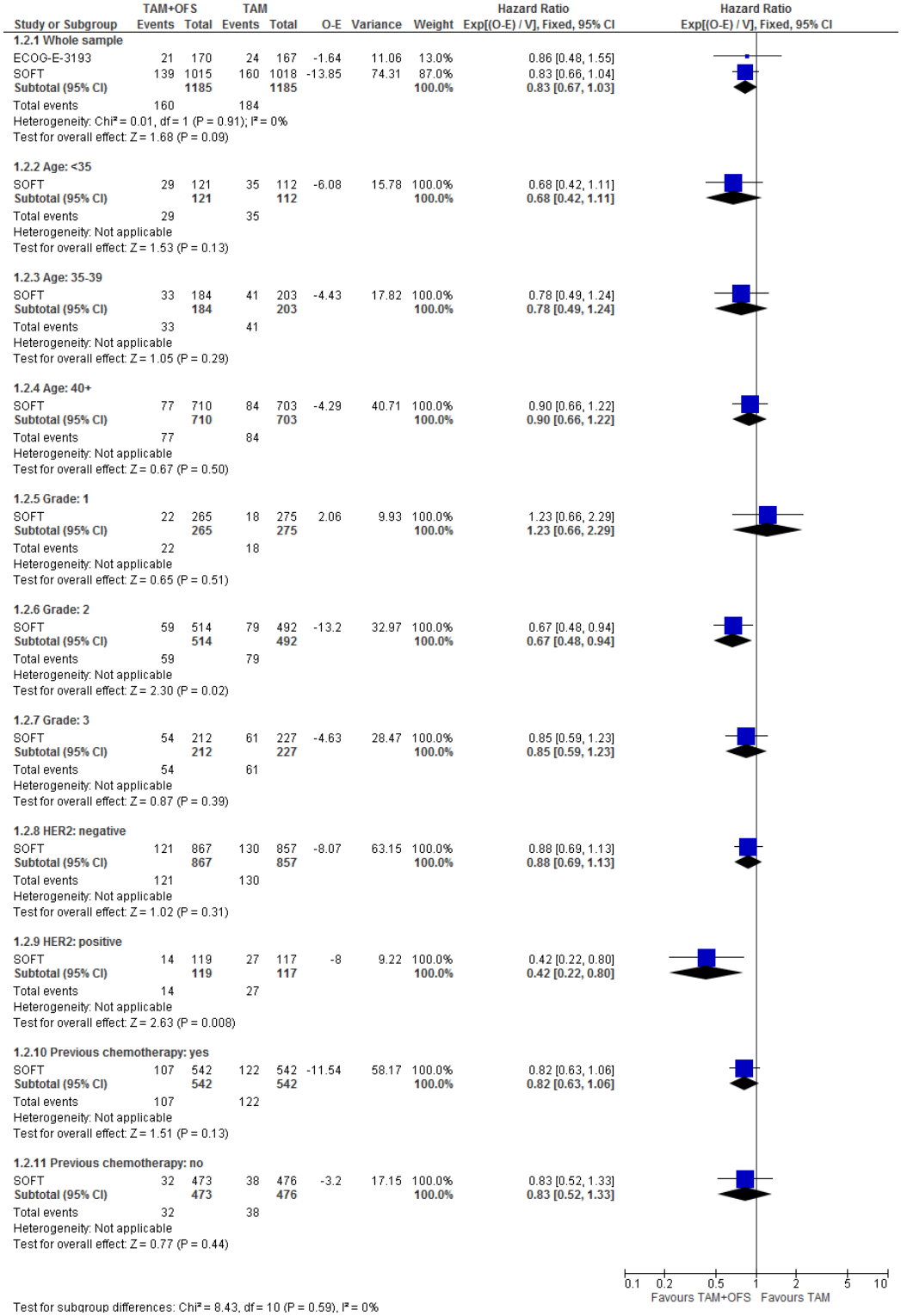


Figure 28: Treatment-related morbidity: vasodilation

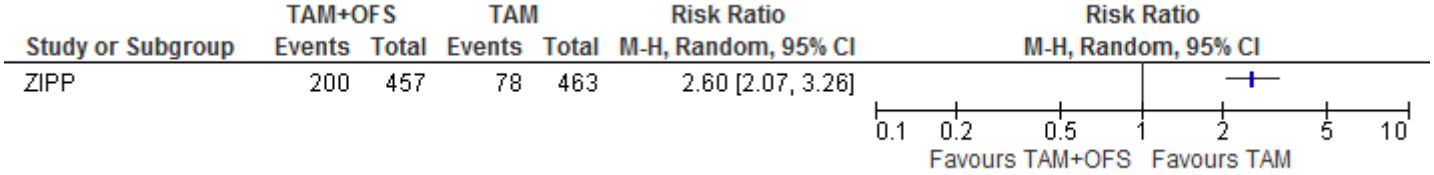


Figure 29: Treatment-related morbidity: weight gain

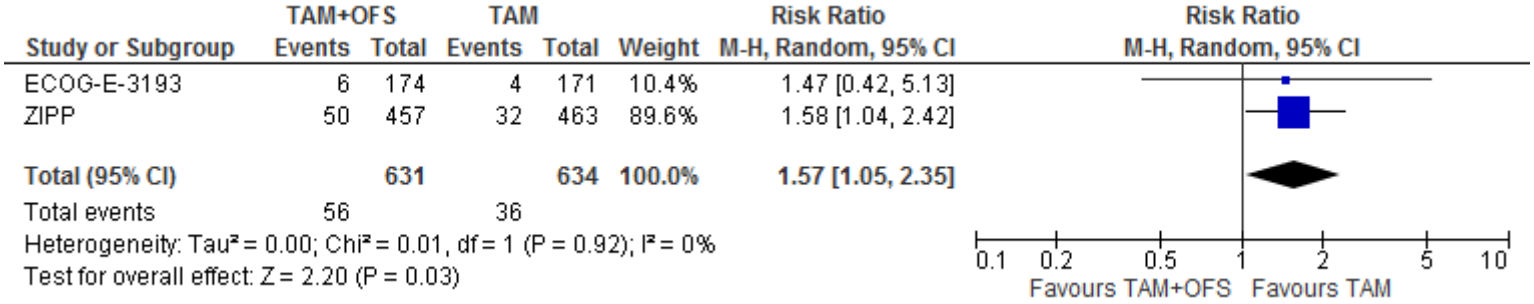


Figure 30: Treatment-related morbidity: arthralgia

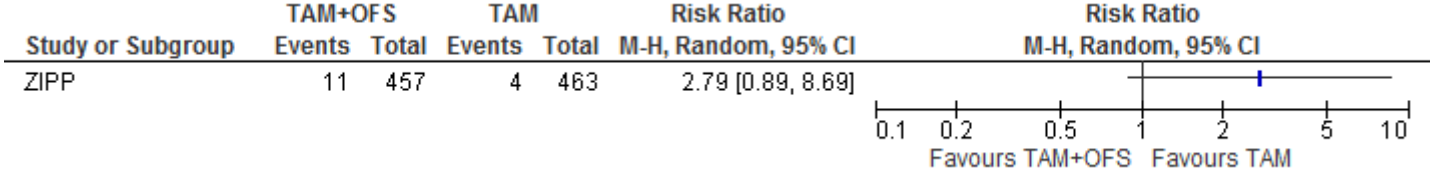


Figure 31: Treatment-related morbidity: anxiety/depression/irritability

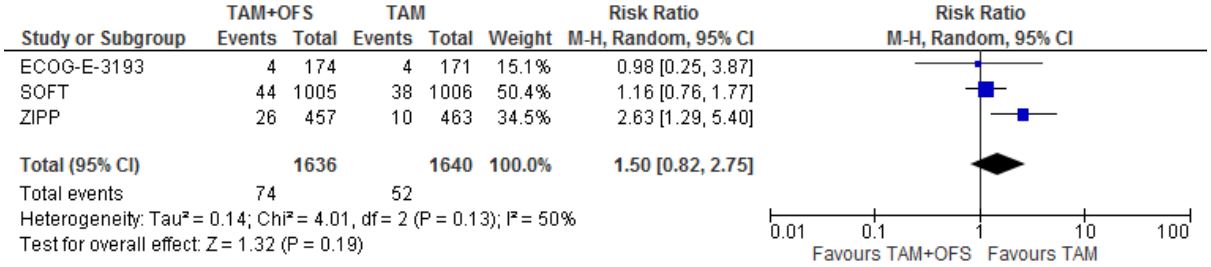


Figure 32: Treatment-related morbidity: sweating

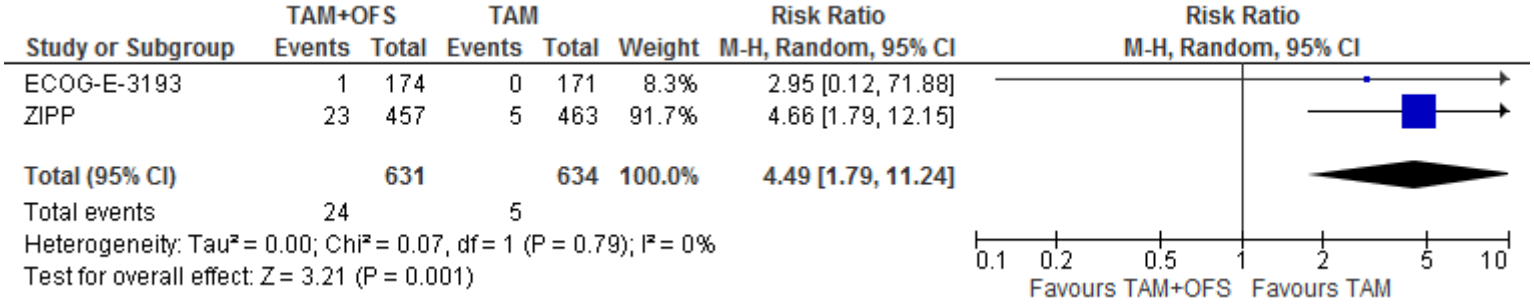


Figure 33: Treatment-related morbidity: hot flushes (grade 3+) at 3 to 5.6 year follow-up

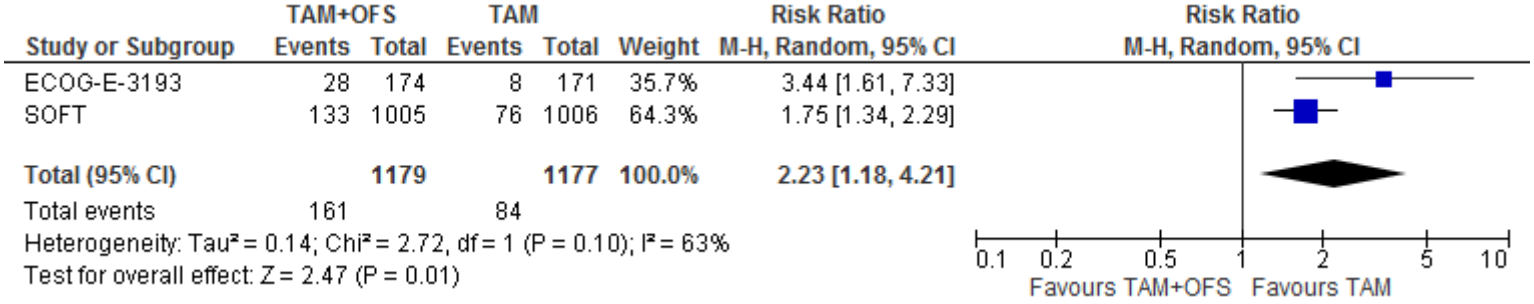


Figure 34: Treatment-related morbidity: hypertension (grade 3+) at 5.6 year follow-up

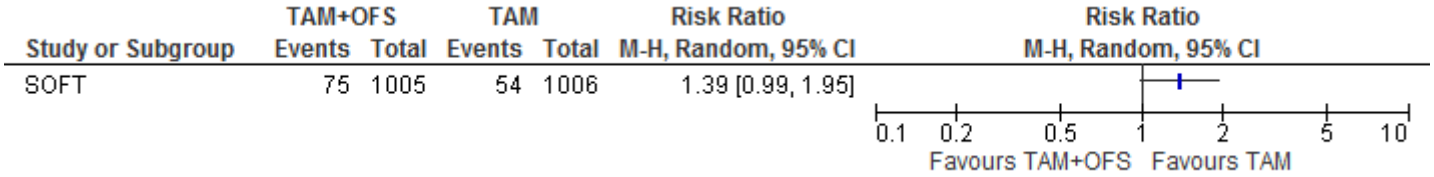


Figure 35: Treatment-related morbidity: cardiac ischemia or infarction (grade 3+) at 5.6 year follow-up

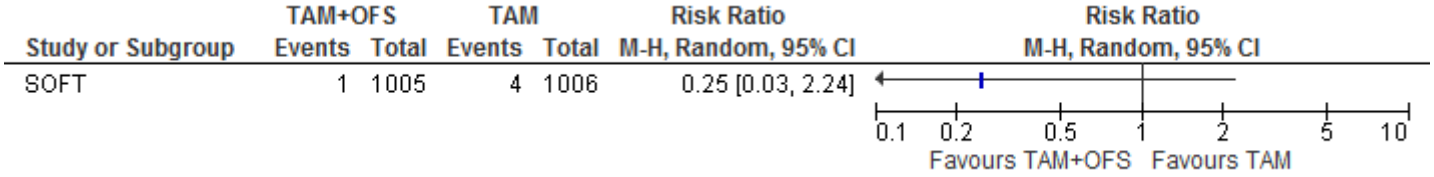


Figure 36: Treatment-related morbidity: thrombosis or embolism (grade 3+) at 5.6 year follow-up

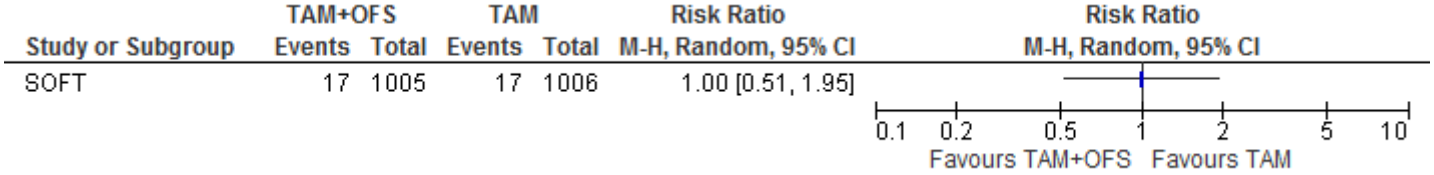


Figure 37: Treatment-related morbidity: musculoskeletal symptoms (grade 3+) at 5.6 year follow-up

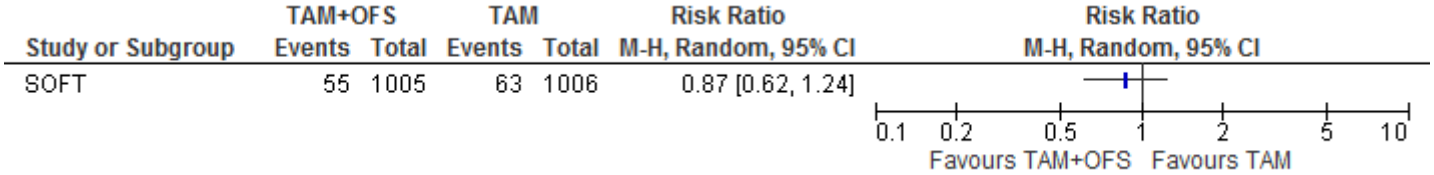


Figure 38: Treatment-related morbidity: osteoporosis (grade 3+) at 5.6 year follow-up

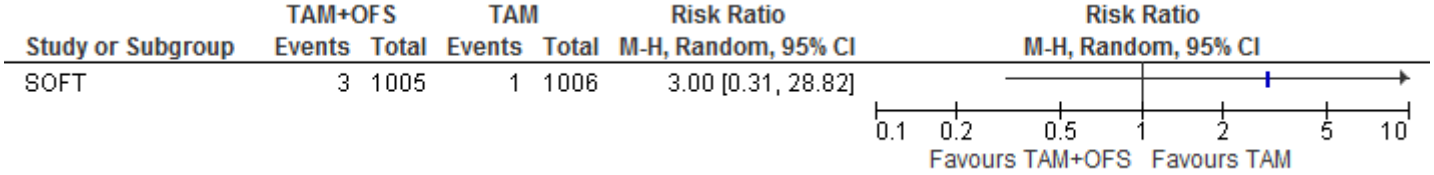


Figure 39: Treatment-related morbidity: fractures (grade 3+) at 5.6 year follow-up

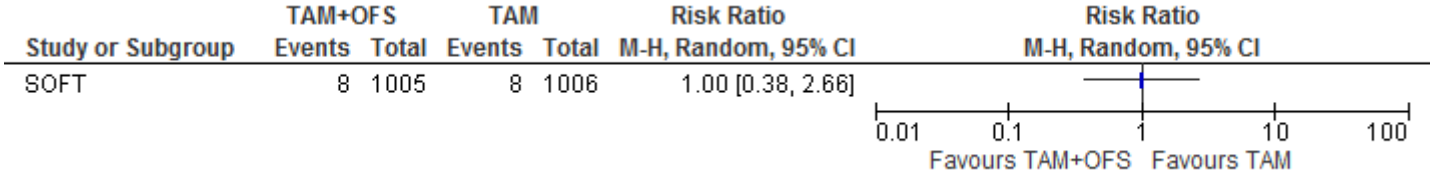


Figure 40: Treatment-related morbidity: vaginal dryness at 3 to 5.6 year follow-up

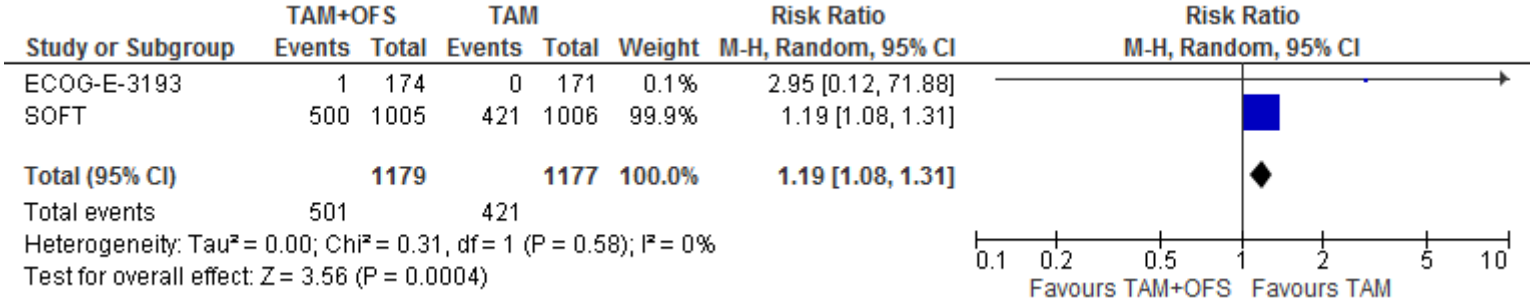


Figure 41: Treatment-related morbidity: changes in libido at 3 to 5.6 year follow-up

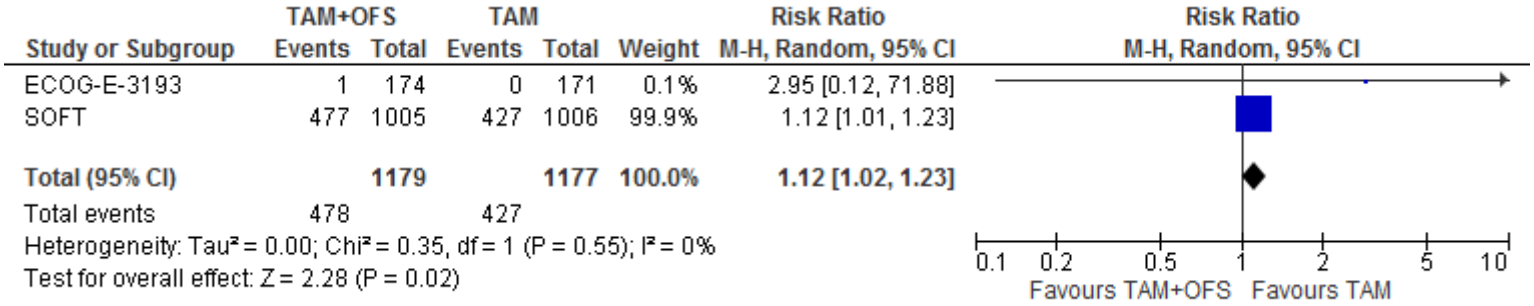


Figure 42: Treatment-related morbidity: CNS cerebrovascular ischemia (grade 3+) at 5.6 year follow-up

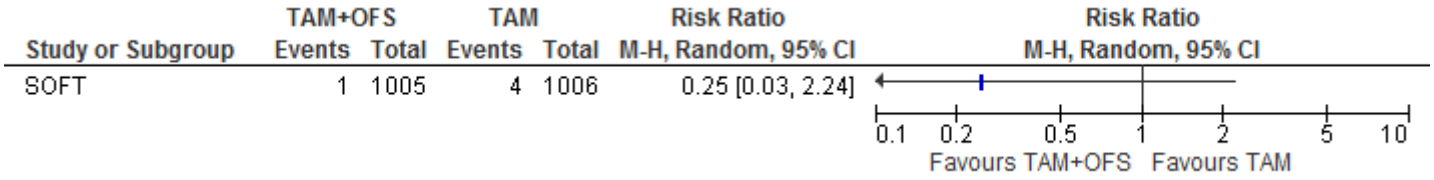


Figure 43: Treatment-related morbidity: CNS haemorrhage (grade 3+) at 5.6 year follow-up

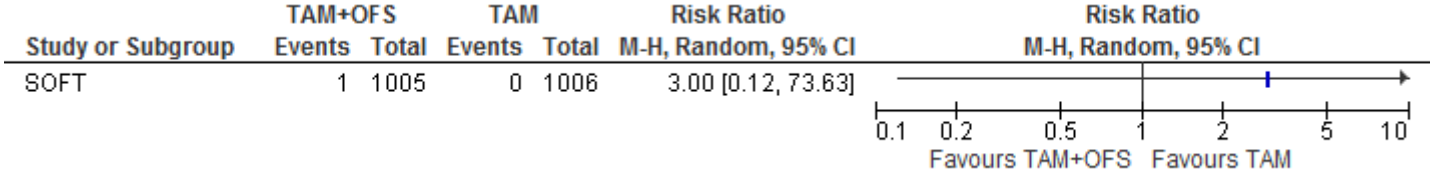


Figure 44: Treatment-related morbidity: vasomotor symptoms measured by Physical Symptoms and Problem List at 3 year follow-up

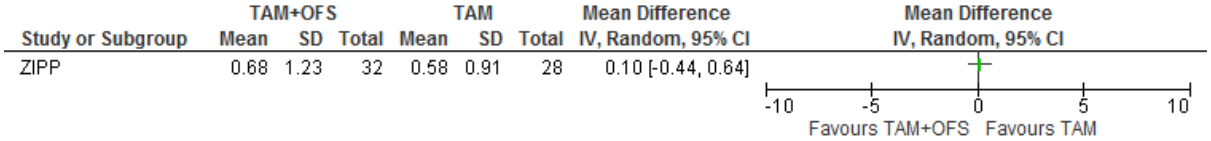


Figure 45: Treatment-related morbidity: vaginal dryness measured by Physical Symptoms and Problem List at 3 year follow-up

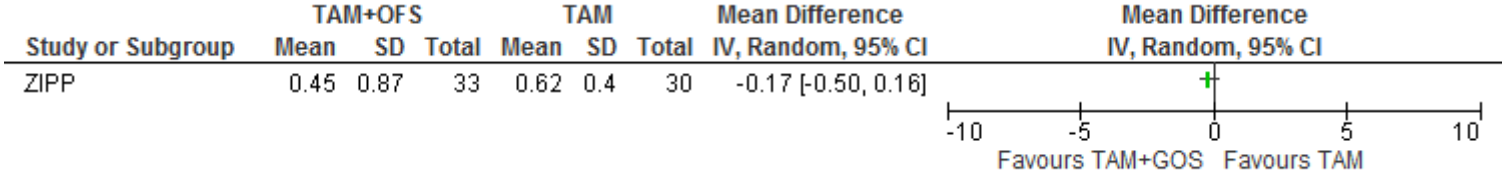


Figure 46: Treatment-related morbidity: changes in total body bone density (g/cm^2) at 2 year follow-up

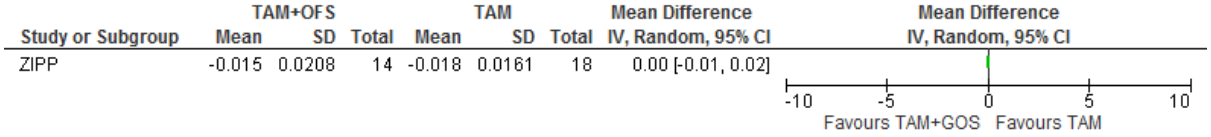


Figure 47: Compliance: treatment completed

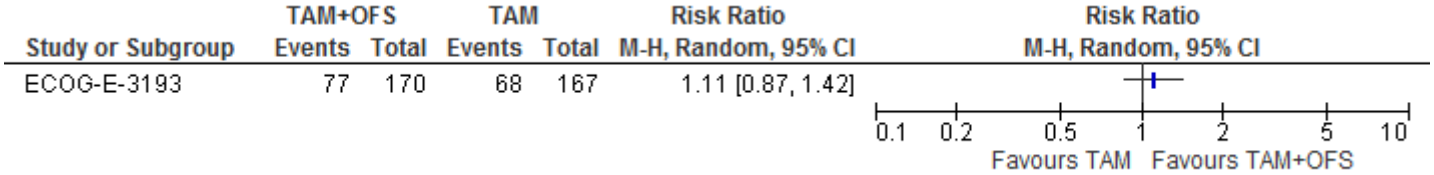


Figure 48: HRQoL: FACT-G

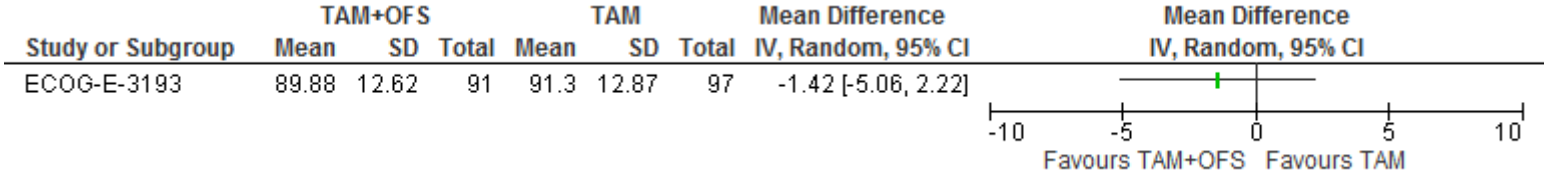
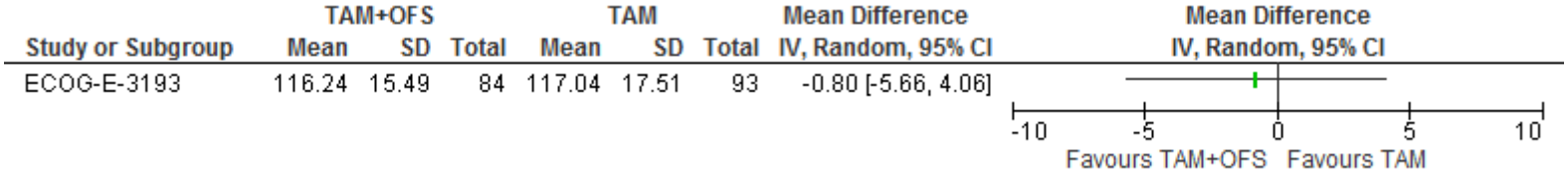


Figure 49: HRQoL: FACT-B



Forest plots for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Comparison 1. Tamoxifen versus no chemoprevention for people with excised DCIS

Figure 50: Disease-free survival at 10 year follow-up

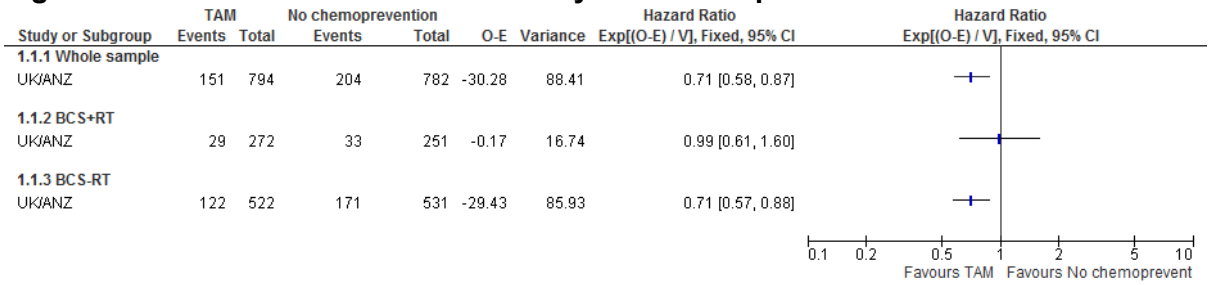


Figure 51: Local recurrence survival at 10 to 13.6 year follow-up

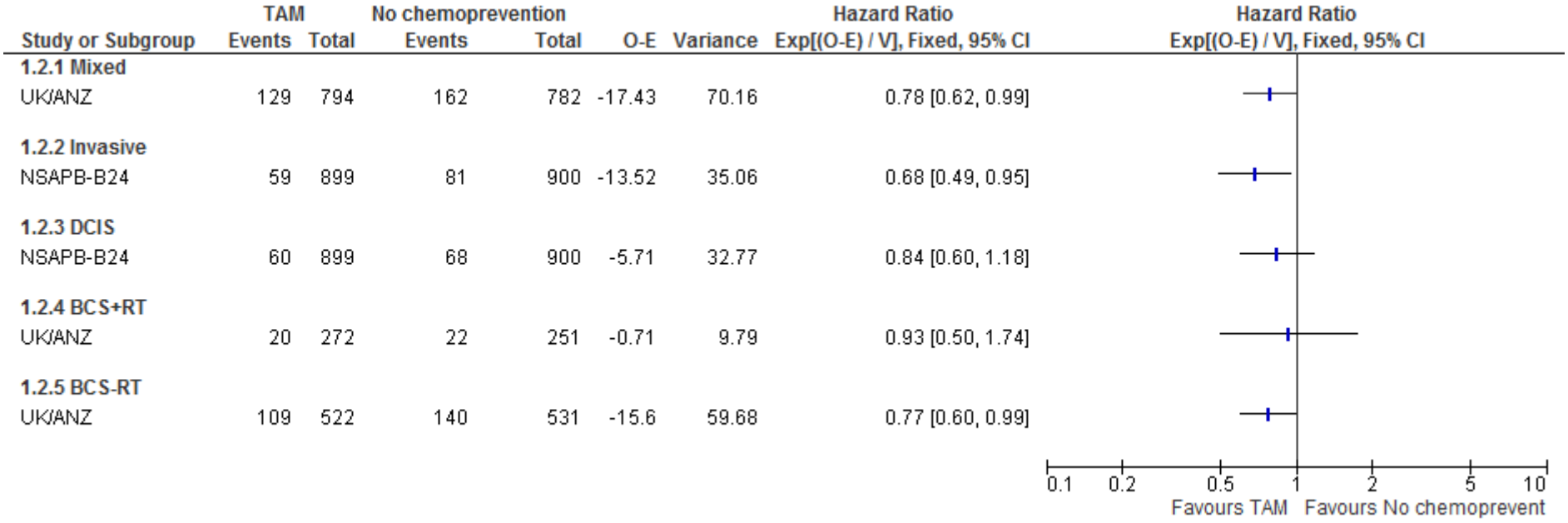


Figure 52: Overall survival at 13.6 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	O-E	Variance	Hazard Ratio Exp[(O-E) / V], Fixed, 95% CI
NSAPB-B24	48	899	49	900	-8.57	56.85	0.86 [0.66, 1.12]

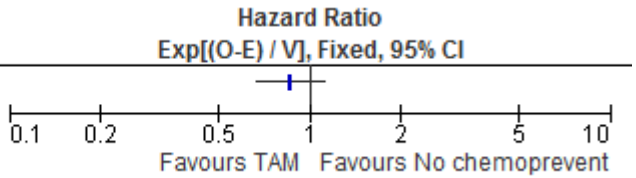


Figure 53: Treatment-related morbidity: vaginal dryness/discharge at 3.3 to 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Weight	Risk Ratio M-H, Random, 95% CI
Guerrieri-Gonzaga 2006	15	58	10	58	4.9%	1.50 [0.74, 3.06]
NSAPB-B24	289	891	178	890	95.1%	1.62 [1.38, 1.91]
Total (95% CI)		**949**		**948**	**100.0%**	**1.62 [1.38, 1.89]**
Total events	304		188			

Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%
Test for overall effect: Z = 5.95 (P < 0.00001)

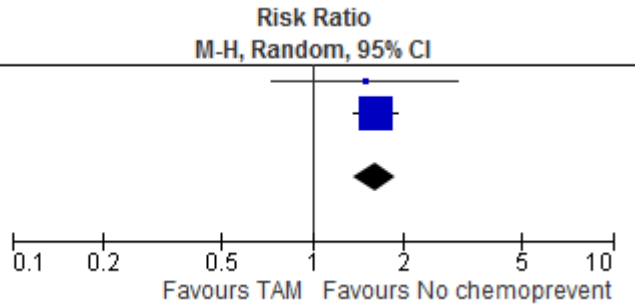


Figure 54: Treatment-related morbidity: grade 3+ toxicities at 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Risk Ratio M-H, Random, 95% CI
NSAPB-B24	48	891	38	890	1.26 [0.83, 1.91]

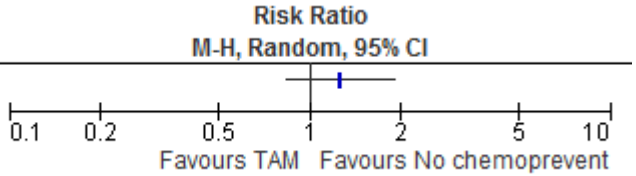


Figure 55: Treatment-related morbidity: phlebitis/thromboembolism at 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Risk Ratio M-H, Random, 95% CI
NSAPB-B24	16	891	7	890	2.28 [0.94, 5.52]

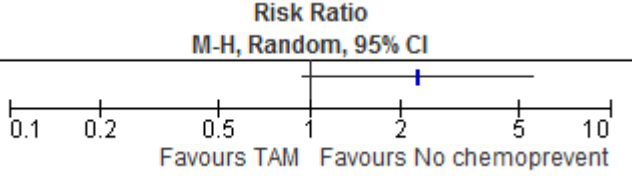


Figure 56: Treatment-related morbidity: mood changes at 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Risk Ratio M-H, Random, 95% CI
NSAPB-B24	94	891	95	890	0.99 [0.75, 1.29]

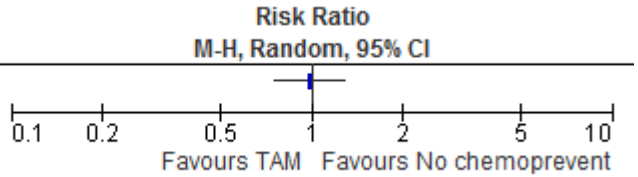


Figure 57: Treatment-related morbidity: menstrual disorders at 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Risk Ratio M-H, Random, 95% CI
NSAPB-B24	171	891	142	890	1.20 [0.98, 1.47]

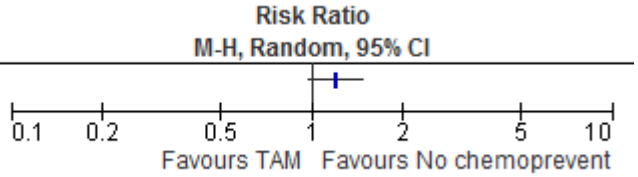


Figure 58: Treatment-related morbidity: hot flashes at 3.3 to 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Weight	Risk Ratio M-H, Random, 95% CI
Guerrieri-Gonzaga 2006	15	58	13	58	1.2%	1.15 [0.60, 2.20]
NSAPB-B24	620	891	525	890	98.8%	1.18 [1.10, 1.27]
Total (95% CI)		**949**		**948**	**100.0%**	**1.18 [1.10, 1.26]**
Total events	635		538			

Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%
Test for overall effect: Z = 4.65 (P < 0.00001)

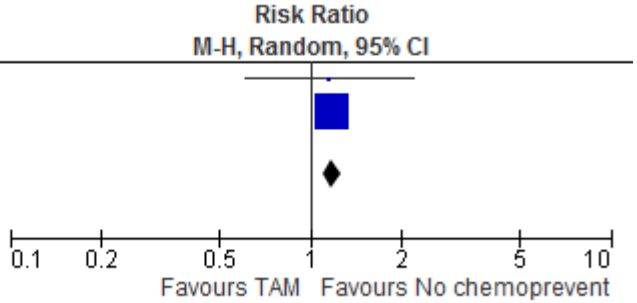


Figure 59: Treatment-related morbidity: fluid retention at 6.2 year follow-up

Study or Subgroup	TAM Events	TAM Total	No chemoprevention Events	No chemoprevention Total	Risk Ratio M-H, Random, 95% CI
NSAPB-B24	291	891	248	890	1.17 [1.02, 1.35]

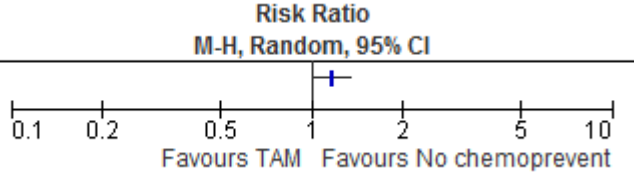


Figure 60: Treatment-related morbidity: ocular/visual at 3.3 year follow-up

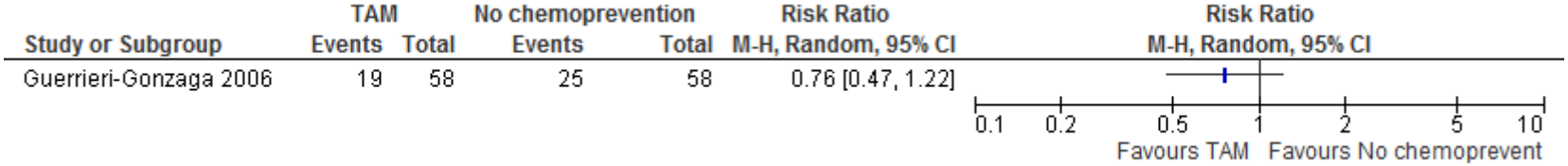


Figure 61: Treatment-related morbidity: dermatological at 3.3 year follow-up

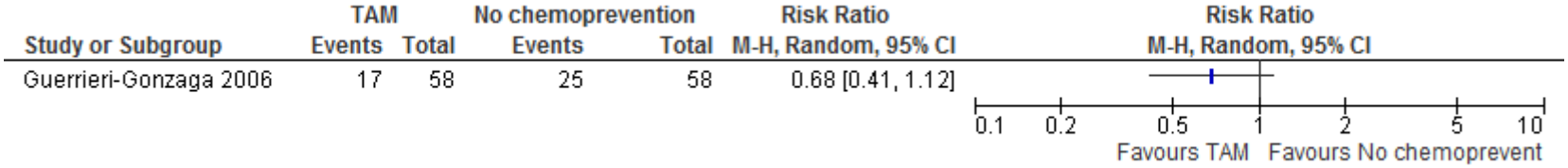


Figure 62: Treatment-related morbidity: dysuria/incontinence at 3.3 year follow-up

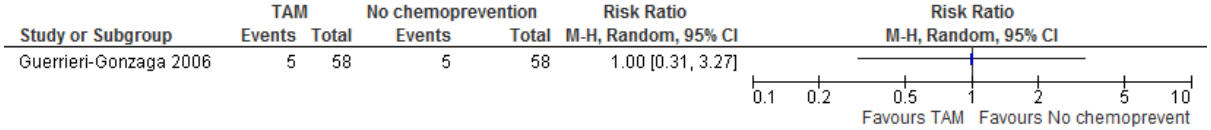


Figure 63: Treatment-related morbidity: vaginal bleeding at 3.3 year follow-up

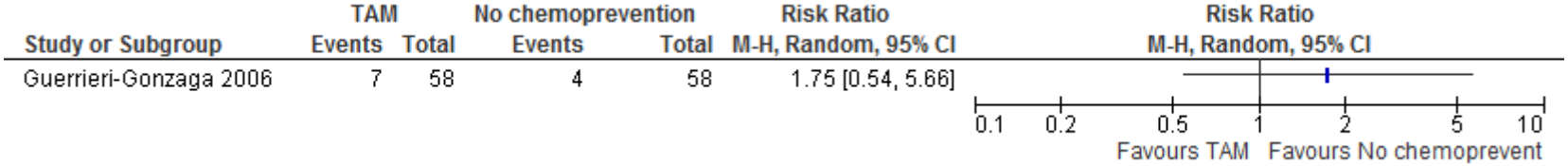


Figure 64: Treatment-related morbidity: endometrial polyps at 3.3 year follow-up

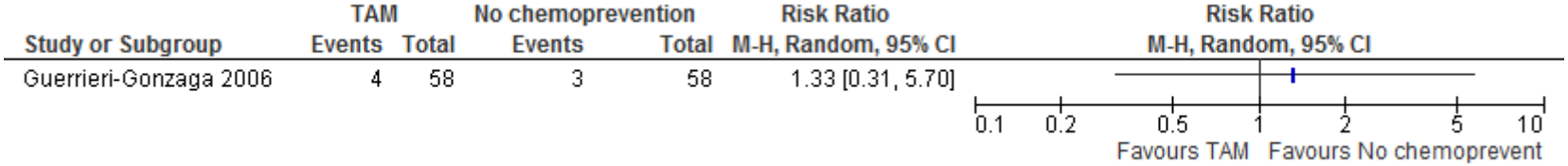
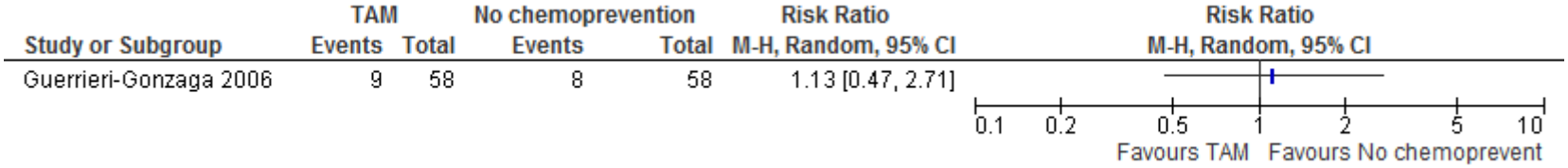


Figure 65: Treatment-related morbidity: sweats/weight gain at 3.3 year follow-up



Appendix F – GRADE tables

GRADE tables for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Table 13: Clinical evidence profile: Comparison 1. Endocrine therapy for greater than 5 years versus endocrine therapy for 5 years only

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ET>5yrs	ET=5yrs	Relative (95% CI)	Absolute	Quality	Importance
Disease-free survival - Whole sample (2.5 to 15 year follow-up)												
7	Randomised trials	No serious risk of bias	Very serious[1]	No serious indirectness[2]	No serious imprecision	None	925/8009 (11.5%)	1103/8046 (13.7%)	HR 0.85 (0.78 to 0.93)	12 fewer per 1000 (from 6 fewer to 18 fewer)	LOW	CRITICAL
Disease-free survival - Grade 3 (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	[3]	None	NR	NR	HR 0.73 (0.29 to 1.84)	-	number of events was not reported - insufficient information to judge imprecision, and therefore overall quality	CRITICAL
Disease-free survival - Continued tamoxifen (5.6 to 15 year follow-up)												
4	Randomised trials	No serious risk of bias	Very serious[4]	No serious indirectness[2]	No serious imprecision	None	766/4257 (18.0%)	839/4223 (19.9%)	HR 0.92 (0.84 to 1.01)	11 fewer per 1000 (from 23 fewer to 1 more)	LOW	CRITICAL
Disease-free survival - Switched to AI (2.5 to 5 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	159/3752 (4.2%)	264/3823 (6.9%)	HR 0.61 (0.5 to 0.74)	26 fewer per 1000 (from 17 fewer to 34 fewer)	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ET>5yrs	ET=5yrs	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (4 to 15 year follow-up)												
6	Randomised trials	No serious risk of bias	Serious[5]	No serious indirectness[6]	No serious imprecision	None	801/7253 (11%)	888/7302 (12.2%)	HR 0.91 (0.83 to 1)	10 fewer per 1000 (from 20 fewer to 0 more)	MODERATE	CRITICAL
Overall survival - Continued tamoxifen (5.6 to 15 year follow-up)												
4	Randomised trials	No serious risk of bias	Serious[7]	No serious indirectness[6]	No serious imprecision	None	710/4284 (16.6%)	771/4249 (18.1%)	HR 0.92 (0.84 to 1.02)	13 fewer per 1000 (from 27 fewer to 3 more)	MODERATE	CRITICAL
Overall survival - Switched to AI (4 to 5 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	91/2969 (3.1%)	117/3053 (3.8%)	HR 0.85 (0.65 to 1.12)	6 fewer per 1000 (from 13 fewer to 4 more)	MODERATE	CRITICAL
Compliance - did not comply with/complete assigned treatment												
4	Randomised trials	No serious risk of bias	Very serious[9]	No serious indirectness[2]	No serious imprecision	None	1649/9793 (16.8%)	852/9765 (8.7%)	RR 1.12 (0.44 to 2.81)	10 more per 1000 (from 49 fewer to 158 more)	LOW	IMPORTANT
Treatment-related morbidity - hot flushes (2 month to 4 year follow-up)												
3	Randomised trials	No serious risk of bias	Very serious[10]	No serious indirectness	Serious[11]	None	1859/3542 (52.5%)	1716/3615 (47.5%)	RR 1.19 (0.93 to 1.53)	90 more per 1000 (from 33 fewer to 252 more)	VERY LOW	CRITICAL
Treatment-related morbidity - secondary cancer – Any (5.6 to 7.6 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[6]	No serious imprecision	None	922/7310 (12.6%)	907/7271 (12.5%)	RR 1.01 (0.93 to 1.1)	1 more per 1000 (from 9	HIGH	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ET>5yrs	ET=5yrs	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 12 more)		
Treatment-related morbidity - secondary cancer - Contralateral breast (6 to 7.6 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None	441/7210 (6.1%)	490/7178 (6.8%)	RR 0.9 (0.79 to 1.02)	7 fewer per 1000 (from 14 fewer to 1 more)	HIGH	CRITICAL
Treatment-related morbidity - secondary cancer – Endometrial (6 to 7.6 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	132/7210 (1.8%)	70/7178 (1%)	RR 1.87 (1.4 to 2.5)	8 more per 1000 (from 4 more to 15 more)	MODERATE	CRITICAL
Treatment-related morbidity - bone fractures (2 month to 7.6 year follow-up)												
4	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[11]	None	230/10185 (2.3%)	214/10253 (2.1%)	RR 1.08 (0.9 to 1.3)	2 more per 1000 (from 2 fewer to 6 more)	MODERATE	CRITICAL
Treatment-related morbidity – arthralgia (2 month to 4 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	754/3742 (20.1%)	622/3825 (16.3%)	RR 1.24 (1.13 to 1.37)	39 more per 1000 (from 21 more to 60 more)	HIGH	CRITICAL
Treatment-related morbidity - cardiac disease/event (2 month to 7.6 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	277/9402 (2.9%)	307/9474 (3.2%)	RR 0.91 (0.69 to 1.19)	3 fewer per 1000 (from 10 fewer to 6 more)	HIGH	CRITICAL
Treatment-related morbidity – hypertension (4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[12]	None	130/2572 (5.1%)	129/2577 (5%)	RR 1.01 (0.8 to 1.28)	1 more per 1000 (from 10	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ET>5yrs	ET=5yrs	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 14 more)		
Treatment-related morbidity – osteoporosis (4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	209/2561 (8.2%)	155/2565 (6%)	RR 1.35 (1.11 to 1.65)	21 more per 1000 (from 7 more to 39 more)	HIGH	CRITICAL
Treatment-related morbidity – myalgia (4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	380/2572 (14.8%)	310/2577 (12%)	RR 1.23 (1.07 to 1.41)	28 more per 1000 (from 8 more to 49 more)	HIGH	CRITICAL
Treatment-related morbidity - any grade 3+ toxicity (2.5 to 5.6 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[13]	Very serious[14]	None	82/883 (9.3%)	59/872 (6.8%)	RR 1.38 (1 to 1.9)	26 more per 1000 (from 0 more to 61 more)	LOW	CRITICAL
Treatment-related morbidity - vaginal dryness (2 month to 4 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[11]	None	192/2959 (6.5%)	161/3046 (5.3%)	RR 1.34 (0.91 to 1.96)	18 more per 1000 (from 5 fewer to 51 more)	MODERATE	CRITICAL
Treatment-related morbidity - vaginal bleeding (2 month to 4 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[15]	None	148/2959 (5%)	197/3046 (6.5%)	RR 1.09 (0.29 to 4.11)	6 more per 1000 (from 46 fewer to 201 more)	LOW	CRITICAL
Treatment-related morbidity - vaginal discharge (2 month to 4 year follow-up)												
2	Randomised trials	No serious	Very serious[16]	No serious indirectness	Very serious[12]	None	105/970 (10.8%)	115/1038 (11.1%)	RR 1.24 (0.46 to 3.3)	27 more per 1000 (from 60	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ET>5yrs	ET=5yrs	Relative (95% CI)	Absolute	Quality	Importance
		risk of bias								fewer to 255 more)		
Treatment-related morbidity – stroke (7.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[14]	None	130/6454 (2%)	119/6440 (1.8%)	RR 1.09 (0.85 to 1.39)	2 more per 1000 (from 3 fewer to 7 more)	LOW	CRITICAL
Treatment-related morbidity - irregular menstruation (4 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[17]	None	146/583 (25%)	154/569 (27.1%)	RR 0.93 (0.76 to 1.12)	19 fewer per 1000 (from 65 fewer to 32 more)	MODERATE	CRITICAL
Treatment-related morbidity - phlebitis/thromboembolic events (2 month to 7.6 year follow-up)												
3	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[8]	None	52/7424 (0.7%)	23/7478 (0.3%)	RR 2.17 (1.32 to 3.57)	4 more per 1000 (from 1 more to 8 more)	MODERATE	CRITICAL
HRQoL - change in SF-36 scores from baseline (2 year follow-up) - Physical health (Better indicated by higher values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	211	171	-	MD 1 higher (0.73 lower to 2.73 higher)	HIGH	IMPORTANT
HRQoL - change in SF-36 scores from baseline (2 year follow-up) - Mental health (Better indicated by higher values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	211	171	-	MD 0.6 lower (2.42 lower to 1.22 higher)	HIGH	IMPORTANT
HRQoL - change in MENQOL scores from baseline (2 year follow-up) - Vasomotor (Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ET>5yrs	ET=5yrs	Relative (95% CI)	Absolute		
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	209	177	-	MD 0.4 higher (0.15 to 0.65 higher)	HIGH	IMPORTANT
HRQoL - change in MENQOL scores from baseline (2 year follow-up) - Psychosocial (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	209	170	-	MD 0.1 lower (0.31 lower to 0.11 higher)	HIGH	IMPORTANT
HRQoL - change in MENQOL scores from baseline (2 year follow-up) - Physical (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	208	178	-	MD 0 higher (0.21 lower to 0.21 higher)	HIGH	IMPORTANT
HRQoL - change in MENQOL scores from baseline (2 year follow-up) - Sexual (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	152	111	-	MD 0.2 higher (0.08 lower to 0.48 higher)	HIGH	IMPORTANT

AI, aromatase inhibitor; CI: Confidence interval; ET, endocrine therapy; HRQoL: health-related quality of life; MENQOL, menopause-specific quality of life; NR, not reported; RR: Risk ratio; SF-36, 36-Item Short Form Survey

[1] *Significant heterogeneity - I squared value 82% - heterogeneity explored in subgroup analyses*

[2] *Serious indirectness in Scottish Adjuvant Tamoxifen Trial due to population; however, this study does not have very much weight in the analysis*

[3] *Number of events were not reported - insufficient information to judge imprecision*

[4] *Significant heterogeneity - I squared value 85% - not possible to further investigate heterogeneity as subgroups of interest identified by the GC were not reported for trials that contributed to this estimate*

[5] *Significant heterogeneity - I squared value 53% - heterogeneity explored in subgroup analyses*

[6] *Serious indirectness in Scottish Adjuvant Tamoxifen Trial and Tormey 1996 due to population; however, neither of these studies have much weight in the analysis*

[7] *Significant heterogeneity - I squared value 71% - not possible to further investigate heterogeneity as subgroups of interest identified by the GC were not reported for trials that contributed to this estimate*

[8] *<300 events*

[9] *Significant heterogeneity - I squared value 99%. High rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes.*
[10] *Random effects model with significant heterogeneity - I squared value 91% - high rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes.*
[11] *95% CI crosses both no effect (1) and GRADE default value for minimally important difference (1.25)*
[12] *<300 events and 95% CI crosses both boundaries for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*
[13] *Serious indirectness in Tormey 1996 due to population but study does not have much weight in the analysis*
[14] *<300 events and 95% crosses both no effect (1) and minimally important difference (1.25) based on GRADE default value*
[15] *95% CI crosses both boundaries for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values*
[16] *Significant heterogeneity - I squared value 87% - high rates of unexplained heterogeneity as subgroups of interest were only identified by the GC for critical outcomes.*
[17] *95% CI crosses both no effect (1) and minimally important difference (0.8) based on GRADE default value*

GRADE tables for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Table 14: Clinical evidence profile: Comparison 1. Ovarian suppression plus tamoxifen versus tamoxifen alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen + ovarian suppression	Tamoxifen only	Relative (95% CI)	Absolute	Quality	Importance
Overall survival - Whole sample (5 to 9.9 year follow-up)												
4	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness[7]	Serious[2]	None	107/2047 (5.2%)	132/2061 (6.4%)	HR 0.81 (0.66 to 1)	12 fewer per 1000 (from 21 fewer to 0 more)	LOW	IMPORTANT
Overall survival - Previous chemotherapy: yes (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	39/542 (7.2%)	57/542 (10.5%)	HR 0.64 (0.42 to 0.97)	37 fewer per 1000 (from 3 fewer to 60 fewer)	LOW	IMPORTANT
Overall survival - Previous chemotherapy: no (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8/473 (1.7%)	2/476 (0.42%)	HR 3.84 (0.81 to 18.18)	12 more per 1000 (from 1 fewer to 69 more)	LOW	IMPORTANT
Disease-free survival - Whole sample (5 to 9.9 year follow-up)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	160/1185 (13.5%)	184/1185 (15.5%)	HR 0.83 (0.67 to 1.03)	25 fewer per 1000 (from 48 fewer to 4 more)	MODERATE	CRITICAL
Disease-free survival - Age: <35 (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	29/121 (24%)	35/112 (31.3%)	HR 0.68 (0.42 to 1.11)	88 fewer per 1000 (from 167 fewer to 28 more)	LOW	CRITICAL
Disease-free survival - Age: 35-39 (5 year follow-up)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen + ovarian suppression	Tamoxifen only	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	33/184 (17.9%)	41/203 (20.2%)	HR 0.78 (0.49 to 1.24)	41 fewer per 1000 (from 97 fewer to 42 more)	LOW	CRITICAL
Disease-free survival - Age: 40+ (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	77/710 (10.8%)	84/703 (11.9%)	HR 0.9 (0.66 to 1.22)	11 fewer per 1000 (from 39 fewer to 24 more)	LOW	CRITICAL
Disease-free survival - Grade: 1 (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	22/265 (8.3%)	18/275 (6.5%)	HR 1.23 (0.66 to 2.29)	14 more per 1000 (from 22 fewer to 78 more)	LOW	CRITICAL
Disease-free survival - Grade: 2 (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	59/514 (11.5%)	79/492 (16.1%)	HR 0.67 (0.48 to 0.94)	50 fewer per 1000 (from 9 fewer to 80 fewer)	LOW	CRITICAL
Disease-free survival - Grade: 3 (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	54/212 (25.5%)	61/227 (26.9%)	HR 0.85 (0.59 to 1.23)	35 fewer per 1000 (from 100 fewer to 51 more)	LOW	CRITICAL
Disease-free survival - HER2: negative (5 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	121/867 (14%)	130/857 (15.2%)	HR 0.88 (0.69 to 1.13)	17 fewer per 1000 (from 44 fewer to 18 more)	LOW	CRITICAL
Disease-free survival - HER2: positive (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	14/119 (11.8%)	27/117 (23.1%)	HR 0.42 (0.22 to 0.8)	126 fewer per 1000	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen + ovarian suppression	Tamoxifen only	Relative (95% CI)	Absolute	Quality	Importance
										(from 41 fewer to 175 fewer)		
Disease-free survival - Previous chemotherapy: yes (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	107/542 (19.7%)	122/542 (22.5%)	HR 0.82 (0.63 to 1.06)	36 fewer per 1000 (from 77 fewer to 12 more)	LOW	CRITICAL
Disease-free survival - Previous chemotherapy: no (5 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	32/473 (6.8%)	38/476 (8%)	HR 0.83 (0.52 to 1.33)	13 fewer per 1000 (from 37 fewer to 24 more)	LOW	CRITICAL
Treatment-related morbidity: vasodilation (follow-up not-reported)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious indirectness[7]	Serious[2]	None	200/457 (43.8%)	78/463 (16.8%)	RR 2.6 (2.07 to 3.26)	270 more per 1000 (from 180 more to 381 more)	VERY LOW	CRITICAL
Treatment-related morbidity: weight gain (follow-up not reported)												
2	Randomised trials	Serious[1]	No serious inconsistency	Serious indirectness[7]	Serious[2]	None	56/631 (8.9%)	36/634 (5.7%)	RR 1.57 (1.05 to 2.35)	32 more per 1000 (from 3 more to 77 more)	VERY LOW	CRITICAL
Treatment-related morbidity: arthralgia (follow-up not-reported)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious indirectness[7]	Serious[2]	None	11/457 (2.4%)	4/463 (0.86%)	RR 2.79 (0.89 to 8.69)	15 more per 1000 (from 1 fewer to 66 more)	VERY LOW	CRITICAL
Treatment-related morbdity: anxiety/depression/irritability (follow-up not-reported)												
3	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	74/1636 (4.5%)	52/1640 (3.2%)	RR 1.5 (0.82 to 2.75)	16 more per 1000 (from 6	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen + ovarian suppression	Tamoxifen only	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 55 more)		
Treatment-related morbidity: sweating (follow-up not reported)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	24/631 (3.8%)	5/634 (0.79%)	RR 4.49 (1.79 to 11.24)	28 more per 1000 (from 6 more to 81 more)	LOW	CRITICAL
Treatment-related morbidity: hot flushes (grade 3+; 3 to 5.6 year follow-up)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	161/1179 (13.7%)	84/1177 (7.1%)	RR 2.23 (1.18 to 4.21)	88 more per 1000 (from 13 more to 229 more)	LOW	CRITICAL
Treatment-related morbidity: hypertension (grade 3+; 5.6 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	75/1005 (7.5%)	54/1006 (5.4%)	RR 1.39 (0.99 to 1.95)	21 more per 1000 (from 1 fewer to 51 more)	LOW	CRITICAL
Treatment related morbidity: cardiac ischemia or infarction (grade 3+; 5.6 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/1005 (0.1%)	4/1006 (0.4%)	RR 0.25 (0.03 to 2.24)	3 fewer per 1000 (from 4 fewer to 5 more)	LOW	CRITICAL
Treatment related morbidity: thrombosis or embolism (grade 3+; 5.6 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	17/1005 (1.7%)	17/1006 (1.7%)	RR 1 (0.51 to 1.95)	0 fewer per 1000 (from 8 fewer to 16 more)	LOW	CRITICAL
Treatment related morbidity: musculoskeletal symptoms (grade 3+; 5.6 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	55/1005 (5.5%)	63/1006 (6.3%)	RR 0.87 (0.62 to 1.24)	8 fewer per 1000 (from 24 fewer to 15 more)	LOW	CRITICAL
Treatment related morbidity: osteoporosis (grade 3+; 5.6 year follow-up)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen + ovarian suppression	Tamoxifen only	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	3/1005 (0.3%)	1/1006 (0.1%)	RR 3 (0.31 to 28.82)	2 more per 1000 (from 1 fewer to 28 more)	LOW	CRITICAL
Treatment related morbidity: fractures (grade 3+; 5.6 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	8/1005 (0.8%)	8/1006 (0.8%)	RR 1 (0.38 to 2.66)	0 fewer per 1000 (from 5 fewer to 13 more)	LOW	CRITICAL
Treatment related morbidity: vaginal dryness (3 to 5.6 year follow-up)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	501/1179 (42.5%)	421/1177 (35.8%)	RR 1.19 (1.08 to 1.31)	68 more per 1000 (from 29 more to 111 more)	MODERATE	CRITICAL
Treatment-related morbidity: changes in libido (3 to 5.6 year follow-up)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision	None	478/1179 (40.5%)	427/1177 (36.3%)	RR 1.12 (1.02 to 1.23)	44 more per 1000 (from 7 more to 83 more)	MODERATE	CRITICAL
Treatment related morbidity: CNS cerebrovascular ischemia (grade 3+; 5.6 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[2]	None	1/1005 (0.1%)	4/1006 (0.4%)	RR 0.25 (0.03 to 2.24)	3 fewer per 1000 (from 4 fewer to 5 more)	LOW	CRITICAL
Treatment related morbidity: CNS hemorrhage (grade 3+; 5.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	1/1005 (0.1%)	0/1006 (0%)	RR 3 (0.12 to 73.63)	-	LOW	CRITICAL
Treatment-related morbidity: vasomotor symptoms measured by Physical Symptoms and Problem List (Better indicated by lower values; 3 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	Very serious[3,7]	Serious[2]	None	32	28	-	MD 0.1 higher (0.44 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen + ovarian suppression	Tamoxifen only	Relative (95% CI)	Absolute	Quality	Importance
										0.64 higher)		
Treatment-related morbidity: vaginal dryness measured by Physical Symptoms and Problem List (Better indicated by lower values; 3 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	Very serious[3,7]	Serious[2]	None	33	30	-	MD 0.17 lower (0.5 lower to 0.16 higher)	VERY LOW	CRITICAL
Changes in total body bone density (g/cm2) (Better indicated by higher values; 2 year follow-up)												
1	Randomised trials	Serious[1]	No serious inconsistency	Very serious[3,7]	Serious[2]	None	14	18	-	MD 0 higher (0.01 lower to 0.02 higher)	VERY LOW	CRITICAL
Compliance: treatment completed												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[2]	None	77/170 (45.3%)	68/167 (40.7%)	RR 1.11 (0.87 to 1.42)	45 more per 1000 (from 53 fewer to 171 more)	MODERATE	IMPORTANT
HRQoL: FACT-G (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	91	97	-	MD 1.42 lower (5.06 lower to 2.22 higher)	VERY LOW	CRITICAL
HRQoL: FACT-B (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	No serious imprecision[5]	None	84	93	-	MD 0.8 lower (5.66 lower to 4.06 higher)	MODERATE	CRITICAL

CI: confidence interval; CNS: central nervous system; FACT-B: Functional assessment of cancer therapy – breast cancer; FACT-G: Functional assessment of cancer therapy – general; HER2: human epidermal growth factor receptor 2; HR: hazard ratio; HRQoL: health-related quality of life; RR: risk ratio

[1] Unclear allocation concealment and/or randomisation sequence generation

[2] Optimal information size not met (Number of events=300 for dichotomous outcomes, N=400 for continuous outcomes)

[3] *29% of TAM+GOS arm and 11% of TAM arm were ER negative*
[4] *MID for FACT-G was 3 points; N<400*
[5] *MID for FACT-B total score was 7 points*
[6] *Patients in the ZIPP and ABC trials received concurrent chemotherapy, but at similar rates in both arms*

GRADE tables for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Table 15: Clinical evidence profile: Comparison 1. Tamoxifen versus no chemoprevention for people with excised DCIS

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	No chemoprevention	Relative (95% CI)	Absolute		
Disease-free survival - Whole sample (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	151/794 (19%)	204/782 (26.1%)	HR 0.71 (0.58 to 0.87)	261 fewer per 1000 (from 261 fewer to 261 fewer)	HIGH	CRITICAL
Disease-free survival - BCS+RT (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	29/272 (10.7%)	33/251 (13.1%)	HR 0.99 (0.61 to 1.60)	131 fewer per 1000 (from 131 fewer to 131 fewer)	MODERATE	CRITICAL
Disease-free survival - BCS-RT (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	122/522 (23.4%)	171/531 (32.2%)	HR 0.71 (0.57 to 0.88)	322 fewer per 1000 (from 322 fewer to 322 fewer)	MODERATE	CRITICAL
Local recurrence – Mixed (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	129/794 (16.2%)	162/782 (20.7%)	HR 0.78 (0.62 to 0.99)	207 fewer per 1000 (from	MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	No chemoprevention	Relative (95% CI)	Absolute		
										207 fewer to 207 fewer)		
Local recurrence – Invasive (13.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	59/899 (6.6%)	81/900 (9%)	HR 0.68 (0.49 to 0.95)	90 fewer per 1000 (from 90 fewer to 90 fewer)	MODERATE	CRITICAL
Local recurrence – DCIS (13.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	60/899 (6.7%)	68/900 (7.6%)	HR 0.84 (0.60 to 1.18)	76 fewer per 1000 (from 76 fewer to 76 fewer)	MODERATE	CRITICAL
Local recurrence - BCS+RT (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	20/272 (7.4%)	22/251 (8.8%)	HR 0.93 (0.50 to 1.74)	88 fewer per 1000 (from 88 fewer to 88 fewer)	MODERATE	CRITICAL
Local recurrence - BCS-RT (10 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	109/522 (20.9%)	140/531 (26.4%)	HR 0.77 (0.60 to 0.99)	264 fewer per 1000 (from 264 fewer to 264 fewer)	MODERATE	CRITICAL
Overall survival (13.6 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[1]	None	48/899 (5.3%)	49/900 (5.4%)	HR 0.86 (0.66 to 1.12)	54 fewer per 1000 (from 54 fewer to 54 fewer)	MODERATE	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	No chemoprevention	Relative (95% CI)	Absolute		
Treatment-related morbidity - vaginal dryness/discharge (3.3 to 6.2 year follow-up)												
2	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None	304/949 (32%)	188/948 (19.8%)	RR 1.62 (1.38 to 1.89)	123 more per 1000 (from 75 more to 176 more)	HIGH	CRITICAL
Treatment-related morbidity - grade 3+ toxicities (6.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	48/891 (5.4%)	38/890 (4.3%)	RR 1.26 (0.83 to 1.91)	11 more per 1000 (from 7 fewer to 39 more)	LOW	CRITICAL
Treatment-related morbidity - phlebitis/thromboembolism (6.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[3]	None	16/891 (1.8%)	7/890 (0.79%)	RR 2.28 (0.94 to 5.52)	10 more per 1000 (from 0 fewer to 36 more)	LOW	CRITICAL
Treatment-related morbidity - mood changes (6.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Very serious[4]	None	94/891 (10.5%)	95/890 (10.7%)	RR 0.99 (0.75 to 1.29)	1 fewer per 1000 (from 27 fewer to 31 more)	LOW	CRITICAL
Treatment-related morbidity - menstrual disorders (6.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	Serious[5]	None	171/891 (19.2%)	142/890 (16%)	RR 1.2 (0.98 to 1.47)	32 more per 1000 (from 3 fewer to 75 more)	MODERATE	CRITICAL
Treatment-related morbidity - hot flashes (3.3 to 6.2 year follow-up)												
2	Randomised trials	No serious	No serious inconsistency	No serious indirectness[2]	No serious imprecision	None	635/949 (66.9%)	538/948 (56.8%)	RR 1.18 (1.1 to 1.26)	102 more per 1000 (from 57	HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	No chemoprevention	Relative (95% CI)	Absolute		
		risk of bias								more to 148 more)		
Treatment-related morbidity - fluid retention (6.2 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	No serious indirectness	No serious imprecision	None	291/891 (32.7%)	248/890 (27.9%)	RR 1.17 (1.02 to 1.35)	47 more per 1000 (from 6 more to 98 more)	HIGH	CRITICAL
Treatment-related morbidity - ocular/visual (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[6]	Very serious[7]	None	19/58 (32.8%)	25/58 (43.1%)	RR 0.76 (0.47 to 1.22)	103 fewer per 1000 (from 228 fewer to 95 more)	VERY LOW	CRITICAL
Treatment-related morbidity - dermatology/skin (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[6]	Very serious[7]	None	17/58 (29.3%)	25/58 (43.1%)	RR 0.68 (0.41 to 1.12)	138 fewer per 1000 (from 254 fewer to 52 more)	VERY LOW	CRITICAL
Treatment-related morbidity - dysuria/incontinence (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[6]	Very serious[4]	None	5/58 (8.6%)	5/58 (8.6%)	RR 1 (0.31 to 3.27)	0 fewer per 1000 (from 59 fewer to 196 more)	VERY LOW	CRITICAL
Treatment-related morbidity - vaginal bleeding (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[6]	Very serious[4]	None	7/58 (12.1%)	4/58 (6.9%)	RR 1.75 (0.54 to 5.66)	52 more per 1000 (from 32 fewer to	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tamoxifen	No chemoprevention	Relative (95% CI)	Absolute		
										321 more)		
Treatment-related morbidity - endometrial polyps (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[6]	Very serious[4]	None	4/58 (6.9%)	3/58 (5.2%)	RR 1.33 (0.31 to 5.7)	17 more per 1000 (from 36 fewer to 243 more)	VERY LOW	CRITICAL
Treatment-related morbidity - sweats/weight gain (3.3 year follow-up)												
1	Randomised trials	No serious risk of bias	No serious inconsistency	Very serious[6]	Very serious[4]	None	9/58 (15.5%)	8/58 (13.8%)	RR 1.13 (0.47 to 2.71)	18 more per 1000 (from 73 fewer to 236 more)	VERY LOW	CRITICAL

BCS: breast-conserving surgery; CI: Confidence interval; HR: hazards ratio; RR: Risk ratio; RT: radiotherapy
[1] <300 events
[2] Very serious indirectness in Guerrieri-Gonzaga 2006 due to population; evidence not downgraded as study only given 4.9% weight in analysis
[3] <300 events; 95% CI crosses boundary of no effect (1) and minimally important difference (1.25) based on GRADE default values
[4] <300 events; 95% CI crosses both boundary for no effect (1) and minimally important differences (0.8 and 1.25) based on GRADE default values
[5] 95% CI crosses boundary of no effect (1) and minimally important difference (1.25) based on GRADE default values
[6] Only 57% of population had excised DCIS
[7] <300 events; 95% CI crosses boundary of no effect (1) and minimally important difference (0.8) based on GRADE default values

Appendix G – Economic evidence study selection

Economic evidence study selection for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

See Supplement 1: Health economics literature review for details of economic study selection.

Economic evidence study selection for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

See Supplement 1: Health economics literature review for details of economic study selection.

Appendix H – Economic evidence tables

Economic evidence tables for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Table 16: Economic evidence table showing the included health economic evidence for the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
Author & year: Erman et al. 2014 **Country:** Canada **Type of economic analysis:** Cost-utility analysis **Source of funding:** Not reported.	• *Standard tamoxifen* Standard tamoxifen treatment given for five years. • *Extended tamoxifen* Tamoxifen treatment given for another five years after standard tamoxifen treatment (tamoxifen treatment extended to ten years). • *Extended aromatase inhibitors* Aromatase inhibitors given instead of tamoxifen for five years after standard tamoxifen treatment (total treatment time of ten years).	**Population characteristics:** Post-menopausal women with early stage (stage I-III) HR+ breast cancer. The average age of the modelled cohort was 65 years old. **Modelling approach:** Post-menopausal women with early stage (stage I-III) HR+ breast cancer. **Source of base-line and effectiveness data:** Clinical data was sourced from RCTs (primarily ATLAS trial) comparing standard tamoxifen with extended tamoxifen or extended aromatase inhibitors. Data from the standard tamoxifen arm was used as the baseline data with relative risks applied for the other treatment options. It was assumed that the event rate was constant over time.	***Extended tamoxifen vs standard tamoxifen*** **Mean cost per patient** • Standard tamoxifen: $9,343.66 (CAD) • Extended tamoxifen: $8,623.06 (CAD) • Incremental: -$720.60 (CAD) - **Mean QALYs per patient:** • Standard tamoxifen: 10.12 QALYs • Extended tamoxifen: 10.38 QALYs • Incremental: 0.26 QALYs **ICER:** Dominant (extended tamoxifen is less costly and more effective) ***Extended aromatase inhibitors vs standard tamoxifen*** **Mean cost per patient** • Standard tamoxifen: $9,343.66 (CAD) • Extended aromatase inhibitors: $9,432.73 (CAD) • Incremental: $89.07 (CAD)	**Perspective:** Canadian health care system. **Currency:** Canadian dollars ($ CAD) **Cost year:** 2012 **Time horizon:** Lifetime **Discounting:** Costs and QALYs were discounted by 5% per year. **Applicability:** The study was deemed to be only partially applicable to the UK because it considered the perspective of the

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
		While most clinical inputs were based on RCT data, some were informed by expert opinion. **Source of cost data:** Unit costs of the medications were sourced from the Ontario Drugs Benefit (ODB) program formulary list. Health care costs relating to breast cancer and adverse events were sourced from published cost-effectiveness studies considering the Canadian health care system. Follow-up was assumed to be the same in all treatment strategies and so was not considered in the analysis. **Source of QoL data:** QoL weights were sourced from published studies in women with breast cancer. Values were estimated using standard gamble or time-trade off methods.	**Mean QALYs per patient:** • Standard tamoxifen: 10.12 QALYs • Extended tamoxifen: 10.62 QALYs • Incremental: 0.50 QALYs **ICER:** $178.14 (CAD) per QALY ***Extended aromatase inhibitors vs Extended tamoxifen*** **Mean cost per patient** • Extended tamoxifen: $8,623.06 (CAD) • Extended aromatase inhibitors: $9,432.73 (CAD) • Incremental: $809.66 (CAD) per QALY **Mean QALYs per patient:** • Extended tamoxifen: 10.38 QALYs • Extended aromatase inhibitors: 10.62 QALYs • Incremental: 0.24 QALYs **ICER:** $3,402.38 (CAD) per QALY **Subgroup analysis:** Not conducted. **Sensitivity analysis:** A series of one-way sensitivity analyses were conducted exploring changes in costs and clinical inputs. The result was found to be sensitive to changes in the cost of aromatase inhibitors and the probability of recurrence when taking aromatase inhibitors or tamoxifen.	Canadian health care system. **Limitations:** The study was generally thought to be of good quality but some potentially serious limitations were noted such as the absence of some potentially key parameters from sensitivity analysis (utility weights). **Other comments:** Incremental values for the comparison against standard tamoxifen were not reported in study but have been estimated here as they were of most relevance to the review question.

Study details	Treatment strategies	Study population, design and data sources	Results	Comments
			Probabilistic sensitivity analysis: Probabilistic sensitivity analysis was conducted. At the conventional threshold of $50,000 (CAD) per QALY, the probability of being cost-effective was 70% for extended aromatase inhibitors, 30% for extended tamoxifen and 0.003% for standard tamoxifen.	

Economic evidence tables for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

No economic evidence was identified for this review question.

Economic evidence tables for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Table 17: Summary table showing the included health economic evidence for the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
Erman 2014	Post-menopausal women with early stage (stage I-III) HR+ breast cancer.	Comparison against standard tamoxifen						A series of one-way sensitivity analyses were conducted exploring changes in costs and clinical inputs. The result was found to be sensitive to changes in the cost of aromatase inhibitors and the probability of recurrence when taking aromatase inhibitors or tamoxifen. Probabilistic sensitivity analysis was conducted. At the conventional threshold of $50,000 (CAD) per QALY, the probability of being cost-effective was 70% for extended aromatase inhibitors, 30% for extended tamoxifen and 0.003% for standard tamoxifen.	The study was deemed to be only partially applicable to the UK because it considered the perspective of the Canadian health care system. The study was generally thought to be of good quality but some potentially serious limitations were noted such as the absence of some potentially key parameters from sensitivity analysis (utility weights).
		Standard tamoxifen	$9,343.66 (CAD)	10.12 QALYs	Reference				
		Extended tamoxifen	$8,623.06 (CAD)	10.38 QALYs	-$720.60 (CAD)	0.26 QALYs	Dominant		
		Extended aromatase inhibitors	$9,432.73 (CAD)	10.62 QALYs	$89.07 (CAD)	0.50 QALYs	$178.14 (CAD)		
		Dominance rank							
		Extended tamoxifen	$8,623.06 (CAD)	10.38 QALYs	Reference				
		Standard tamoxifen	$9,343.66 (CAD)	10.12 QALYs	$720.60 (CAD)	-0.26 QALYs	Dominated		
		Extended aromatase inhibitors	$9,432.73 (CAD)	10.62 QALYs	$809.66 (CAD)	0.24 QALYs	$3,402.38 (CAD) per QALY		

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability and limitations
	Comments: Strategies compared using 'dominance rank' approach to determine optimal strategy overall. Strategies are first ranked in terms of cost (least costly to most costly). The second intervention in the list is then compared against the first strategy. Subsequent strategies are then compared against the previous strategy that was found to be cost-effective. Strategies compared against standard tamoxifen were not reported in study but have been estimated here as they were of most relevance to the review question.								

Health economic evidence profiles for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

No economic evidence was identified for this review question.

Health economic evidence profiles for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

Health economic analysis for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

No health economic analysis was carried out for this review question.

Health economic analysis for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

No health economic analysis was carried out for this review question.

Health economic analysis for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

No health economic analysis was carried out for this review question.

Appendix K – Excluded studies

Excluded studies for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

Clinical studies

Excluded studies - RQ4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?	
Study	**Reason for exclusion**
Different Durations of Adjuvant Anastrozole Therapy After 2 to 3 Years Tamoxifen Therapy in Breast Cancer, Physician Data Query (PDQ), 2006	Protocol only
Abetz, L, Barghout, V, Loge, C, Arbuckle, R, No differences in quality of life for letrozole relative to placebo in post-menopausal women with early breast cancer regardless of age:results from the MA-17 study, European journal of cancer, 3, 96, 2005	Conference abstract
Al-Mubarak, M., Tibau, A., Templeton, A. J., Cescon, D. W., Ocana, A., Seruga, B., Amir, E., Extended adjuvant tamoxifen for early breast cancer: a meta-analysis, 9, e88238, 2014	Insufficient presentation of results
Bilimoria, Mm, Jordan, Vc, The duration of adjuvant tamoxifen therapy, Cancer treatment and research, 94, 181-93, 1998	Book chapter
Chapman, J. A., Meng, D., Shepherd, L., Parulekar, W., Ingle, J. N., Muss, H. B., Palmer, M., Yu, C., Goss, P. E., Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer, Journal of the National Cancer Institute, 100, 252-60, 2008	Insufficient presentation of results
Crivellari, D., Late-extended adjuvant treatment: Does it work?, Aging Health, 4, 237-240, 2008	Evaluation of MA.17
DeGrendele, H, O'Shaughnessy, Ja, Benefit of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer, Clinical breast cancer, 4, 311-2, 2003	Brief overview
Earl, H., Gray, R., Kerr, D., Lee, M., The optimal duration of adjuvant tamoxifen treatment for breast cancer remains uncertain: randomize into aTTom, Clinical Oncology (Royal College of Radiologists)Clin Oncol (R Coll Radiol), 9, 141-3, 1997	Editorial - summary of aim of aTTom
Goldvaser, H., AlGorashi, I., Ribnikar, D., Seruga, B., Templeton, A. J., Ocana, A., Amir, E., Efficacy of extended adjuvant therapy with aromatase inhibitors in early breast cancer among common clinicopathologically-defined	Contains comparisons outside scope

Excluded studies - RQ4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?	
Study	**Reason for exclusion**
subgroups: A systematic review and meta-analysis, Cancer Treatment ReviewsCancer Treat Rev, 60, 53-59, 2017	
Goldvaser, H., Barnes, T. A., Seruga, B., Cescon, D. W., Ocana, A., Ribnikar, D., Amir, E., Toxicity of Extended Adjuvant Therapy With Aromatase Inhibitors in Early Breast Cancer: A Systematic Review and Meta-analysis, Journal of the National Cancer InstituteJ Natl Cancer Inst, 110, 01, 2018	Contains comparisons outside scope
Goodwin, R. A., Jamal, R., Booth, C. M., Goss, P. E., Eisenhauer, E. A., Tu, D., Shepherd, L. E., Prognostic and predictive effects of diabetes, hypertension, and coronary artery disease among women on extended adjuvant letrozole: NCIC CTG MA.17, European journal of cancer, 58, 97-103, 2016	Re-analysis of MA.17 - subgroups not of interest
Goss, P, Ingle, J, Martino, S, Robert, N, Muss, H, Shepherd, L, Outcomes of Women Who Were Premenopausal at Diagnosis of Early Stage Breast Cancer in the NCIC CTG MA17 Trial, 69, 2010	Conference abstract
Goss, P., Update on the MA.17 extended adjuvant trial, Best Practice and Research: Clinical Endocrinology and Metabolism, 20, S5-S13, 2006	Conference abstract
Goss, P., Breaking the 5-year barrier: Results from the MA.17 extended adjuvant trial in women who have completed adjuvant tamoxifen treatment, European Journal of Cancer, Supplement, 4, 10-15, 2006	Conference abstract
Goss, P. E., Letrozole in the extended adjuvant setting: MA.17.[Erratum appears in Breast Cancer Res Treat. 2008 Nov;112(2):369], Breast Cancer Research & Treatment, 105 Suppl 1, 45-53, 2007	Includes non-random assignment (those that switched after trial was unblinded)
Goss, P. E., Ingle, J. N., Martino, S., Robert, N. J., Muss, H. B., Livingston, R. B., Davidson, N. E., Perez, E. A., Chavarri-Guerra, Y., Cameron, D. A., Pritchard, K. I., Whelan, T., Shepherd, L. E., Tu, D., Impact of premenopausal status at breast cancer diagnosis in women entered on the placebo-controlled NCIC CTG MA17 trial of extended adjuvant letrozole, Annals of Oncology, 24, 355-61, 2013	Re-analysis of MA.17 - subgroups not of interest
Goss, P. E., Ingle, J. N., Martino, S., Robert, N. J., Muss, H. B., Piccart, M. J., Castiglione, M. M., Tu, D., Shepherd, L. E., Pater, J. L., Updated analysis of the NCIC CTG MA.17 randomized placebo (P) controlled trial of letrozole (L) after five years of tamoxifen in postmenopausal women with early stage breast cancer, Journal of clinical oncology, 22, 847, 2004	Abstract only
Goss, P. E., Ingle, J. N., Martino, S., Robert, N. J., Muss, H. B., Piccart, M. J., Castiglione, M., Tu, D., Shepherd, L. E., Pritchard, K. I., Livingston, R. B., Davidson, N. E., Norton, L., Perez, E. A., Abrams, J. S., Cameron, D. A., Palmer, M. J., Pater, J. L., National Cancer Institute of Canada Clinical Trials Group, M. A., Efficacy of letrozole extended adjuvant therapy according to estrogen receptor and progesterone receptor status of the primary tumor: National Cancer Institute of Canada Clinical Trials Group MA.17, Journal of clinical oncology, 25, 2006-11, 2007	Insufficient presentation of results

Excluded studies - RQ4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?	
Study	**Reason for exclusion**
Goss, P. E., Ingle, J. N., Pater, J. L., Martino, S., Robert, N. J., Muss, H. B., Piccart, M. J., Castiglione, M., Shepherd, L. E., Pritchard, K. I., Livingston, R. B., Davidson, N. E., Norton, L., Perez, E. A., Abrams, J. S., Cameron, D. A., Palmer, M. J., Tu, D., Late extended adjuvant treatment with letrozole improves outcome in women with early-stage breast cancer who complete 5 years of tamoxifen.[Erratum appears in J Clin Oncol. 2008 Jul 20;26(21):3659], Journal of clinical oncology, 26, 1948-55, 2008	Non-random assignment
Goss, P. E., Ingle, J. N., Pritchard, K. I., Robert, N. J., Muss, H., Gralow, J., Gelmon, K., Whelan, T., Strasser-Weippl, K., Rubin, S., Sturtz, K., Wolff, A. C., Winer, E., Hudis, C., Stopeck, A., Beck, J. T., Kaur, J. S., Whelan, K., Tu, D., Parulekar, W. R., Extending aromatase-inhibitor adjuvant therapy to 10 years, New England Journal of Medicine, 375, 209-219, 2016	Comparison outside scope
Goss,P.E., Preventing Relapse Beyond 5 Years: The MA.17 Extended Adjuvant Trial, Seminars in Oncology, 33, 8-12, 2006	Summary of MA.17 papers
Goss,P.E., Ingle,J.N., Martino,S., Robert,N.J., Muss,H.B., Piccart,M.J., Castiglione,M., Tu,D., Shepherd,L.E., Pritchard,K.I., Livingston,R.B., Davidson,N.E., Norton,L., Perez,E.A., Abrams,J.S., Therasse,P., Palmer,M.J., Pater,J.L., A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer, New England Journal of Medicine, 349, 1793-1802, 2003	Same outcomes as Goss 2005/Ingle 2006 reported over shorter follow-up periods
Ibrahim, E. M., Al-Hajeili, M. R., Bayer, A. M., Abulkhair, O. A., Refae, A. A., Extended adjuvant endocrine therapy in early breast cancer: a meta-analysis of published randomized trials, Medical OncologyMed Oncol, 34, 131, 2017	Contains comparisons outside scope
Ingle, J. N., Tu, D., Pater, J. L., Martino, S., Robert, N. J., Muss, H. B., Piccart, M. J., Castiglione, M., Shepherd, L. E., Pritchard, K. I., Livingston, R. B., Davidson, N. E., Norton, L., Perez, E. A., Abrams, J. S., Cameron, D. A., Palmer, M. J., Goss, P. E., Duration of letrozole treatment and outcomes in the placebo-controlled NCIC CTG MA.17 extended adjuvant therapy trial, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 99, 295-300, 2006	Insufficient presentation of results
Ingle, J. N., Tu, D., Pater, J. L., Muss, H. B., Martino, S., Robert, N. J., Piccart, M. J., Castiglione, M., Shepherd, L. E., Pritchard, K. I., Livingston, R. B., Davidson, N. E., Norton, L., Perez, E. A., Abrams, J. S., Cameron, D. A., Palmer, M. J., Goss, P. E., Intent-to-treat analysis of the placebo-controlled trial of letrozole for extended adjuvant therapy in early breast cancer: NCIC CTG MA.17, Annals of Oncology, 19, 877-82, 2008	Includes non-random assignment (those that switched after trial was unblinded)
Ingle, J., Tu, D., Shepherd, L., Palmer, M., Pater, J., Goss, P., NCIC CTG MA.17: Intent to treat analysis (ITT) of randomized patients after a median follow-up of 54 months, Journal of clinical oncology, 24, 549, 2006	Conference abstract

Excluded studies - RQ4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?	
Study	**Reason for exclusion**
Jin, H., Tu, D., Zhao, N., Shepherd, L. E., Goss, P. E., Longer-term outcomes of letrozole versus placebo after 5 years of tamoxifen in the NCIC CTG MA.17 trial: analyses adjusting for treatment crossover, Journal of clinical oncology, 30, 718-21, 2012	Includes non-random assignment (those that switched groups after trial was unblinded)
Josefsson,M.L., Leinster,S.J., Aromatase inhibitors versus tamoxifen as adjuvant hormonal therapy for oestrogen sensitive early breast cancer in post-menopausal women: Meta-analyses of monotherapy, sequenced therapy and extended therapy, Breast, 19, 76-83, 2010	Includes comparisons outside scope
Liedke, P. E., Tu, D., Shepherd, L., Chavarri-Guerra, Y., Pritchard, K. I., Stearns, V., Goss, P. E., New onset vasomotor symptoms but not musculoskeletal symptoms associate with clinical outcomes on extended adjuvant letrozole - Analyses from NCIC CTG MA.17, BreastBreast, 27, 99-104, 2016	Additional subgroup analysis not of interest to committee
Markopoulos,C., Dafni,U., Misitzis,J., Zobolas,V., Tzoracoleftherakis,E., Koukouras,D., Xepapadakis,G., Papadiamantis,J., Venizelos,B., Antonopoulou,Z., Gogas,H., Extended adjuvant hormonal therapy with exemestane has no detrimental effect on the lipid profile of postmenopausal breast cancer patients: final results of the ATENA lipid substudy, Breast Cancer Research, 11, R35-, 2009	Outcomes outside scope
Moy, B., Tu, D., Shepherd, L. E., Pater, J. L., Whelan, T. J., Ingle, J. N., Goss, P. E., NCIC CTG MA.17: Tolerability of letrozole among ethnic minority women, Journal of clinical oncology, 24, 6018, 2006	Conference abstract
Moy,B., Tu,D., Pater,J.L., Ingle,J.N., Shepherd,L.E., Whelan,T.J., Goss,P.E., Clinical outcomes of ethnic minority women in MA.17: a trial of letrozole after 5 years of tamoxifen in postmenopausal women with early stage breast cancer, Annals of Oncology, 17, 1637-1643, 2006	Subgroup analysis not of interest
Perez, E. A., Josse, R. G., Pritchard, K. I., Ingle, J. N., Martino, S., Findlay, B. P., Shenkier, T. N., Tozer, R. G., Palmer, M. J., Shepherd, L. E., Liu, S., Tu, D., Goss, P. E., Effect of letrozole versus placebo on bone mineral density in women with primary breast cancer completing 5 or more years of adjuvant tamoxifen: a companion study to NCIC CTG MA.17, Journal of clinical oncology, 24, 3629-35, 2006	Outcomes outside scope
Petrelli, F., Coinu, A., Cabiddu, M., Ghilardi, M., Lonati, V., Barni, S., Five or more years of adjuvant endocrine therapy in breast cancer: a meta-analysis of published randomised trials, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 140, 233-40, 2013	Insufficient information to assess quality
Pritchard, K. I., Goss, P. E., Shepherd, L., The extended adjuvant NCIC CTG MA.17 trials: initial and rerandomization studies, Breast, 15 Suppl 1, S14-20, 2006	Summary of MA.17 papers
Raina, V, The Atlas trial: Tamoxifen for a longer duration for early breast cancer, National Medical Journal of India, 26, 2013	Insufficient presentation of results

Excluded studies - RQ4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?	
Study	**Reason for exclusion**
Ryden, L., Heibert Arnlind, M., Vitols, S., Hoistad, M., Ahlgren, J., Aromatase inhibitors alone or sequentially combined with tamoxifen in postmenopausal early breast cancer compared with tamoxifen or placebo - Meta-analyses on efficacy and adverse events based on randomized clinical trials, Breast, 26, 106-14, 2016	Includes comparisons outside scope
Stewart, H. J., Forrest, A. P., Everington, D., McDonald, C. C., Dewar, J. A., Hawkins, R. A., Prescott, R. J., George, W. D., Randomized comparison of 5 years of adjuvant tamoxifen with continuous therapy for operable breast cancer, Cancer/Radiotherapie, 1, 267, 1997	Non-English language
Whelan, T., Goss, P., Ingle, J., Pater, J., Shepherd, L., Palmer, M., Tu, D., Robert, N., Martino, S., Muss, H., Assessment of quality of life (QOL) in MA.17, a randomized placebo-controlled trial of letrozole in postmenopausal women following five years of tamoxifen, Journal of clinical oncology, 22, 517, 2004	Conference abstract
Whelan,T.J., Goss,P.E., Ingle,J.N., Pater,J.L., Tu,D., Pritchard,K., Liu,S., Shepherd,L.E., Palmer,M., Robert,N.J., Martino,S., Muss,H.B., Assessment of quality of life in MA.17: a randomized, placebo-controlled trial of letrozole after 5 years of tamoxifen in postmenopausal women, Journal of Clinical Oncology, 23, 6931-6940, 2005	Same patients and outcomes as Muss 2008 - change in scores reported rather than actual scores at follow-up

aTTom, Adjuvant Tamoxifen Treatment Offers More?

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Excluded studies for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

Clinical studies

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Anonymous,, Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Early Breast Cancer Trialists' Collaborative Group, Lancet, 339, 1-15, 1992	Duplicate
Anonymous,, Meta-analysis confirms value of risk-reducing salpingo-oophorectomy for women with BRCA mutations, Journal of the National Cancer Institute, 101, 69, 2009	Summary
Anonymous,, Ovarian ablation in early breast cancer: overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group, Lancet, 348, 1189-96, 1996	Comparisons outside scope
Anonymous,, Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy: 133 randomised trials involving 31,000 recurrences and 24,000 deaths among 75,000 women. Part I, Obstetrical and Gynecological Survey, 47, 405-407, 1992	Comparisons outside scope
Anonymous,, Adjuvant treatment of premenopausal breast cancer with Zoladex and Tamoxifen, Breast Cancer Research and Treatment, 57, 30, 1999	Conference abstract
Arriagada, R, Le, Mg, Spielmann, M, Mauriac, L, Bonneterre, J, Namer, M, Hill, C, Tursz, T, Randomized trial of adjuvant ovarian suppression in 926 premenopausal patients with early breast cancer treated with adjuvant chemotherapy, American society of clinical oncology, 22, 4, 2003	Comparison outside scope
Asiri, M. A., Tunio, M. A., Abdulmoniem, R., Is radiation-induced ovarian ablation in breast cancer an obsolete procedure? Results of a meta-analysis, Breast Cancer Targets and TherapBreast Cancer (Dove Med Press), 8, 109-16, 2016	Review contains comparisons outside scope
Baum, M., O'Shaughnessy, J. A., Management of premenopausal women with early-stage breast cancer: is there a role for ovarian suppression?, Clinical breast cancer, 3, 260-7, 2002	Narrative review
Bellet, M, Gray, Kp, Francis, Pa, Lang, I, Ciruelos, E, Lluch, A, Climent, Ma, Catalan, G, Costa, Rf, Catalan, R, Rajasekaran, A, Morales, J, Vazquez, J, Fleming, Gf, Price, Kn, Regan, Mm, Estrogen levels in premenopausal (prem) patients (pts) with hormone-receptor positive (HR+) early breast cancer (BC) receiving adjuvant triptorelin (Trip) plus exemestane (E) or tamoxifen (T) in the SOFT trial: SOFT-EST substudy, Journal of clinical oncology, 32, 2014	Conference abstract

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Bellet, M., Gray, K. P., Francis, P. A., Lang, I., Ciruelos, E., Lluch, A., Climent, M. A., Catalan, G., Avella, A., Bohn, U., Gonzalez-Martin, A., Ferrer, R., Catalan, R., Azaro, A., Rajasekaran, A., Morales, J., Vazquez, J., Fleming, G. F., Price, K. N., Regan, M. M., Twelve-Month Estrogen Levels in Premenopausal Women With Hormone Receptor-Positive Breast Cancer Receiving Adjuvant Triptorelin Plus Exemestane or Tamoxifen in the Suppression of Ovarian Function Trial (SOFT): The SOFT-EST Substudy, Journal of clinical oncology, 34, 1584-93, 2016	Outcomes outside scope
Berglund,G., Nystedt,M., Bolund,C., Sjoden,P.O., Rutquist,L.E., Effect of endocrine treatment on sexuality in premenopausal breast cancer patients: a prospective randomized study, Journal of Clinical Oncology, 19, 2788-2796, 2001	Outcomes outside scope
Blamey, Rw, Zoladex and nolvadex: an evaluation of sequential versus combination (Z & N) therapy in the treatment of advanced breast cancer in pre-menopausal women, Breast Cancer Research and Treatment, 27, 151, 1993	Conference abstract
Boer, R. D., A randomised trial of buserelin and tamoxifen in metastatic breast cancer, Breast cancer research, 2 (1) (no pagination), 2000	Population outside scope - metastatic BC
Brunt, Am, Bliss, Jm, Benghiat, A, Dawson, C, Dewar, J, Harnett, An, Hopwood, P, Lawrence, D, Trask, C, The impact on quality of life of adding chemotherapy (CT) or ovarian suppression (OS) to adjuvant tamoxifen (TAM): Outcomes from the UK NCRI Adjuvant Breast Cancer (ABC) trial [abstract], Annual Meeting Proceedings of the American Society of Clinical Oncology, 729, 2004	Conference abstract
Brunt, Am, Bliss, Jm, Johnson, L, Lawrence, D, Yarnold, J, Results from the UK NCRI adjuvant breast cancer (ABC) international trial: Polychemotherapy and ovarian ablation in women with early breast cancer prescribed 5 years tamoxifen, British Journal of Cancer, 91, S1, 2004	Conference abstract
Buijs, C., de Vries, E. G., Mourits, M. J., Willemse, P. H., The influence of endocrine treatments for breast cancer on health-related quality of life, Cancer Treatment Reviews, 34, 640-55, 2008	Contains comparisons outside scope
Burstein, H. J., Lacchetti, C., Anderson, H., Buchholz, T. A., Davidson, N. E., Gelmon, K. E., Giordano, S. H., Hudis, C. A., Solky, A. J., Stearns, V., Winer, E. P., Griggs, J. J., Adjuvant Endocrine Therapy for Women With Hormone Receptor-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update on Ovarian Suppression, Journal of clinical oncology, 34, 1689-701, 2016	Contains comparisons outside scope
Chlebowski, R. T., Pan, K., Col, N. F., Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 26, 26, 2016	Contains comparisons outside scope

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Chlebowski, R. T., Pan, K., Col, N. F., Ovarian suppression in combination endocrine adjuvant therapy in premenopausal women with early breast cancer, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 161, 185-190, 2017	Insufficient information about included studies; no new studies idenitified
Clarke,M., Meta-analyses of adjuvant therapies for women with early breast cancer: The Early Breast Cancer Trialists' Collaborative Group overview, Annals of Oncology, 17, x59-x62, 2006	Overview
Cuzick, J., Use of LHRH-agonists as adjuvant therapy for breast cancer, Expert Opinion on Therapeutic TargetsExpert Opin Ther Targets, 12, 1065-71, 2008	Commentary
Del Mastro, L., Levaggi, A., Giraudi, S., Pronzato, P., Luteinising hormone releasing hormone agonists (LH-RHa) in premenopausal early breast cancer patients: current role and future perspectives, Cancer Treatment Reviews, 37, 208-11, 2011	Narrative review
Dellapasqua,S., Colleoni,M., Gelber,R.D., Goldhirsch,A., Adjuvant endocrine therapy for premenopausal women with early breast cancer, Journal of Clinical Oncology, 23, 1736-1750, 2005	Contains comparisons outside scope
D'Hondt, V., Piccart, M., Controversies in the adjuvant treatment of breast cancer: New adjuvant endocrine treatment strategies, Annals of oncology, 15, iv23-iv29, 2004	Narrative review
D'Orazio,A., O'Shaughnessy,J.A., What is the role of ovarian function suppression in the treatment of premenopausal breast cancer patients?, Clinical Breast Cancer, 4, 101-103, 2003	Narrative review
Ferretti, G., Felici, A., Carlini, P., Cognetti, F., Re: Ovarian ablation or suppression in premenopausal early breast cancer: results from the International Adjuvant Breast Cancer Ovarian Ablation or Suppression randomized trial, Journal of the National Cancer Institute, 99, 1344-5, 2007	Commentary
Fleming, G, Francis, P, Phase III Randomized Study of Ovarian Function Suppression in Combination With Tamoxifen Versus Ovarian Function Suppression in Combination With Exemestane Versus Tamoxifen Alone in Premenopausal Women With Endocrine-Responsive Breast Cancer, Physician Data Query (PDQ), 2003	Overview of ongoing trial
Freedman, O. C., Fletcher, G. G., Gandhi, S., Mates, M., Dent, S. F., Trudeau, M. E., Eisen, A., Adjuvant endocrine therapy for early breast cancer: a systematic review of the evidence for the 2014 Cancer Care Ontario systemic therapy guideline, Current OncologyCurr, 22, S95-S113, 2015	Contains comparisons outside scope

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
George, Wd, Phase III randomised study of adjuvant tamoxifen with or without ovarian suppression and/or cyclophosphamide/methotrexate/fluorouracil (CMF) in premenopausal women with operable invasive breast cancer, Physician Data Query (PDQ), 1994	Overview of trial
Goel,S., Sharma,R., Hamilton,A., Beith,J., LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women, Cochrane Database of Systematic Reviews, 2009. Article Number, -, 2009	Contains comparisons outside scope
Goel,Shom, Sharma,Rohini, Hamilton,Anne, Beith,Jane, LHRH agonists for adjuvant therapy of early breast cancer in premenopausal women, Cochrane Database of Systematic Reviews, -, 2009	Contains comparisons outside scope
Goldhirsch, A, Gelber, Rd, Francis, Pa, Regan, Mm, Fleming, Gf, Lang, I, Ciruelos, Em, Bellet, M, Bonnefoi, H, Climent, Ma, Pavesi, L, Burstein, Hj, Martino, S, Davidson, Ne, Geyer, Jr Ce, Walley, Ba, Coleman, Re, Kerbrat, P, Rabaglio-Poretti, M, Coates, As, Randomized comparison of adjuvant tamoxifen (T) plus ovarian function suppression (OFS) versus tamoxifen in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Analysis of the SOFT trial, Cancer Research, 75, 2015	Conference abstract
Goldhirsch, A., Colleoni, M., Regan, M., Improved adjuvant endocrine therapy for premenopausal women with endocrine responsive disease, EcancermedicalscienceEcancermedicalscience, 9, 544, 2015	Overview
Goodwin, P. J., Black, J. T., Bordeleau, L. J., Ganz, P. A., Health-related quality-of-life measurement in randomized clinical trials in breast cancer - Taking stock, Journal of the National Cancer Institute, 95, 263-281, 2003	Contains comparisons outside scope
Gray, R., Clarke, M., Collins, R., Peto, R., The EBCTCG overview of adjuvant therapy of breast cancer. What are the implications for future studies? Early Breast Cancer Trialists' Collaborative Group, Annals of the New York Academy of Sciences, 698, 339-48, 1993	Narrative review
Hackshaw, A., Luteinizing hormone-releasing hormone (LHRH) agonists in the treatment of breast cancer, Expert Opinion on PharmacotherapyExpert Opin Pharmacother, 10, 2633-9, 2009	Narrative review
Hackshaw, A., Baum, M., Fornander, T., Nordenskjold, B., Nicolucci, A., Monson, K., Forsyth, S., Reczko, K., Johansson, U., Fohlin, H., Valentini, M., Sainsbury, R., Long-term effectiveness of adjuvant goserelin in premenopausal women with early breast cancer, Journal of the National Cancer Institute, 101, 341-9, 2009	Same trial (ZIPP) as Baum - same outcomes, just with longer follow-up period.
Hackshaw, A., Jitlal, M., Kadalayil, L., Long-term follow up of clinical trials: Is it worth it?, Clinical Trials, 7 (4), 418, 2010	Abstract only
Higgins,M.J., Davidson,N.E., What is the current status of ovarian suppression/ablation in women with premenopausal early-stage breast cancer?, Current Breast Cancer Reports, 1, 42-47, 2009	Narrative review

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Hoffken, K., Kath, R., The role of LH-RH analogues in the adjuvant and palliative treatment of breast cancer, Recent Results in Cancer ResearchRecent Results Cancer Res, Fortschritte der Krebsforschung. Progres dans les recherches sur le cancer. 153, 61-70, 2000	Expert review
Houghton, J, Preliminary report: zoladex and tamoxifen as adjuvant treatment in premenopausal breast cancer, Breast Cancer Research and Treatment, 50, 234, 1998	Conference abstract
Houghton, J, Baum, M, Rutqvist, Le, Nordenskiold, B, Nicolucci, A, Sawyer, W, The Zipp trial of adjuvant Zoladex in premenopausal patients with early breast cancer: an update at five years, American society of clinical oncology, 2000	Early publication from the ZIPP trial - abstract only
Howell, A., Howell, S. J., Evans, D. G., New approaches to the endocrine prevention and treatment of breast cancer, Cancer Chemotherapy & PharmacologyCancer Chemother Pharmacol, 52 Suppl 1, S39-44, 2003	Narrative review
Hubalek,M., Brantner,C., Marth,C., Adjuvant endocrine therapy of premenopausal women with early breast cancer: An overview, Wiener Medizinische Wochenschrift, 160, 167-173, 2010	Narrative review
Jakesz, R, Gnant, M, Hausmaninger, H, Samonigg, H, Kubista, E, Steindorfer, P, Kwasny, W, Tausch, C, Steger, G, Combination Goserelin and Tamoxifen is more effective than CMF in premenopausal patients with hormone-responsive tumors in a multicenter trial of the Austrian Breast Cancer Study Group (ABCSG), Breast Cancer Research and Treatment, 57, 25, 1999	Conference abstract
Jian-wei, L, Guangyu, L, Yajie, J, Xia, Y, Zhimin, S, Da, P, Zefei, J, Dedian, C, Bin, Z, Binghe, X, Switching to anastrozole plus goserelin versus continued tamoxifen for adjuvant therapy of premenopausal early-stage breast cancer: Preliminary results from a randomized trial, European Journal of Cancer. (var.pagings), 51, S315, 2015	Conference abstract
Jonat,W., Role of LHRH agonists in premenopausal women with oestrogen receptor-positive breast cancer: The ZEBRA experience, European Journal of Cancer, 38, S39-S40, 2002	Overview
Jonat,W., Luteinizing hormone-releasing hormone analogues--the rationale for adjuvant use in premenopausal women with early breast cancer, British Journal of Cancer, 78 Suppl 4, 5-8, 1998	Narrative review
Kaufmann, M., von Minckwitz, G., The emerging role of hormonal ablation as adjuvant therapy in node+ and node- pre-/perimenopausal patients, Breast, 10, 123-129, 2001	Narrative review
Kiesel,L.A., Rody,A., Greb,R.R., Szilagyi,A., Clinical use of GnRH analogues, Clinical Endocrinology, 56, 677-687, 2002	Narrative review
Kim, H. A., Ahn, S. H., Nam, S. J., Park, S., Ro, J., Im, S. A., Jung, Y. S., Yoon, J. H., Hur, M. H., Choi, Y. J., Lee, S. J., Jeong, J., Cho, S. H., Kim, S. Y., Lee, M. H., Kim, L. S., Moon, B. I., Kim, T. H., Park, C., Kim, S. J., Jung, S. H., Park, H.,	Protocol - no outcomes reported

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Gwak, G. H., Kang, S. H., Kim, J. G., Kim, J., Choi, S. Y., Lim, C. W., Kim, D., Yoo, Y., Song, Y. J., Kang, Y. J., Jung, S. S., Shin, H. J., Lee, K. J., Han, S. H., Lee, E. S., Han, W., Kim, H. J., Noh, W. C., The role of the addition of ovarian suppression to tamoxifen in young women with hormone-sensitive breast cancer who remain premenopausal or regain menstruation after chemotherapy (ASTRRA): study protocol for a randomized controlled trial and progress, BMC cancer, 16, 319, 2016	
Klijn, J. G., Beex, L. V., Mauriac, L., van Zijl, J. A., Veyret, C., Wildiers, J., Jassem, J., Piccart, M., Burghouts, J., Becquart, D., Seynaeve, C., Mignolet, F., Duchateau, L., Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study, Journal of the National Cancer Institute, 92, 903-11, 2000	Population outside scope - Metastatic BC
Klijn, Jgm, Beex, L, Mauriac, L, Zijl, J, Veyret, C, Wildiers, J, Combined treatment with the LHRH-agonist buserelin (LHRH-A) and tamoxifen (TAM) vs single treatment with each drug alone in premenopausal metastatic breast cancer. Final results of EORTC study 10881, Ann-Oncol, 9, 11, 1998	Population outside scope - metastatic BC
Kwon, A H, Yamada, O, Uetsuji, S, Matsui, Y, Kamiyama, Y, Prophylactic laparoscopic ovarian ablation for premenopausal breast cancer: medical and economic efficacy (Structured abstract), Surgical Laparoscopy and Endoscopy, 7, 223-227, 1997	Non-RCT
Lemieux, J., Goodwin, P. J., Bordeleau, L. J., Lauzier, S., Theberge, V., Quality-of-life measurement in randomized clinical trials in breast cancer: An updated systematic review (2001-2009), Journal of the National Cancer Institute, 103, 178-231, 2011	Contains comparisons outside scope
LHRH-agonists in Early Breast Cancer Overview group, Cuzick, J., Ambroisine, L., Davidson, N., Jakesz, R., Kaufmann, M., Regan, M., Sainsbury, R., Use of luteinising-hormone-releasing hormone agonists as adjuvant treatment in premenopausal patients with hormone-receptor-positive breast cancer: a meta-analysis of individual patient data from randomised adjuvant trials, Lancet, 369, 1711-23, 2007	Contains comparisons outside scope
Lohrisch, C., Piccart, M., Breast cancer: new aspects of adjuvant hormonal therapy, Annals of oncology, 11 Suppl 3, 13-25, 2000	Narrative review
Love, R. R., Adjuvant Surgical Oophorectomy Plus Tamoxifen in Premenopausal Women With Operable Hormone Receptor-Positive Breast Cancer: A Global Treatment Option, Clinical breast cancer, 16, 233-7, 2016	Narrative review
Martinetti, A, Celio, L, Ferrari, L, Miceli, R, Seregni, E, Pozzi, P, Buzzoni, R, Oestrogen suppression and bone metabolism markers in premenopausal breast cancer patients treated with an LHRH analogue alone or in combination with an aromatase inhibitor, Tumori, 84 Suppl, 121, 1998	Abstract only - compares LHRH vs LHRH AI (N=21)

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Mitsuyama, S., Nomura, Y., Ohno, S., Miyauchi, M., Yamamoto, N., Kimura, T., Saku, M., Miura, S., Yoshikawa, N., Tsujinaka, T., Koh, J., Ishida, T., Abe, O., Ohashi, Y., [Assessment of goserelin treatment in adjuvant therapy for premenopausal patients with breast cancer in Japan-zoladex breast cancer study group trial-B], Gan to Kagaku Ryoho [Japanese Journal of Cancer & Chemotherapy]Gan To Kagaku Ryoho, 32, 2071-7, 2005	RCT - Japanese language insufficient detail in the English abstract to include in the analysis
Montagna, E., Cancello, G., Colleoni, M., The aromatase inhibitors (plus ovarian function suppression) in premenopausal breast cancer patients: ready for prime time?, Cancer Treatment Reviews, 39, 886-90, 2013	Narrative review
Namer, M., [Adjuvant treatments of breast cancer], Bulletin du CancerBull Cancer, 81, 2-4, 1994	Commentary in French on the Oxford meta-analysis
Ng, R., Pond, G. R., Tang, P. A., MacIntosh, P. W., Siu, L. L., Chen, E. X., Correlation of changes between 2-year disease-free survival and 5-year overall survival in adjuvant breast cancer trials from 1966 to 2006, Annals of oncology, 19, 481-486, 2008	Contains comparisons outside scope
Noh, W. C., Hur, M. H., Ahn, S. H., Jung, Y., Lee, S. J., Lee, E. S., Park, B. W., Jong, J., Han, S., Park, C. H., ASTRRA study: A randomised phase III study for evaluating the role of the addition of ovarian function suppression (OFS) to tamoxifen in young women (<45 years) with hormone-sensitive breast cancer who remain in premenopause or regain menstruation after chemotherapy - A Korean Breast Cancer Study Group (KBCSG) trial, European Journal of Cancer, Supplement, 8 (3), 67-68, 2010	Conference abstract
Nordenskjold, B, Adjuvant treatment of premenopausal breast cancer with zoladex and tamoxifen: Results from randomised trials by the Cancer Research Campaign (CRC) Breast Cancer Trials Group, The Stockholm Breast Cancer Study Group, the South East Sweden Breast Cancer Group and Gruppo Interdisciplinare Valutazione Intervention Oncologia (GIVIO) [abstract no: 268b], European journal of cancer, 35, S83, 1999	Conference abstract
Nystedt,M., Berglund,G., Bolund,C., Brandberg,Y., Fornander,T., Rutqvist,L.E., Randomized trial of adjuvant tamoxifen and/or goserelin in premenopausal breast cancer--self-rated physiological effects and symptoms, Acta Oncologica, 39, 959-968, 2000	Overlapping sample - same outcomes reported over shorter follow-up period
Pagani, O, Regan, Mm, Walley, B, Fleming, Gf, Colleoni, M, Lang, I, Gomez, Hl, Tondini, C, Burstein, Hj, Perez, Ea, Ciruelos, E, Stearns, V, Bonnefoi, Hr, Martino, S, Geyer, Ce, Rabaglio-Poretti, M, Coates, As, Gelber, Rd, Goldhirsch, A, Francis, Pa, Randomized comparison of adjuvant aromatase inhibitor (AI) exemestane (E) plus ovarian function suppression (OFS) vs tamoxifen (T) plus OFS in premenopausal women with hormone receptor-positive (HR+) early breast cancer (BC): Joint analysis of IBCSG TEXT and SOFT trials, Journal of clinical oncology, 32, 2014	Conference abstract

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Paridaens, Rj, Gelber, S, Cole, Bf, Gelber, Rd, ThÑ?rlimann, B, Price, K, Holmberg, S, Crivellari, D, Coates, As, Goldhirsch, A, Evaluation of Adjuvant! Online to predict the effect of optimal endocrine therapy (ovarian function suppression plus tamoxifen) for premenopausal breast cancer patients with estrogen-receptor-positive breast cancer [abstract no. 585], Journal of clinical oncology, 27, 27, 2009	Conference abstract
Park, W. C., Role of ovarian function suppression in premenopausal women with early breast cancer, Journal of Breast Cancer, 19, 341-348, 2016	Narrative review
Perez,E.A., Management recommendations for adjuvant systemic breast cancer therapy, Breast Disease, 21, 15-21, 2004	Narrative review
Phillips, K. A., Regan, M. M., Ribi, K., Francis, P. A., Puglisi, F., Bellet, M., Spazzapan, S., Karlsson, P., Budman, D. R., Zaman, K., Abdi, E. A., Domchek, S. M., Feng, Y., Price, K. N., Coates, A. S., Gelber, R. D., Maruff, P., Boyle, F., Forbes, J. F., Ahles, T., Fleming, G. F., Bernhard, J., Adjuvant ovarian function suppression and cognitive function in women with breast cancer, British Journal of Cancer, 114, 956-64, 2016	Outcomes outside scope
Phillips, K-A, Feng, Y, Ribi, K, Bernhard, J, Puglisi, F, Bellet, M, Spazzapan, S, Karlsson, P, Budman, Dr, Zaman, K, Abdi, Ea, Domchek, Sm, Regan, Mm, Coates, As, Gelber, Rd, Maruff, P, Boyle, F, Forbes, Jf, Fleming, Gf, Francis, Pa, Co-SOFT: The cognitive function substudy of the suppression of ovarian function trial (SOFT), Cancer Research, 75, 2015	Conference abstract
Pritchard, K. I., Ovarian ablation as adjuvant therapy for early-stage breast cancer, Cancer Treatment & ResearchCancer Treat Res, 94, 158-80, 1998	Expert review
Qiu, L., Fu, F., Huang, M., Lin, Y., Chen, Y., Chen, M., Wang, C., Evaluating the Survival Benefit Following Ovarian Function Suppression in Premenopausal Patients with Hormone Receptor Positive Early Breast Cancer, Scientific ReportsSci, 6, 26627, 2016	Contains comparisons outside scope
Regan, M. M., Francis, P. A., Pagani, O., Fleming, G. F., Walley, B. A., Viale, G., Colleoni, M., Lang, I., Gomez, H. L., Tondini, C., Pinotti, G., Price, K. N., Coates, A. S., Goldhirsch, A., Gelber, R. D., Absolute benefit of adjuvant endocrine therapies for premenopausal women with hormone receptor-positive, Human epidermal growth factor receptor 2-Negative early breast cancer: TEXT and SOFT Trials, Journal of clinical oncology, 34, 2221-2230, 2016	Overview
Ribi, K, Luo, W, Bernhard, J, Francis, Pa, Bellet, M, Burstein, Hj, Pavesi, L, Parmar, V, Tondini, C, Visini, M, Torres, R, Karlsson, P, Spazzapan, S, Avella, A, Ruhstaller, T, Puglisi, F, Regan, Mm, Coates, As, Gelber, Rd, Fleming, Gf, Patient-reported endocrine symptoms, sexual functioning and quality of life (QoL) in the IBCSG SOFT trial: Adjuvant treatment with tamoxifen (T) alone versus tamoxifen plus ovarian function suppression (OFS) in premenopausal women with hormone receptor-po, Cancer Research, 75, 2015	Conference abstract

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Ribi, K., Luo, W., Bernhard, J., Francis, P. A., Burstein, H. J., Ciruelos, E., Bellet, M., Pavesi, L., Lluch, A., Visini, M., Parmar, V., Tondini, C., Kerbrat, P., Perello, A., Neven, P., Torres, R., Lombardi, D., Puglisi, F., Karlsson, P., Ruhstaller, T., Colleoni, M., Coates, A. S., Goldhirsch, A., Price, K. N., Gelber, R. D., Regan, M. M., Fleming, G. F., Adjuvant Tamoxifen Plus Ovarian Function Suppression Versus Tamoxifen Alone in Premenopausal Women With Early Breast Cancer: Patient-Reported Outcomes in the Suppression of Ovarian Function Trial, Journal of clinical oncology, 34, 1601-10, 2016	Insufficient presentation of results
Saha, P., Regan, M. M., Pagani, O., Francis, P. A., Walley, B. A., Ribi, K., Bernhard, J., Luo, W., Gomez, H. L., Burstein, H. J., Parmar, V., Torres, R., Stewart, J., Bellet, M., Perello, A., Dane, F., Moreira, A., Vorobiof, D., Nottage, M., Price, K. N., Coates, A. S., Goldhirsch, A., Gelber, R. D., Colleoni, M., Fleming, G. F., Soft,, Text Investigators, International Breast Cancer Study, Group, Treatment Efficacy, Adherence, and Quality of Life Among Women Younger Than 35 Years in the International Breast Cancer Study Group TEXT and SOFT Adjuvant Endocrine Therapy Trials, Journal of Clinical OncologyJ Clin Oncol, 35, 3113-3122, 2017	Insufficient presentation of results
Sainsbury,R., Ovarian ablation in the adjuvant treatment of premenopausal and perimenopausal breast cancer, British Journal of Surgery, 90, 517-526, 2003	Contains comparisons outside scope
Saito, Y., Suzuki, Y., Tokuda, Y., [Hormone therapy for breast cancer], Nippon Rinsho - Japanese Journal of Clinical MedicineNippon Rinsho, 65 Suppl 6, 543-8, 2007	Japanese language review of other RCTs
Sharma,R., Beith,J., Hamilton,A., Systematic review of LHRH agonists for the adjuvant treatment of early breast cancer, Breast, 14, 181-191, 2005	Contains comparisons outside scope
Shparyk Ia, V., [Zoladex: new approaches to hormone therapy], Likarska SpravaLik Sprava, 44-50, 1996	Russian language, appears to be a review article
Stewart, H. J., Open randomized trials in the management of primary breast cancer, European Journal of Surgical OncologyEur J Surg Oncol, 21, 233-237, 1995	Narrative review
Sverrisdottir, A, Gross, J, Johansson, H, Jacobsson, H, Gustafsson, T, Rotstein, S, Fornander, T, Bone turnover in goserelin and tamoxifen treated premenopausal patients in an adjuvant trial, Breast (Edinburgh, Scotland), 22, S84, 2013	Conference abstract
Sverrisdottir, A, Johansson, H, Johansson, U, Bergh, J, Rotstein, S, Rutqvist, Le, Abstract S1-5: Interaction between Goserelin and Tamoxifen in a Controlled Clinical Trial of Adjuvant Endocrine Therapy in Premenopausal Breast Cancer, 70, 2010	Conference abstract

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
Sverrisdottir, A., Johansson, H., Johansson, U., Bergh, J., Rotstein, S., Rutqvist, L., Fornander, T., Interaction between goserelin and tamoxifen in a prospective randomised clinical trial of adjuvant endocrine therapy in premenopausal breast cancer, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 128, 755-63, 2011	Outcome outside scope
Sverrisdottir,A., Nystedt,M., Johansson,H., Fornander,T., Adjuvant goserelin and ovarian preservation in chemotherapy treated patients with early breast cancer: results from a randomized trial, Breast Cancer Research and Treatment, 117, 561-567, 2009	Outcome outside scope (fertility preservation)
Uslu, A., Zengel, B., Akpinar, G., Postaci, H., Yetis, H., Corumlu, B., Kebapci, E., Aykas, A., The outcome effect of double-hormonal therapy in premenopausal breast cancer patients with high nodal-status: Result of a prospective randomized trial, Indian journal of cancer, 51, 582-6, 2014	Population outside scope - all receiving chemotherapy
Wells, Um, Moritz, S, Riley, Dl, Houghton, J, Baum, M, Odling-Smee, W, Preliminary report: the CRC adjuvant breast cancer trial for patients under the age of fifty, Breast (Edinburgh, Scotland), 6, 255, 1997	Conference abstract
Whelan, T. J., Pritchard, K. I., Managing patients on endocrine therapy: focus on quality-of-life issues, Clinical cancer research, 12, 1056s-1060s, 2006	Narrative review
Willsher, Pc, Robertson, Jfr, Jackson, L, Pinder, S, Blamey, Rw, Tamoxifen therapy for stage III breast cancer: report on two randomized trials, Breast (Edinburgh, Scotland), 4, 238, 1995	Conference abstract
Wolff, A. C., Davidson, N. E., Still waiting after 110 years: The optimal use of ovarian ablation as adjuvant therapy for breast cancer, Journal of clinical oncology, 24, 4949-4951, 2006	Narrative review
Yan, S., Li, K., Jiao, X., Zou, H., Tamoxifen with ovarian function suppression versus tamoxifen alone as an adjuvant treatment for premenopausal breast cancer: a meta-analysis of published randomized controlled trials, OncoTargets and therapyOnco Targets Ther, 8, 1433-41, 2015	Insufficient presentation of results and study characteristics
Yang, B., Shi, W., Yang, J., Liu, H., Zhao, H., Li, X., Jiao, S., Concurrent treatment with gonadotropin-releasing hormone agonists for chemotherapy-induced ovarian damage in premenopausal women with breast cancer: a meta-analysis of randomized controlled trials, Breast, 22, 150-7, 2013	Comparisons outside scope
Yang, H., Yu, X., Zong, X., Chen, D., Ding, X., Yu, Y., Zou, D., He, X., Feng, W., Chen, J., Mo, W., Wang, C., Goserelin plus tamoxifen versus tamoxifen alone in pre-or peri-menopausal patients with hormone receptor-positive early-stage breast cancer: A randomized, controlled clinical trial in China, Journal of Clinical Oncology. Conference, 34, 2016	Conference abstract
Yang, H., Zong, X., Yu, Y., Shao, G., Zhang, L., Qian, C., Bian, Y., Xu, X., Sun, W., Meng, X., Ding, X., Chen, D., Zou, D., Xie, S., Zheng, Y., Zhang, J., He, X., Sun, C., Yu, X., Ni, J., Combined effects of goserelin and tamoxifen on estradiol	Outcomes outside scope

Excluded studies - RQ4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?	
Study	**Reason for exclusion**
level, breast density, and endometrial thickness in premenopausal and perimenopausal women with early-stage hormone receptor-positive breast cancer: a randomised controlled clinical trial, British Journal of Cancer, 109, 582-8, 2013	
Yarnold, Jr, Phase III randomised study of adjuvant tamoxifen, ovarian suppression, and/or chemotherapy in women with T1-3a, N0-1, M0 breast cancer, Physician Data Query (PDQ), 1995	Overview of trial in progress
Yarnold, Jr, Bliss, Jm, Earl, H, George, D, Lawrence, D, Mortazavi, Sh, Ovarian ablation (OA) in pre-menopausal women with early breast cancer prescribed 5 years tamoxifen (T) or T plus chemotherapy (CT)-results from the UK NCRI Adjuvant Breast Cancer (ABC) international trial of 2,144 patients, Proceedings of the American Society of Clinical Oncology, 22, 2004	Conference abstract
Yi, H. W., Comparisons of anxiety and depression between premenopausal women who received tamoxifen and goserelin versus tamoxifen alone to manage breast cancer: A 12-month prospective randomized study, European journal of cancer, 57, S138, 2016	Conference abstract
Yi, Hw, Nam, Sj, Kim, Sw, Lee, Je, Lee, Sk, Bae, Sy, Park, S, Paik, H-J, Ryu, Jm, Depression and anxiety after adjuvant ovarian function suppression in premenopausal breast cancer patients, Cancer Research, 76, 2016	Conference abstract
Zhang, P., Li, C. Z., Jiao, G. M., Zhang, J. J., Zhao, H. P., Yan, F., Jia, S. F., Hu, B. S., Wu, C. T., Effects of ovarian ablation or suppression in premenopausal breast cancer: A meta-analysis of randomized controlled trials, European Journal of Surgical OncologyEur J Surg Oncol, 43, 1161-1172, 2017	Contains comparisons outside scope
Zickl, L, Francis, P, Fleming, G, Pagani, O, Walley, B, Price, Kn, SOFT and TEXT: Trials of tamoxifen and exemestane with and without ovarian function suppression for premenopausal women with hormone receptor-positive early breast cancer 113, Cancer Research, 72, Abstract no: OT2-2-01, 2012	Conference abstract

AI, aromatase inhibitor; BC, breast cancer; LHRH, Luteinizing-hormone releasing hormone; RCT, randomised controlled trial; ZIPP, Zoladex in pre-menopausal patients trial

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Excluded studies for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

Clinical studies

Excluded studies - RQ10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?	
Study	Reason for Exclusion
Anonymous,, Final results from the NSABP Breast Cancer Prevention Trial, Oncology (Williston Park, N.Y.), 19, 1800, 2005	Narrative review
Anonymous,, NSABP researchers report on the tamoxifen breast cancer prevention trial, Oncology, 12, 1198, 1998	Narrative review
Baroni, G., Pedotti, A., Orecchia, R., Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ, Lancet, 362, 1155; author reply 1155-1156, 2003	Letter
Baum, M, Houghton, J, Riley, D, Tamoxifen to prevent breast cancer, Lancet (London, England), 338, 114, 1991	Letter
Cersosimo, R. J., Hernandez, L., Gagnon, L., Tamoxifen for prevention of breast cancer, Annals of Pharmacotherapy, 37, 268-273, 2003	Populations: non-DCIS
Cummings,F.J., Evolving uses of hormonal agents for breast cancer therapy, Clinical Therapeutics, 24, C3-C25, 2002	Contains non-DCIS populations
Cuzick,J., Sestak,I., Bonanni,B., Costantino,J.P., Cummings,S., Decensi,A., Dowsett,M., Forbes,J.F., Ford,L., LaCroix,A.Z., Mershon,J., Mitlak,B.H., Powles,T., Veronesi,U., Vogel,V., Wickerham,D.L., Selective oestrogen receptor modulators in prevention of breast cancer: An updated meta-analysis of individual participant data, The Lancet, 381, 1827-1834, 2013	Population: non-DCIS
Detre, S. I., Ashley, S., Mohammed, K., Smith, I. E., Powles, T. J., Dowsett, M., Immunohistochemical Phenotype of Breast Cancer during 25-Year Follow-up of the Royal Marsden Tamoxifen Prevention Trial, Cancer Prevention Research, 10, 171-176, 2017	Population: non-DCIS
Fabian,C.J., Kimler,B.F., Selective estrogen-receptor modulators for primary prevention of breast cancer, Journal of clinical oncology : official journal of the American Society of Clinical Oncology, 23, 1644-1655, 2005	Overview of medications
Fisher, B., Land, S., Mamounas, E., Dignam, J., Fisher, E. R., Wolmark, N., Prevention of invasive breast cancer in women with ductal carcinoma in situ: an update of the National Surgical Adjuvant Breast and Bowel Project experience, Seminars in oncology, 28, 400-18, 2001	Non-systematic review
Force, R. W., Tamoxifen for breast cancer prevention, The Journal of family practice, 47, 336-337, 1998	Summary of Veronesi 1998

Excluded studies - RQ10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?	
Ford, L. G., Johnson, K. A., Tamoxifen Breast Cancer Prevention Trial--an update, Progress in clinical and biological research, 396, 271-282, 1997	Narrative review
Ganz, P. A., Day, R., Ware Jr, J. E., Redmond, C., Fisher, B., Base-line quality-of-life assessment in the national surgical adjuvant breast and bowel project breast cancer prevention trial, Journal of the National Cancer Institute, 87, 1372-1382, 1995	Population: non-DCIS
Goss, P. E., Ingle, J. N., Ales-Martinez, J. E., Cheung, A. M., Chlebowski, R. T., Wactawski-Wende, J., McTiernan, A., Robbins, J., Johnson, K. C., Martin, L. W., Winquist, E., Sarto, G. E., Garber, J. E., Fabian, C. J., Pujol, P., Maunsell, E., Farmer, P., Gelmon, K. A., Tu, D., Richardson, H., Exemestane for breast-cancer prevention in postmenopausal women, New England Journal of Medicine, 364, 2381-2391, 2011	Population: only 3% had DCIS - cannot be extracted separately
Goss, P. E., Richardson, H., Chlebowski, R., Johnston, D., Sarto, G. E., Maunsell, E., Ingle, J. N., Ales-Martinez, J. E., National Cancer Institute of Canada Clinical Trials Group MAR3 trial: Evaluation of exemestane to prevent breast cancer in postmenopausal women, Clinical breast cancer, 7, 895-900, 2007	Narrative review
Goss, P. E., Willett, L. R., Exemestane prevented invasive breast cancer in postmenopausal women at moderately increased risk, Annals of internal medicine, 155, JC4-03, 2011	Commentary
Grimison, P. S., Australian New Zealand Breast Cancer Trials, Group, Coates, A. S., Forbes, J. F., Cuzick, J., Furnival, C., Craft, P. S., Snyder, R. D., Thornton, R. M., Lindsay, D. F., Simes, R. J., Tamoxifen (TAM) for the prevention of breast cancer: Importance of specific aspects of health-related quality of life (HRQL) to global health status in the ANZ BCTG substudy of IBIS-1 (ANZ 92P1), Journal of clinical oncology, 26, 1516, 2008	Conference abstract
Houghton, J., Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ of the breast in the UK, Australia, and New Zealand: Randomised controlled trial, Lancet, 362, 95-102, 2003	Same sample and outcomes as Cuzick 2011; longer follow-up period preferred by GC
Hutchings, O., Evans, G., Fallowfield, L., Cuzick, J., Howell, A., Effect of early American results on patients in a tamoxifen prevention trial (IBIS). International Breast Cancer Intervention Study, Lancet, 352, 1222, 1998	Summary
Jenkins, V. A., Ambroisine, L. M., Atkins, L., Cuzick, J., Howell, A., Fallowfield, L. J., Effects of anastrozole on cognitive performance in postmenopausal women: a randomised, double-blind chemoprevention trial (IBIS II), The Lancet Oncology, 9, 953-961, 2008	Population: non-DCIS
Jones, Al, Chemoprevention of breast cancer (The British tamoxifen trials), Journal canadien des maladies infectieuses [Canadian journal of infectious diseases], 6, 193c, 1995	Population: non-DCIS

Excluded studies - RQ10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?	
Kane, R. L., Virnig, B. A., Shamliyan, T., Wang, S. Y., Tuttle, T. M., Wilt, T. J., The impact of surgery, radiation, and systemic treatment on outcomes in patients with ductal carcinoma in situ, Journal of the National Cancer Institute. MonographsJ Natl Cancer Inst Monogr, 2010, 130-3, 2010	Contains non-DCIS populations and non-RCTs
Kinsey-Trotman, S., Shi, Z., Fosh, B., Breast ductal carcinoma in situ: A literature review of adjuvant hormonal therapy, Oncology Reviews, 10, 60-64, 2016	Contains non-DCIS populations
Kotwall, C. A., Breast cancer treatment and chemoprevention, Canadian Family Physician, 45, 1917-1924, 1999	Contains non-DCIS populations
Land, S. R., Wickerham, D. L., Costantino, J. P., Ritter, M. W., Vogel, V. G., Lee, M., Pajon, E. R., Wade, Iii J. L., Dakhil, S., Lockhart Jr, J. B., Wolmark, N., Ganz, P. A., Patient-reported symptoms and quality of life during treatment with tamoxifen or raloxifene for breast cancer prevention: The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial, Journal of the American Medical Association, 295, 2742-2751, 2006	Population: non-DCIS
Lippman,M.E., Cummings,S.R., Disch,D.P., Mershon,J.L., Dowsett,S.A., Cauley,J.A., Martino,S., Effect of raloxifene on the incidence of invasive breast cancer in postmenopausal women with osteoporosis categorized by breast cancer risk, Clinical Cancer Research, 12, 5242-5247, 2006	Population: non-DCIS
Love, R. R., Breast cancer prevention, Oncologist, 7, 100-2, 2002	Commentary
Machia, J., Breast cancer: risk, prevention, & tamoxifen, The American journal of nursing, 101, 26-35; quiz 36, 2001	Opinion paper
Mallick, S., Benson, R., Julka, P. K., Breast cancer prevention with anti-estrogens: review of the current evidence and future directions, Breast Cancer, 23, 170-177, 2016	Narrative review
Maunsell, E., Goss, P. E., Chlebowski, R. T., Ingle, J. N., Ales-Martinez, J. E., Sarto, G. E., Fabian, C. J., Pujol, P., Ruiz, A., Cooke, A. L., Hendrix, S., Thayer, D. W., Rowland, K. M., Dube, P., Spadafora, S., Pruthi, S., Lickley, L., Ellard, S. L., Cheung, A. M., Wactawski-Wende, J., Gelmon, K. A., Johnston, D., Hiltz, A., Brundage, M., Pater, J. L., Tu, D., Richardson, H., Quality of life in MAP.3 (Mammary Prevention 3): A randomized, placebo-controlled trial evaluating exemestane for prevention of breast cancer, Journal of clinical oncology, 32, 1427-1436, 2014	Population: cannot extract data separately for those with DCIS
McKeon, V. A., The breast cancer prevention trial. Should Women at risk take tamoxifen?, AWHONN lifelines / Association of Women's Health, Obstetric and Neonatal Nurses, 2, 20-25, 1998	Population: non-DCIS
McKeon, V. A., The Breast Cancer Prevention Trial: evaluating tamoxifen's efficacy in preventing breast cancer, Journal of obstetric, gynecologic, and neonatal nursing : JOGNN / NAACOG, 26, 79-90, 1997	Population: non-DCIS

Excluded studies - RQ10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?	
Mocellin, S., Goodwin, A., Pasquali, S., Risk-reducing medication for primary breast cancer: A network meta-analysis, Cochrane Database of Systematic Reviews, 2016 (5) (no pagination), 2016	Protocol
Mocellin, S., Pilati, P., Briarava, M., Nitti, D., Breast Cancer Chemoprevention: A Network Meta-Analysis of Randomized Controlled Trials, Journal of the National Cancer Institute, 108 (2) (no pagination), 2016	Contains non-DCIS populations
Moon, K. T., Effectiveness of medications to prevent primary breast cancer, American Family Physician, 81, 1149-1150, 2010	Editorial
Nelson, H. D., Smith, M. E. B., Griffin, J. C., Fu, R., Use of medications to reduce risk for primary breast cancer: A systematic review for the U.S. preventive services task force, Annals of internal medicine, 158, 604-614, 2013	Population: non-DCIS
Olin, J. L., St. Pierre, M., Aromatase Inhibitors in Breast Cancer Prevention, Annals of Pharmacotherapy, 48, 1605-1610, 2014	Population: non-DCIS
O'Shaughnessy, J. A., Chemoprevention of breast cancer, Journal of the American Medical Association, 275, 1349-1353, 1996	Case report
Osterweil, N., Multimodal DCIS therapy with tamoxifen cuts breast ca deaths, Oncology Report, 9, 2011	Conference proceedings
Petrelli, F., Barni, S., Tamoxifen added to radiotherapy and surgery for the treatment of ductal carcinoma in situ of the breast: a meta-analysis of 2 randomized trials, Radiotherapy & OncologyRadiother Oncol, 100, 195-9, 2011	Insufficient study information
Powles, T. J., Breast cancer prevention, Breast cancer research, 2, 10-12, 2000	Narrative review
Powles, T. J., Is raloxifene ready to be used for prevention of breast cancer?, International Journal of Fertility and Women's Medicine, 51, 203-204, 2006	Editorial
Powles, T. J., Jones, A. L., Ashley, S. E., O'Brien, M. E. R., Tidy, V. A., Treleavan, J., Cosgrove, D., Nash, A. G., Sacks, N., Baum, M., McKinna, J. A., Davey, J. B., The Royal Marsden Hospital pilot tamoxifen chemoprevention trial, Breast Cancer Research and Treatment, 31, 73-82, 1994	Population: non-DCIS
Powles, T. J., Tillyer, C. R., Jones, A. L., Ashley, S. E., Treleaven, J., Davey, J. B., McKinna, J. A., Prevention of breast cancer with tamoxifen - an update on the Royal Marsden Hospital Pilot Programme, European journal of cancer, 26, 680-684, 1990	Population: non-DCIS
Powles, Tj, Use of tamoxifen for chemoprevention of breast cancer, Ann-Oncol, 9, 1, 1998	Conference abstract
Powles, Tj, Davey, Jb, McKinna, A, A feasibility trial of tamoxifen chemoprevention of breast cancer in Great Britain, Cancer investigation, 6, 621-4, 1988	Population: non-DCIS

Excluded studies - RQ10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?	
Powles, Tj, Eeles, R, Salmon, A, Tidy, A, Ashley, S, Dowsett, M, Update of the Royal Marsden Hospital tamoxifen breast cancer chemoprevention trial, Proceedings of American Society of Clinical Oncology, 22, 94, 2003	Population: non-DCIS
Powles, Tj, Hickish, Tf, Kedar, R, Update of the Royal Marsden Hospital tamoxifen prevention programme in healthy women at increased risk of breast cancer, Proceedings of American Society of Clincial Oncology, 13, 169, 1994	Population: non-DCIS
Powles, Tj, McKinna, A, Davey, J, Chemoprevention of breast cancer, Journal of endocrinology, 137, S32, 1993	Conference abstract
Powles, Tj, Tillyer, Cr, Jones, Al, Ashley, Se, Treleaven, J, Davey, Jb, McKinna, Ja, Prevention of breast cancer with tamoxifen--an update on the Royal Marsden Hospital pilot programme, European journal of cancer (Oxford, England : 1990), 26, 680-4, 1990	Population: non-DCIS
Powles,T., Eeles,R., Ashley,S., Easton,D., Chang,J., Dowsett,M., Tidy,A., Viggers,J., Davey,J., Interim analysis of the incidence of breast cancer in the Royal Marsden Hospital tamoxifen randomised chemoprevention trial, Lancet, 352, 98-101, 1998	Population: non-DCIS
Powles,T.J., Ashley,S., Tidy,A., Smith,I.E., Dowsett,M., Twenty-year follow-up of the Royal Marsden randomized, double-blinded tamoxifen breast cancer prevention trial, Journal of the National Cancer Institute, 99, 283-290, 2007	Population: non-DCIS
Powles,T.J., Hardy,J.R., Ashley,S.E., Farrington,G.M., Cosgrove,D., Davey,J.B., Dowsett,M., McKinna,J.A., Nash,A.G., Sinnett,H.D., Tillyer,C.R., Treleaven,J.G., A pilot trial to evaluate the acute toxicity and feasibility of tamoxifen for prevention of breast cancer, British Journal of Cancer, 60, 126-131, 1989	Population: non-DCIS
Prichard,R.S., Hill,A.D.K., Dijkstra,B., McDermott,E.W., O'Higgins,N.J., The prevention of breast cancer, British Journal of Surgery, 90, 772-783, 2003	Contains non-DCIS populations
Pritchard, K. I., Is tamoxifen effective in prevention of breast cancer?, Lancet, 352, 80-81, 1998	Commentary
Shen,Y., Costantino,J.P., Qin,J., Tamoxifen chemoprevention treatment and time to first diagnosis of estrogen receptor-negative breast cancer, Journal of the National Cancer Institute, 100, 1448-1453, 2008	Population: non-DCIS
Shoker, B., Tamoxifen treatment for DCIS - NSABP B-24 trial, Breast cancer research, 1, 62-63, 1999	Commentary
Signori,C., Dubrock,C., Richie,J.P., Prokopczyk,B., Demers,L.M., Hamilton,C., Hartman,T.J., Liao,J., El-Bayoumy,K., Manni,A., Administration of omega-3 fatty acids and Raloxifene to women at high risk of breast cancer: Interim feasibility and biomarkers analysis from a clinical trial, European Journal of Clinical Nutrition, 66, 878-884, 2012	Population: non-DCIS

Excluded studies - RQ10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?	
Sledge, Jr Gw, Whither chemoprevention?, Clinical breast cancer, 3, 173, 2002	Editorial
Slomski, C. A., The Breast Cancer Prevention Trial, Journal of the american medical women's association (1972), 47, 149-151, 1992	Protocol summary
Smigel,K., Breast Cancer Prevention Trial shows major benefit, some risk, Journal of the National Cancer Institute, 90, 647-648, 1998	Editorial
Sporn, M. B., Dowsett, S. A., Mershon, J., Bryant, H. U., Role of raloxifene in breast cancer prevention in postmenopausal women: Clinical evidence and potential mechanisms of action, Clinical Therapeutics, 26, 830-840, 2004	Contains non-DCIS populations
Staley, H., McCallum, I., Bruce, J., Postoperative Tamoxifen for ductal carcinoma in situ: Cochrane systematic review and meta-analysis, Breast (Edinburgh, Scotland), 23, 546-51, 2014	Insufficient information regarding study quality
Staley,Helen, McCallum,Iain, Bruce,Julie, Postoperative tamoxifen for ductal carcinoma in situ, Cochrane Database of Systematic Reviews, -, 2012	Insufficient information regarding study quality
Stollerman, G. H., Bisno, A. L., Breast cancer prevention by tamoxifen and raloxifene, Hospital Practice, 34, 33-34, 1999	Commentary
Sweeney, F. W., Newton, W. P., Tamoxifen for the prevention of breast cancer in high-risk women, The Journal of family practice, 48, 90-91, 1999	Summary of Fisher 1998
Tjalma, W. A., Radiotherapy and tamoxifen in women with completely excised ductal carcinoma in situ, Lancet, 362, 1156-1157, 2003	Letter
Veronesi,A., Pizzichetta,M.A., Ferlante,M.A., Zottar,M., Magri,M.D., Crivellari,D., Foladore,S., Tamoxifen as adjuvant after surgery for breast cancer and tamoxifen or placebo as chemoprevention in healthy women: different compliance with treatment, Tumori, 84, 372-375, 1998	Population: non-DCIS
Virnig, B. A., Shamliyan, T., Tuttle, T. M., Kane, R. L., Wilt, T. J., Diagnosis and management of ductal carcinoma in situ (DCIS), Evidence Report/Technology AssessmentEvid rep/technol assess, 1-549, 2009	Contains interventions/comparisons outside scope
Virnig,B.A., Tuttle,T.M., Shamliyan,T., Kane,R.L., Ductal carcinoma in Situ of the breast: A systematic review of incidence, treatment, and outcomes, Journal of the National Cancer Institute, 102, 170-178, 2010	Contains interventions/comparisons outside scope
Zhang, A., Postoperative tamoxifen in women with ductal carcinoma in situ, American Journal of Nursing, 113, 41, 2013	Summary

DCIS, ductal carcinoma in situ

Economic studies

See Supplement 1: Health economics literature review for list of excluded economic studies.

Appendix L – Research recommendations

Research recommendations for 4.1 What is the optimal duration of adjuvant endocrine therapy for people with oestrogen-receptor positive breast cancer?

No research recommendations were made for this review question.

Research recommendations for 4.2 What is the effectiveness of ovarian suppression in addition to endocrine therapy in pre-menopausal women with oestrogen-positive breast cancer?

No research recommendations were made for this review question.

Research recommendations for 10.4 What is the role of chemoprevention in women following initial treatment for ductal carcinoma in situ (DCIS)?

No research recommendations were made for this review question