National Institute for Health and Care Excellence

Final

Early and locally advanced breast cancer: diagnosis and management

[B] Evidence reviews for management of the positive axilla

NICE guideline NG101

Evidence reviews

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Final

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

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Contents

Management of the positive axilla

This evidence report contains information on 2 reviews relating to the management of the positive axilla.

- Review question 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?
- Review question 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Review question 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Introduction

Removal of the lymph glands in the armpit or axilla (axillary lymph node dissection; ALND) in people with breast cancer has been used to both determine the level of cancer involvement in the lymph glands (stage the axilla), and to treat any breast cancer in the axillary lymph glands. Removal of the first draining lymph node(s) by sentinel lymph node biopsy (SLNB) is an established procedure to stage the axilla.

In the previous guideline CG80 (NICE 2009) it was recommended that ALND be performed for people with evidence of cancer in the lymph glands either by needle biopsy following ultrasound, or following SLNB where the sentinel lymph node contains cancer deposits greater than 0.2 mm in size (micrometastases or macrometastases).

ALND is associated with higher rates of complications such as lymphoedema and shoulder stiffness which could potentially be avoided if it is safe to omit axillary treatment.

The aim of this review is to determine whether axillary treatment (further surgery or radiotherapy) can be safely omitted in some people with tumour deposits in their axillary lymph nodes greater than 0.2 mm.

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	Adults (18 or over) with invasive breast cancer and axillary lymph node metastasis but no distant metastases (M0) following sentinel node biopsy or axillary node sampling or radiological biopsy
Intervention	No axillary treatment
Comparison	Axillary treatment (axillary radiotherapy or axillary lymph node clearance)
Outcome	**Critical** • Locoregional breast cancer recurrence • Treatment-related morbidity • Health-related quality of life **Important** • Overall survival • Breast cancer specific survival • Rate of adjuvant therapy

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. Methods specific to this review question are described in the review protocol in appendix A.

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

Clinical evidence

A systematic review (Schmidt-Hansen 2016) was identified for this review question; therefore, the literature search was conducted using the date limit from the review (March 2015). Additional information from newer publications of 2 of the trials included in the systematic review was also incorporated (Giuliano 2017 and Savolt 2017).

Included studies

Five studies (number of participants, N=3919) were included in the review; the protocol for this review question included both men and women but all available evidence was from women. Three randomised control trials (RCTs) compared ALND following sentinel lymph node dissection (SLND) to SLND alone (American College of Surgeons Oncology Group-Z0011 [ACOSOG-Z0011]; Agència d'Avaluació de Tecnologia i Recerca Mèdiques-048-13-2000 [ATTRM-048-13-2000] and International Breast Cancer Study Group-23-01 [IBCSG-23-01]). Two RCTs compared ALND to axillary radiotherapy (After mapping of the axilla: radiotherapy or surgery [AMAROS] and the optimal treatment of the axilla - surgery or radiotherapy [OTOASOR]) following SLND; these trials were included as indirect evidence in lieu of any evidence comparing axillary radiotherapy with no axillary treatment. Evidence from these studies is summarised in the clinical GRADE evidence profiles below (Table 3 to Table 5).

The ATTRM-048-13-2000 and IBCSG-23-01 trials included only patients with micro-metastatic disease in sentinel lymph nodes, whereas ACOSOG-Z0011 included patients with 1 or 2 positive sentinel lymph nodes.

The clinical studies included in this evidence review are summarised in Table 2 and evidence from these are summarised in the clinical GRADE evidence profiles below (Table 3 to Table 5). 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. Three RCTs are ongoing comparing ALND to SLND (NCT01796444; Wang 2013 and Borstkanker Onderzoek Groep 2013-07 [BOOG 2013-07]; van Roozendaal 2015) and ALND or axillary radiotherapy plus adjuvant treatment versus adjuvant treatment alone (Positive Sentinel node: adjuvant therapy alone versus adjuvant therapy plus clearance or axillary radiotherapy. An RCT of axillary treatment in women with early stage breast cancer who have metastases in one or two Sentinel Nodes [POSNOC]; Goyal 2015).

Summary of clinical studies included in the evidence review

Table 2 provides a summary of the included studies.

Table 2: Summary of included studies

Study	Additional inclusion criteria	Interventions/comparison
Schmidt-Hansen 2016	• **ATTRM-048-13-2000**: Age ≤ 75 years, Tumour size < 3.5 cm, clinical N0, Breast conservation therapy or mastectomy as the primary treatment. Sentinel lymph node micrometastases (≥ 1 metastatic cell deposit no larger than 2 mm up until 2002 and then ≥ 1 metastatic cell deposit 0.2-2 mm). • **IBCSG-23-01:** Tumour diameter of ≤ 5 cm, clinical N0. One or more sentinel lymph node	• **SLND + ALND versus SLND only trials** ○ ATTRM-048-13-2000 ○ IBCSG-23-01 ○ ACOSOG Z0011 • **ALND v axillary RT trials** ○ AMAROS

Study	Additional inclusion criteria	Interventions/comparison
	micrometastases (≤2 mm), but no macro-metastatic disease. Isolated tumour cells were eventually included within the definition of micro-metastases. Mastectomy or conservative breast surgery. • **ACOSOG Z0011:** Age ≥ 18 years. Tumour size < 5 cm, clinical N0. Breast conservation therapy, 1-2 sentinel lymph node metastases and ECOG status ≤ 2. • **AMAROS**: Tumour size 0.5-3.0 cm, Sentinel nodes with only isolated tumour cells were also not regarded as sentinel node positive. Women were randomised before surgery to the treatment they would receive if their sentinel lymph node biopsy proved positive. • **OTOASOR:** Tumour size < 3 cm. Women were randomised before surgery to the treatment they would receive if their sentinel lymph node biopsy (SLNB) proved positive.	○ OTOASOR

ACOSOG-Z011, American College of Surgeons Oncology Group-Z0011; ALND, axillary lymph node dissection; AMAROS, After mapping of the axilla: radiotherapy or surgery; EORTC, European Organisation for Research and Treatment of Cancer; IBCSG-23-01, International Breast Cancer Study Group-23-01; OTOASOR, The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy; RT, radiotherapy; SLN, SLND, sentinel lymph node dissection

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question are presented in Table 3 to Table 5.

The ATTRM-048-13-2000 trial was assessed as being at high risk of reporting bias because it did not report adverse events. It was also assessed as at risk of both patient selection and detection bias because there was inadequate detail on patient selection and outcome assessment. In IBCSG-23-01 the authors did not report statistical analyses of adverse events or complications. The results were assessed as being at high risk of detection bias due to lack of blinding.

Blinding was unclear in the ACOSOG Z0011 trial and 30-day short-term adverse event data were not reported for all the participants. The outcome data for long-term complications were missing for progressively larger proportions of participants in both treatment groups. As a result the trial was assessed as being at risk of detection bias for all outcomes and at risk of attrition bias for the short-term adverse events outcome; for the long-term complications outcome the results were assessed as being at high risk of attrition bias.

The ACOSOG-Z0011, ATTRM-048-13-2000 and IBCSG-23-01 trials all randomised patients after the results of SLND were known, so these trials were assessed as being at risk of recruitment bias. The AMAROS and OTOASOR trials randomised patients before sentinel lymph node biopsy.

The AMAROS trial was open label and did not report short-term adverse events or long-term complications other than lymphoedema and shoulder mobility for which either progressively larger or unclear proportions of data were missing, respectively. For this reason the results from the AMAROS trial were assessed as being at high risk of detection, attrition and reporting bias.

The OTOASOR trial did not report adverse events in detail; there was also little information about patient selection and allocation as well as about potential blinding of outcome assessment, so its results were assessed as being at risk of selection and detection bias.

Table 3: Summary clinical evidence profile: Comparison 1.1 SLND plus ALND versus SLND in people with breast cancer with sentinel node micrometastases

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with SLND alone	Corresponding risk with SLND+ALND			
Overall survival (OS) Follow-up: median 5 years	98% OS at 5 years[5]	98% OS at 5 years (96% to 99%)	HR 1.12 (0.59 to 2.15)	931 (1 study)	Low[1,3]
Disease-free survival (DFS) Follow-up: median 5 years	88% DFS at 5 years[5]	85% DFS at 5 years (80% to 89%)	HR 1.24 (0.88 to 1.73)	1158 (2 studies)	Very low[1,3,6]
Breast cancer recurrence in the axilla Follow-up: median 5 years	9 per 1000	4 per 1000 (1 to 18)	RR 0.42 (0.08 to 2.11)	1158 (2 studies)	Very low[2,3]
Local breast cancer recurrence Follow-up: median 5 years	17 per 1000	22 per 1000 (9 to 54)	RR 1.26 (0.50 to 3.16)	931 (1 study)	Very low[2,3]
Distant breast cancer recurrence Follow-up: median 5 years	44 per 1000	58 per 1000 (35 to 95)	RR 1.31 (0.8 to 2.15)	1158 (2 studies)	Very low[2,3]
Short term adverse events - Wound infection Follow-up: 30 days	0 per 1000	0 per 1000 (0 to 0)	RR 3.02 (0.12 to 73.93)	931 (1 study)	Very low[2,3,4]
Long term adverse events - Objective lymphoedema Follow-up: 12 months	33 per 1000	132 per 1000 (76 to 229)	RR 3.99 (2.30 to 6.92)	900 (1 study)	Very low[2,3]
Long term adverse events) - Axillary paraesthesia / sensory neuropathy Follow-up: 12 months	121 per 1000	183 per 1000 (134 to 251)	RR 1.51 (1.10 to 2.07)	900 (1 study)	Very low[2,3]

ALND: axillary lymph node dissection; CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio; SLND, sentinel lymph node dissection.

[1] Unclear or inadequate allocation concealment. Not blinded, but this is unlikely to influence survival outcomes.

[2] Unclear or inadequate allocation concealment. No blinding - potential risk of detection bias.

[3] <300 events.

[4] 95% confidence interval crosses boundary for no effect (1) and minimally important difference

[5] 5 year survival values taken from the SLND arm of IBCSG 23-01

[6] Downgraded for indirectness - disease free survival was a composite outcome defined as time to death or first recurrence of breast cancer

Table 4: Summary clinical evidence profile: Comparison 1.2 SLND plus ALND versus SLND in those with sentinel node micro or macrometastases

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk with SLND	Corresponding risk with SLND+ALND			
Overall survival (OS) Follow-up: median 9.3 years	86% OS at 10 years[5]	84% OS at 10 years (79% to 87%)	HR 1.18 (0.81 to 1.61)	856 (1 study)	Low[1,3]
Disease-free survival (DFS) Follow-up: median 9.3 years	80% DFS at 10 years[5]	78% DFS at 10 years (74% to 82%)	HR 1.17 (0.85 to 1.62)	853 (1 study)	Very low[1,3,6]
Breast cancer recurrence in the axilla Follow-up: median 9.3 years	11 per 1000	5 per 1000 (1 to 24)	RR 0.42 (0.08 to 2.13)	856 (1 study)	Very low[2,3]
Local breast cancer recurrence Follow-up: median 9.3 years	28 per 1000	45 per 1000 (22 to 92)	RR 1.64 (0.81 to 3.34)	856 (1 study)	Very low[2,3]
Short term adverse events - Wound infection Follow-up: 30 days	30 per 1000	83 per 1000 (42 to 163)	RR 2.80 (1.43 to 5.49)	744 (1 study)	Very low[2,3]
Short term adverse events - Axillary seroma Follow-up: 30 days	57 per 1000	142 per 1000 (88 to 231)	RR 2.51 (1.55 to 4.08)	744 (1 study)	Very low[2,3]
Short term adverse events - Axillary paraesthesia Follow-up: 30 days	116 per 1000	466 per 1000 (345 to 631)	RR 4.02 (2.98 to 5.44)	744 (1 study)	Very low[2,3]
Long term adverse events - Objective lymphoedema Follow-up: 12 months	62 per 1000	107 per 1000 (58 to 201)	RR 1.73 (0.93 to 3.24)	468 (1 study)	Very low[2,3,4]
Long term adverse events - Subjective lymphoedema Follow-up: 12 months	45 per 1000	129 per 1000 (69 to 241)	RR 2.87 (1.53 to 5.38)	556 (1 study)	Very low[2,3]
Long term adverse events) - Axillary paraesthesia / sensory neuropathy Follow-up: 12 months	90 per 1000	394 per 1000 (261 to 592)	RR 4.40 (2.92 to 6.61)	555 (1 study)	Very low[2,3]

ALND: axillary lymph node dissection; CI: Confidence interval; HR: Hazard ratio; RR: Risk ratio; SLND, sentinel lymph node dissection.

[1] Unclear or inadequate allocation concealment. Not blinded, but this is unlikely to influence survival outcomes.

[2] Unclear or inadequate allocation concealment. No blinding - potential risk of detection bias.

[3] <300 events.

[4] 95% confidence interval crosses boundary for no effect (1) and minimally important difference

[5] 10 year survival values taken from the SLND arm of ACOSOG-Z0011

[6] Downgraded for indirectness - disease free survival was a composite outcome defined as time to death or first recurrence of breast cancer

Table 5: Summary clinical evidence profile: Comparison 2. ALND versus axillary radiotherapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk axillary RT	Corresponding risk ALND			
Overall survival – median follow up 6 to 8 years	5 year OS 93%[3]	5 year OS 93% (91% to 94%)	HR 1.00 (0.81 to 1.24)	1899 (2 studies)	Very low[4,5]
Disease free survival– median follow up 6 to 8 years	5 year DFS 83%[3]	5 year DFS 84% (74% to 87%)	HR 0.93 (0.76 to 1.13)	1899 (2 studies)	Very low[2,5,7]
Breast cancer recurrence in the axilla	14 per 1000	8 per 1000 (4 to 20)	RR 0.58 (0.24 to 1.42)	1899 (2 studies)	Low[2,5]
Long term adverse events - lymphoedema Arm circumference increase > 10%	59 per 1000	78 per 1000 (47 to 130)	RR 1.33 (0.80 to 2.22)	820 (1 study)	Very low[1,2,5,6]
Long term adverse events - lymphoedema Clinical signs	151 per 1000	278 per 1000 (210 to 367)	RR 1.84 (1.39 to 2.43)	820 (1 study)	Very low[1,2,5]
Long term adverse events - shoulder motion Range of motion in 4 excursions compared between arms Follow-up: 12 months	NR	NR	No significant difference reported	N – not reported (1 study)	Low[1,2]
Quality of life EORTC-QLQ-C30 and QLQ-BR23	NR	NR	No significant difference reported	N – not reported (1 study)	Low[1,2]

ALND: axillary lymph node dissection; CI: Confidence interval; EORTC, European Organisation for Research and Treatment of Cancer; HR: Hazard ratio; NR: not reported; RR: Risk ratio; RT, radiotherapy.
[1] No blinding - risk of detection bias
[2] Progressively higher rates of attrition with longer follow up - risk of attrition bias
[3] 5 year survival values taken from the axillary RT arm of AMAROS
[4] Considerable heterogeneity (I2 > 80%; random effects model could not be used)
[5] <300 events
[6] 95% confidence interval crosses boundary for no effect (1) and minimally important difference
[7] Downgraded for indirectness - disease free survival was a composite outcome defined as time to death or first recurrence of breast cancer

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 1.1. ALND following SLND vs SLND alone in people with sentinel lymph node micrometastases

Critical outcomes

Locoregional recurrence

- There is very low quality evidence from 2 RCTs (N=1158; median follow-up 5 years) of no clinically important difference in the rates of local or axillary recurrence of breast cancer after ALND or SLND alone in women with sentinel lymph node micrometastases.

Treatment-related morbidity

- There is very low quality evidence from 1 RCT (N=900) of a clinically important increased risk of lymphoedema and axillary paraesthesia at 1 year after surgery in women with sentinel lymph node micrometastases who received ALND as compared to SLND alone.

Health-related quality of life

- No evidence was found for this outcome.

Important outcomes

Overall survival

- There is low quality evidence from 2 RCTs (N=1158; median follow-up 5 years) of no clinically important difference in overall survival after ALND or SLND alone in women with sentinel lymph node micrometastases.

Disease-free survival

- There is very low quality evidence from 2 RCTs (N=1158; median follow-up 5 years) of no clinically important difference in disease-free survival after ALND or SLND alone in women with sentinel lymph node micrometastases.

Breast cancer specific survival

- No evidence was found for this outcome.

Rate of adjuvant therapy

- No evidence was found for this outcome.

Comparison 1.2. ALND following SLND vs SLND alone in people with sentinel lymph node micro or macrometastasis

Critical outcomes

Locoregional recurrence

- There is low quality evidence from 1 RCT (N=856; median follow up 9.3 years) in women with sentinel lymph node micro or macrometastases of no clinically important difference in the rates of local or axillary breast cancer recurrence following ALND or SLND alone.

Treatment-related morbidity

- There is very low quality evidence from 1 RCT (N=744) in women with sentinel lymph node micro or macrometastases of a clinically important increased risk of lymphoedema and axillary paraesthesia at 1 year after surgery in those who received ALND compared to SLND.
- There is very low quality evidence from 1 RCT(N=744) in women with sentinel lymph node micro or macrometastases of a clinically important increased risk of wound infection, axillary seroma and axillary paraesthesia within 30 days of surgery in those who receive ALND compared to SLND alone.

Health-related quality of life

- No evidence was found for this outcome.

Important outcomes

Overall survival

- There is low quality evidence from 1 RCT (N=856; median follow up 9.3 years) of no clinically important difference in overall survival following ALND or SLND alone in women with sentinel lymph node micro or macrometastases.

Disease-free survival

- There is low quality evidence from 1 RCT (N=856; median follow up 9.3 years) of no clinically important difference in disease-free survival following ALND or SLND alone in women with sentinel lymph node micro or macrometastases.

Breast cancer specific survival

- No evidence was found for this outcome.

Rate of adjuvant therapy

- No evidence was found for this outcome.

Comparison 2: ALND versus axillary radiotherapy

Critical outcomes

Locoregional recurrence

- No evidence was found for this outcome.

Treatment-related morbidity

- There is very low quality evidence from 1 RCT (N=820) of a clinically important increased risk of clinical signs of lymphoedema following ALND when compared to axillary radiotherapy as treatment for positive sentinel axillary lymph nodes.

Health-related quality of life

- There is low quality evidence from 1 RCT (N= 820) of no clinically important difference between shoulder motion and quality of life following ALND and axillary radiotherapy as treatment for positive sentinel axillary lymph nodes.

Important outcomes

Overall survival

- There is very low quality evidence from 2 RCTs (N=1899; median follow-up 6 to 8 years) of no clinically important difference in overall survival following ALND or axillary radiotherapy in women with positive sentinel axillary lymph nodes

Disease-free survival

- There is very low quality evidence from 2 RCTs (N=1899; median follow-up 6 to 8 years) of no clinically important difference in disease free survival following ALND or axillary radiotherapy in women with positive sentinel axillary lymph nodes

Breast cancer specific survival

- No evidence was found for this outcome.

Rate of adjuvant therapy

- No evidence was found for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee prioritised locoregional breast cancer recurrence, treatment-related morbidity and health-related quality of life as critical outcomes. This was because the treatments considered in this topic aim to prevent recurrence in the axillary lymph nodes but potentially cause side effects adversely affecting quality of life. Overall survival, breast cancer specific survival and rate of adjuvant therapy were selected as important outcomes. These were not prioritised as critical outcomes because axillary recurrence is potentially treatable meaning survival is unlikely to be impacted in this selected population.

Health-related quality of life was only available for the comparison of axillary lymph node dissection versus axillary radiotherapy following sentinel lymph node dissection. No data were available for breast cancer specific survival or rate of adjuvant therapy. Although not specified in the review protocol disease free survival was included as an outcome in the evidence report, but was downgraded for indirectness because it was a composite of other outcomes (time to death or breast cancer recurrence).

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. For the comparisons of (ALND following SLND versus SLND alone (in people with micrometastases ± macrometastases) the quality of the evidence for overall survival was low; for locoregional recurrence, disease-free survival and treatment-related morbidity the quality was very low. For the comparison of ALND versus axillary radiotherapy following SLND the quality of the evidence for overall survival and treatment-related morbidity was very low and for disease-free survival, recurrence and health-related quality of life the quality was low.

Of the 3 studies comparing ALND following SLND with SLND alone, 2 included only patients with sentinel lymph node micrometastases whilst the third included patients with sentinel lymph node micro or macrometastases. The committee noted that the studies did not always differentiate between isolated tumour cells and micrometastases, although they were also aware that distinguishing between them is often difficult and without prognostic significance (that is, the outcome for isolated tumour cells and micrometastases is essentially the same).

The committee noted that the ACOSOG Z0011 trial was at risk of a range of bias issues, particularly recruitment bias due to participants being randomised after the sentinel lymph node results were known, radiotherapy treatment fields being altered in people randomised to have ALND and some patients being given radiotherapy off protocol, as well as attrition bias as data for long-term complications were only available for a subset of participants. The committee therefore gave less weight to the results of this study when making their recommendations.

The committee also noted that the AMAROS and OTOASOR trials did not compare against no axillary treatment as specified in the review protocol. However as there were no other studies that compared axillary radiotherapy with no treatment, the committee agreed to use these studies as indirect evidence for this treatment modality.

Benefits and harms

The committee agreed that no new evidence had been identified that supported changing the recommendation from the previous guideline CG80 (NICE 2009) to not offer further axillary treatment to people with only isolated tumour cells in their sentinel lymph nodes. Therefore this recommendation was retained. Equally no new evidence had been identified that supported changing the recommendations from the previous guideline CG80 (NICE 2009) to offer axillary clearance to people who have a preoperative ultrasound-guided needle biopsy with pathologically proven involvement of the axillary lymph nodes. Therefore this recommendation was also retained. The committee confirmed that this meant that recommendations about axillary treatment for those with sentinel node micro or macrometastases do not apply to those with a positive preoperative ultrasound-guided needle biopsy of their axillary lymph nodes, as this group would be offered axillary clearance (as recommended in the previous NICE guideline CG80).

The evidence did not identify any improvement in survival or recurrence when using axillary treatment in people with micrometastases in their sentinel lymph nodes, but there are harms (lymphoedema and axillary paraesthesia) associated with such treatment. Therefore the committee agreed to recommend this treatment should not be used for this group of people.

ALND provides staging information but is associated with more adverse events. Radiotherapy is associated with fewer adverse events but does not provide any staging information. Given that the evidence showed that ALND and axillary radiotherapy are equivalent in terms of effectiveness, the committee agreed that either form of axillary treatment should be recommended for people with macrometastases. However, it was noted that this may lead to over-treatment with radiotherapy of the supraclavicular fossa (SCF) in some patients as staging information will not be available. This means that people who would not have had the SCF irradiated if the ALND had demonstrated that fewer than 4 axillary lymph nodes were involved, would receive radiotherapy to the breast, axilla and prophylactically to the SCF.

The committee decided against recommending no further axillary treatment for all people with macrometastatic disease, because evidence supporting this approach came only from the ACOSOG Z0011 trial which was at risk of bias due to the issues noted above.

The committee agreed that if someone has 1 or 2 sentinel node macrometastases, the balance between the benefits and harms of treatment are less clear. Given that (based on the committee's clinical experience) in approximately two-thirds of cases, no additional positive nodes are found during full clearance of someone with 1 or 2 macrometastases, the substantial morbidity associated with full axillary clearance may not be warranted. In addition, systemic therapy may be enough to treat any further positive nodes. Therefore the committee recommended that discussion of the risks and benefits of having no further axillary treatment should be considered. The committee thought that this unclear benefit of full axillary clearance would typically be in those who were assessed preoperatively as node negative on ultrasound and clinical examination, subsequently found to have 1 or 2 sentinel

node macrometastases but with otherwise favourable prognostic factors such as T2, ER+ and HER2- breast cancer.

The committee considered that the potential benefits would be less lymphoedema, fewer surgical complications and a reduction in the number of operations. The potential harms would be the potential for increased regional recurrence in those people not having further axillary treatment, however the committee agreed that the rates of this would likely be very low.

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 agreed that, in current practice, the vast majority of people with macrometastases would have ALND. The recommendation to offer ALND or radiotherapy treatment may lead to a reduction in surgical procedures and an increase in radiotherapy. The impact on radiotherapy services will include an increase in planning time and treatment time if the breast plus axilla plus SCF are treated, and this in turn may impact on radiotherapy capacity. Therefore radiotherapy costs may increase but this may be offset by a reduction in surgical costs (and possibly lead to a net decrease in overall costs to the NHS) so it is not expected that the recommendations will have a significant resource impact.

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Review question 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Introduction

Breast cancer-related lymphoedema refers to chronic swelling of the arm (and less often the breast) occurring following axillary interventions (surgery and/or radiotherapy) for breast cancer. This affects around a fifth of all people treated for early stage breast cancer and occurs more commonly in some sub-groups. Factors recognised to influence the development of lymphoedema include the extent of surgery, radiotherapy and infection. The onset of lymphoedema can occur at any time after axillary intervention and when present can result in limited physical function and/or adverse psychological and social effects. Hence, lymphoedema is a lifelong concern for breast cancer survivors.

Many treatment strategies and lifestyle modifications have been suggested to help prevent lymphoedema in breast cancer survivors but the effectiveness of any of them is unclear. These strategies can also themselves result in morbidity. This review aims to clarify which strategies are evidence-based and are effective at preventing lymphoedema.

PICO table

See Table 6 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 6: Summary of the protocol (PICO) table

Population	Adults (18 or over) with breast cancer who have undergone axillary intervention without established lymphoedema
Intervention	Any strategy with the aim of preventing lymphoedema, including: • Advice on interventions to avoid , such as venepuncture, flu jab, blood pressure • Active management of infection and injury (antibiotic) • Compression garments • Education • Diet/exercise • Simple lymph drainage massage • Skin care • Physiotherapy
Comparison	No strategies aimed at preventing lymphoedema
Outcome	**Critical** • Lymphoedema • HRQoL **Important** • Intervention-related morbidity • Arm and shoulder function • Psychological morbidity

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. Methods specific to this review question are described in the review protocol in appendix A.

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

Clinical evidence

Included studies

Thirteen studies (N=2520) were included in the review; this included 10 RCTs (Anderson, 2012; Cinar, 2008; Devoogdt, 2011; Hansdorfer-Korzon, 2016; Harder, 2015; Kilbreath, 2012; Sagen, 2009; Schmitz, 2010; Torres Lacomba, 2010; Zimmermann, 2012), one non-randomised control trial (Sato 2014) and 2 comparative cohort studies (Fu 2010; Lu 2015); the protocol for this review question included both men and women but all available evidence was from women.

One RCT compared compression garments to no treatment (Hansdorfer-Korzon, 2016). Two RCTs compared exercise to education (Anderson, 2012; Kilbreath, 2012), 1 RCT compared exercise to activity restriction (Sagen, 2009), 1 RCT compared exercise to no exercise (Schmitz, 2010), and 1 RCT compared an exercise and yoga program to exercise only (Harder, 2015). One RCT compared manual lymph drainage (MLD) to standard physiotherapy (Zimmermann, 2012) and 1 other RCT compared MLD, a prevention guideline, and exercises to prevention guidelines and exercises only (Devoogdt, 2011). one RCT compared physiotherapy to unsupervised exercises (Cinar, 2008) and 1 RCT compared physiotherapy and education to education only (Torres Lacomba, 2010). Evidence from 3 RCTs that had an intervention in the control arm as part of usual care (prevention guidelines and exercises in Devoogdt, (2011), exercise in Harder, (2015) and physiotherapy in Zimmermann, (2012)) were downgraded for indirectness; however, evidence was not downgraded when education was included in the control arm (Anderson, 2012; Kilbreath, 2012) because education is part of the usual NHS care.

One non-randomised controlled trial (NRCT) compared an education program to no education (Sato, 2009) and 2 retrospective cohort studies compared education interventions to no education (Fu, 2010; Lu, 2015).

The clinical studies included in this evidence review are summarised in Table 7 and evidence from these are summarised in the clinical GRADE evidence profile below (Table 8). 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 7: Summary of included studies

Study	Additional inclusion/exclusion criteria	Interventions/Comparisons
Randomised controlled trials		
Anderson 2012	Women with newly diagnosed stage I-III breast cancer with axillary or sentinel lymph node dissection and can take part in moderate exercise training	Intervention: individualised exercise, methods to prevent lymphoedema, and education including diet and counselling Control: usual care (patient education) only
Cinar 2008	Women with modified radical mastectomy	Intervention: 15 sessions of an individual rehabilitation program and home-based activity program Control: received a form with the exercises to perform at home
Devoogdt 2011	Women with operable breast cancer who had unilateral surgery with axillary lymph node dissection	Treatment: prevention guidelines, exercise therapy, and manual lymph drainage Control: prevention guidelines and exercise therapy
Hansdorfer-Korzon 2016	Women with newly diagnosed breast cancer who had total mastectomy without breast reconstruction and with axillary lymph node removal	Intervention: Compression corset Control: No physiotherapeutic treatment
Harder 2015	Women with early-stage breast cancer (stages I-III) with axillary intervention	Intervention: standard care post-operative exercises plus a 10-week self-practice general yoga programme (yoga DVD) Control: standard care post-operative exercises
Kilbreath 2012	Women operated for stage I-III breast cancer with axillary intervention	All the women received information about postoperative arm exercises and prevention of lymphoedema Intervention: Home program of resistance training and stretches with weekly supervised weight training and follow up

Study	Additional inclusion/exclusion criteria	Interventions/Comparisons
		Control: No exercise program
Sagen 2009	Women with early stage breast cancer who had removal of breast or breast conserving surgery with dissection of axillary nodes and with or without radiotherapy, chemotherapy, or hormone treatment	Intervention: No activity restriction Control: Activity restriction
Schmitz 2010	Breast cancer survivor women at risk of lymphoedema (history of nonmetastatic unilateral breast cancer diagnosis 1 to 5 years ago, </=50 BMI, minimum removal of 2 lymph nodes, no history of lymphoedema, and no planned surgery or at least 1 month away during the study)	Intervention: Weight-lifting Control: No exercise
Torres Lacomba 2010	Women who had unilateral breast cancer surgery with axillary lymph node dissection	Intervention: Early physiotherapy and an educational strategy Control arm: Educational strategy only
Zimmermann 2012	Women being operated for primary breast cancer	Intervention: Standard program of physiotherapy plus MLD Control: Standard program of physiotherapy
Non-randomised controlled trials		
Sato, F., Ishida, T., Ohuchi, N., The perioperative educational program for improving upper arm dysfunction in patients with breast cancer: A controlled trial, Tohoku journal of experimental medicine, 232, 115-122, 2014	Women with operated breast cancer	Intervention: An educational program to prevent or improve arm morbidity outcomes in breast cancer patients post-surgery Control: No educational program
Comparative cohort studies		
Fu, M. R., Chen, C. M., Haber, J., Guth, A. A., Axelrod, D., The effect of providing information about lymphoedema on the cognitive and symptom outcomes of breast cancer survivors, Annals of Surgical Oncology, 17, 1847-1853, 2010	Women with treated breast cancer	Intervention: Women who received information about BCRL Control: Women who did not receive information about BCRL
Lu, S. R., Hong, R. B., Chou, W., Hsiao, P. C., Role of physiotherapy and patient education in lymphoedema control following breast cancer surgery, Therapeutics	Women with newly diagnosed stage 0-3 breast cancer and had tumour resection with ALND	Intervention: patient-centred education program Control: no education program

Study	Additional inclusion/exclusion criteria	Interventions/Comparisons
and Clinical Risk Management, 11, 319-327, 2015		

See appendix D for full evidence tables.

Quality assessment of clinical studies included in the evidence review

The clinical evidence profiles for this review question (interventions to prevent lymphoedema after axillary intervention) are presented in Table 8 to Table 13.

The included evidence was of moderate to very low quality. The main reasons for downgrading the evidence were imprecision around the estimates due to a small number of events of interest and wide confidence intervals, and risk of bias due to unavailability of data regarding comparability between groups at baseline.

Table 8: Summary clinical evidence profile: Comparison 1. Exercise plus usual care compared to usual care alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
Change in arm volume (ml) - 3 months		The mean change in arm volume - 3 months in the intervention groups was 3 higher (18.68 lower to 24.68 higher)		204 (1 study)	Moderate[1,7]
Change in arm volume (ml) - 6 months		The mean change in arm volume - 6 months in the intervention groups was 0 higher (21.8 lower to 21.8 higher)		204 (1 study)	Moderate[1,7]
Change in arm volume (ml)- Follow-up after 1 year		The mean change in arm volume - follow-up after 1 year in the intervention groups was 14.92 lower (42.82 lower to 12.99 higher)		308 (2 studies)	Low[1,2,7]
Lymphoedema (Exceeds BIS ratio) - 8 weeks	149 per 1000	65 per 1000 (24 to 178)	RR 0.44 (0.16 to 1.2)	151 (1 study)	Very low[3,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
Lymphoedema (Exceeds BIS ratio) - 6 months	132 per 1000	82 per 1000 (30 to 218)	RR 0.62 (0.23 to 1.65)	141 (1 study)	Very low[3,5]
Lymphoedema (>2cm interlimb circumference) - 8 weeks	68 per 1000	78 per 1000 (25 to 245)	RR 1.15 (0.37 to 3.62)	151 (1 study)	Very low[3,5]
Lymphoedema (>2cm interlimb circumference) - 6 months	59 per 1000	68 per 1000 (19 to 245)	RR 1.16 (0.33 to 4.16)	141 (1 study)	Very low[3,5]
Lymphoedema (>2cm interlimb circumference) - 12 months	44 per 1000	15 per 1000 (2 to 142)	RR 0.34 (0.04 to 3.22)	134 (1 study)	Low[5,6]
Lymphoedema(>/=10% difference) - First assessment after intervention	108 per 1000	80 per 1000 (47 to 139)	RR 0.74 (0.43 to 1.28)	502 (3 studies)	Very low[1,3,5,6]
Lymphoedema(>/=10% difference) - Follow-up	119 per 1000	85 per 1000 (45 to 160)	RR 0.71 (0.38 to 1.34)	345 (2 studies)	Very low[1,3,5]
Leg press (lb) - 12 months		The mean leg press (lb) - 12 months in the intervention groups was 11 lower (27.2 lower to 5.2 higher)		153 (1 study)	Low[6,8]
Bench press (lb) - 12 months		The mean bench press (lb) - 12 months in the intervention groups was 11 higher (6.91 to 15.09 higher)		122 (1 study)	Moderate[6,7]
Forward flexion (range of motion in º) - 8 weeks		The mean forward flexion (range of motion) - 8 weeks in the intervention groups was 6.4 higher (1.67 to 11.13 higher)		151 (1 study)	Very low[3,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
Forward flexion (range of motion in º) - 6 months		The mean forward flexion (range of motion) - 6 months in the intervention groups was 1.9 higher (4.41 lower to 8.21 higher)		141 (1 study)	Low[3,7]
Abduction (range of motion in º) - 8 weeks		The mean abduction (range of motion) - 8 weeks in the intervention groups was 5.2 higher (0.04 to 10.36 higher)		151 (1 study)	Very low[3,8]
Abduction (range of motion in º) - 6 months		The mean abduction (range of motion) - 6 months in the intervention groups was 10 higher (3.59 to 16.41 higher)		141 (1 study)	Very low[3,8]
External rotation (range of motion in º) - 8 weeks		The mean external rotation (range of motion) - 8 weeks in the intervention groups was 2.1 higher (2.19 lower to 6.39 higher)		151 (1 study)	Low[3,7]
External rotation (range of motion in º) - 6 months		The mean external rotation (range of motion) - 6 months in the intervention groups was 1.2 lower (6.2 lower to 3.8 higher)		141 (1 study)	Low[3,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
Horizontal extension (range of motion in º) - 8 weeks		The mean horizontal extension (range of motion) - 8 weeks in the intervention groups was 2.4 higher (2.23 lower to 7.03 higher)		151 (1 study)	Low[3,7]
Horizontal extension (range of motion in º) - 6 months		The mean horizontal extension (range of motion) - 6 months in the intervention groups was 5.8 higher (0.63 to 10.97 higher)		141 (1 study)	Very low[3,8]
Abduction (strength in N) - 8 weeks		The mean abduction (strength) - 8 weeks in the intervention groups was 10.2 higher (0.48 to 19.92 higher)		151 (1 study)	Very low[3,8]
Abduction (strength in N) - 6 months		The mean abduction (strength) - 6 months in the intervention groups was 3 higher (8.56 lower to 14.56 higher)		141 (1 study)	Low[3,7]
Forward Flexion (strength in N) - 8 weeks		The mean forward flexion (strength) - 8 weeks in the intervention groups was 7.2 higher (0.89 lower to 15.29 higher)		151 (1 study)	Very low[3,8]
Forward Flexion (strength in N) - 6 months		The mean forward flexion (strength) - 6		141 (1 study)	Very low[3,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
		months in the intervention groups was 3.8 higher (5.74 lower to 13.34 higher)			
Horizontal extension (strength in N) - 8 weeks		The mean horizontal extension (strength) - 8 weeks in the intervention groups was 4.2 higher (4.14 lower to 12.54 higher)		151 (1 study)	Low[3,7]
Horizontal extension (strength in N) - 6 months		The mean horizontal extension (strength) - 6 months in the intervention groups was 3 higher (5.92 lower to 11.92 higher)		141 (1 study)	Low[3,7]
Horizontal flexion (strength in N) - 8 weeks		The mean horizontal flexion (strength) - 8 weeks in the intervention groups was 2.8 higher (7.53 lower to 13.13 higher)		151 (1 study)	Low[3,7]
Horizontal flexion (strength in N) - 6 months		The mean horizontal flexion (strength) - 6 months in the intervention groups was 3.8 lower (13.15 lower to 5.55 higher)		141 (1 study)	Very low[3,8]
Physical activity (metabolic equivalent per week: MET-min/week) - 12 months		The mean physical activity (metabolic equivalent per week: met-min/week) - 12		118 (1 study)	Low[6,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
		months in the intervention groups was 600.6 higher (599.62 to 601.58 higher)			
Total metres walked in 6 minutes		The mean total metres walked in 6 minutes in the intervention groups was 34.3 higher (8.61 to 59.99 higher)		104 (1 study)	Very low[2,8]
No pain ("0" VAS score) - 3 months	470 per 1000	183 per 1000 (118 to 287)	RR 0.39 (0.25 to 0.61)	204 (1 study)	Low[1,9]
No pain ("0" VAS score) - 6 months	640 per 1000	397 per 1000 (301 to 518)	RR 0.62 (0.47 to 0.81)	204 (1 study)	Low[1,4]
No pain ("0" VAS score) - 2 years	640 per 1000	595 per 1000 (480 to 742)	RR 0.93 (0.75 to 1.16)	204 (1 study)	Low[1,4]
Change in number of symptoms reported - 12 months		The mean change in number of symptoms reported - 12 months in the intervention groups was 0.09 lower (0.72 lower to 0.54 higher)		147 (1 study)	Low[6,7]
Change in symptom severity - 12 months		The mean change in symptom severity - 12 months in the intervention groups was 0.01 higher (0.29 lower to 0.31 higher)		147 (1 study)	Low[6,7]
FACT-B total score		The mean FACT-B total score in the intervention groups was 1.38 higher		104 (1 study)	Low[2,7]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Usual care alone	Corresponding risk Exercise plus usual care			
		(3.4 lower to 6.16 higher)			
BR23 breast symptoms - 8 weeks post-intervention		The mean BR23 breast symptoms - 8 weeks post-intervention in the intervention groups was 1 higher (4.3 lower to 6.3 higher)		151 (1 study)	Low[3,7]
BR23 breast symptoms - 6 months		The mean BR23 breast symptoms - 6 months in the intervention groups was 4 higher (2.15 lower to 10.15 higher)		141 (1 study)	Very low[3,8]
BR23 - Arm symptoms - 8 weeks (post-intervention)		The mean BR23 - arm symptoms - 8 weeks (post-intervention) in the intervention groups was 3 higher (1.96 lower to 7.96 higher)		151 (1 study)	Very low[3,8]
BR23 - Arm symptoms - 6 months		The mean BR23 - arm symptoms - 6 months in the intervention groups was 4 higher (1.96 lower to 9.96 higher)		141 (1 study)	Very low[3,8]

BIS: bioelectrical impedance spectroscopy; BR23: EORTC-BR23 quality of life questionnaire; CI: confidence interval; FACT-B: functional assessment of cancer therapy for breast cancer; MET: metabolic equivalent of task; RR: risk ratio; VAS: visual analogue scale; (º) = in degree; (N) = in Newton

[1]Sagen 2009 - outcome assessors and investigators were not blinded

[2]Anderson 2012 - unclear allocation concealment and unblinded trial

[3]Kilbreath 2012 - unclear randomisation, unclear blinding

[4] 95%CI crossed null effect and one boundary of default MID; <300 events

[5] 95%CI crossed null effect and two boundaries of default MID; <300 events

[6] Schmitz 2010 - participants were not blinded

[7] N<400

[8] 95%CI crossed null effect and one boundary of default MID; N<400

[9] <300 events

Table 9: Summary clinical evidence profile: Comparison 2. Physiotherapy versus control

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Physiotherapy			
Lymphoedema	230 per 1000	115 per 1000 (34 to 384)	RR 0.50 (0.15 to 1.67)	173 (2 studies)	Very low[1,2,3]
Change in volume ratio (%) from baseline - 12 months		The mean change in volume ratio (%) from baseline - 12 months in the intervention groups was 3.5 lower (5.89 to 1.11 lower)		120 (1 study)	Moderate[2,5]
Change in circumferential difference, cm - 6 months follow-up		The mean change in circumferential difference, cm - 6 months follow-up in the intervention groups was 0.83 lower (2.01 lower to 0.35 higher)		57 (1 study)	Very low[1,4]
Flexion (º)- 6 months follow-up		The mean flexion - 6 months follow-up in the intervention groups was 15.38 higher (10.75 to 20.01 higher)		57 (1 study)	Very low[1,3]
Extension (º) - 6 months follow-up		The mean extension - 6 months follow-up in the intervention groups was 2.63 higher (1.29 lower to 6.55 higher)		57 (1 study)	Very low[1,4]
Internal rotation (º) - 6 months follow-up		The mean internal rotation at 6 months follow-up in the intervention groups was 5.55 higher (1.08 lower to 12.18 higher)		57 (1 study)	Very low[1,4]
External rotation (º) - 6 months follow-up		The mean internal rotation at 6 months follow-up in the intervention groups was 8.24 higher (1.66 to 14.82 higher)		57 (1 study)	Very low[1,4]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk Physiotherapy			
Adduction (º) - 6 months follow-up		The mean adduction - 6 months follow-up in the intervention groups was 0.17 lower (3.72 lower to 3.38 higher)		57 (1 study)	Very low[1,3]
Abduction (º)- 6 months follow-up		The mean abduction - 6 months follow-up in the intervention groups was 21.29 higher (13.06 to 29.52 higher)		57 (1 study)	Very low[1,3]
Functional questionnaire score - 6 months follow-up (lower, better)		The mean functional questionnaire score - 6 months follow-up in the intervention groups was 1.24 lower (1.97 to 0.51 lower)		57 (1 study)	Very low[1,4]

CI: confidence interval; RR: risk ratio; (º)= Degree
1 Cinar 2008 - Unclear randomisation, unclear blinding, unclear attrition bias
2 Torres Lacomba 2010 - Unclear blinding
3 95%CI crossed null effect and two- boundaries of default MID; Optimal information size not met (events=300/N=400)
4 95%CI crossed null effect and one boundary of default MID; N<400
5 N<400

Table 10: Summary clinical evidence profile: Comparison 3: Manual lymph node drainage versus usual care

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk| Manual lymphatic drainage			
Lymphoedema (>=200ml increase) - 3 months	74 per 1000	104 per 1000 (38 to 286)	RR 1.4 (0.51 to 3.86)	158 (1 study)	Very low [1,2,3]
Lymphoedema (>=200ml increase) - 6 months	148 per 1000	142 per 1000 (67 to 304)	RR 0.96 (0.45 to 2.05)	158 (1 study)	Very low [1,2,3]
Lymphoedema (>=200ml increase) - 12 months	190 per 1000	239 per 1000 (131 to 441)	RR 1.26 (0.69 to 2.32)	154 (1 study)	Very low [1,2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk| Manual lymphatic drainage			
Lymphoedema (>=2cm increase) - 3 months	74 per 1000	104 per 1000 (38 to 286)	RR 1.4 (0.51 to 3.86)	158 (1 study)	Very low [1,2,3]
Lymphoedema (>=2cm increase) - 6 months	136 per 1000	156 per 1000 (73 to 331)	RR 1.15 (0.54 to 2.44)	158 (1 study)	Very low [1,2,3]
Lymphoedema (>=2cm increase) - 12 months	203 per 1000	267 per 1000 (150 to 474)	RR 1.32 (0.74 to 2.34)	154 (1 study)	Very low [1,2,3]
Change in arm volume (ml) - 3 months		The mean change in arm volume (ml) - 3 months in the intervention groups was 46.63 lower (186.5 lower to 93.24 higher)		225 (2 studies)	Very low [1,2,4,5,6,7,9]
Change in arm volume (ml) - 6 months		The mean change in arm volume (ml) - 6 months in the intervention groups was 91.74 lower (342.87 lower to 159.39 higher)		225 (2 studies)	Very low [1,2,4,6,7,8]
Change in arm volume (ml) - 12 months		The mean change in arm volume (ml) - 12 months in the intervention groups was 11 lower (54.33 lower to 32.33 higher)		154 (1 study)	Very low [1,2,9]
Physical health (QoL) - 3 months		The mean physical health (QoL) - 3 months in the intervention groups was 0 higher (10.24 lower to 10.24 higher)		158 (1 study)	Very low [1,2,9]
Physical health (QoL) - 6 months		The mean physical health (QoL) - 6 months in the intervention groups was 5 higher (6.89 lower to 16.89 higher)		158 (1 study)	Very low [1,2,9]
Physical health (QoL) - 12 months		The mean physical health (QoL) - 12 months in the intervention groups		154 (1 study)	Very low [1,2,9]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Control	Corresponding risk| Manual lymphatic drainage			
		was 3 lower (14.39 lower to 8.39 higher)			
Mental Health QoL - 3 months		The mean mental health QoL - 3 months in the intervention groups was 3 higher (8.23 lower to 14.23 higher)		158 (1 study)	Very low [1,2,9]
Mental Health QoL - 6 months		The mean mental health QoL - 6 months in the intervention groups was 6 higher (5.82 lower to 17.82 higher)		158 (1 study)	Very low [1,2,7]
Mental Health QoL - 12 months		The mean mental health QoL - 12 months in the intervention groups was 2 lower (12.78 lower to 8.78 higher)		154 (1 study)	Very low [1,2,9]

CI: confidence interval; QoL: quality of life; RR: risk ratio
[1] Devoogdt 2011- Unclear randomisation and unblinded participants
[2] Devoogdt 2011 – Prevention guidelines and exercise therapy were given in both arms - downgraded by 1 level
[3] 95%CI crossed null effect and 2 boundaries of default MID; <300 events
[4] Zimmermann 2012 - Unclear randomisation, blinding, and attrition
[5] I2=77%
[6] I2=91%
[7] 95%CI crossed one boundary of default MID; N<400
[8] Zimmerman 2012 – Physiotherapy was given in both arms - downgraded by 1 level
[9] N<400

Table 11: Summary clinical evidence profile: Comparison 4. Compression corset versus no compression corset

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Without compression corset	Corresponding risk With compression corset			
Number of women with pain reduction	333 per 1000	580 per 1000 (270 to 1000)	RR 1.74 (0.81 to 3.7)	37 (1 study)	Very low[1,2]

CI: confidence interval; RR: risk ratio
[1]Hansdorfer-Korzon 2016 - Unclear randomisation, blinding, and attrition and high risk of selective reporting
[2]95%CI crossed null effect and one boundary of default MID; <300 events

Table 12: Summary clinical evidence profile: Comparison 5. Yoga plus exercise versus exercise alone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Exercise alone	Corresponding risk Yoga plus exercise			
Change in arm function (higher score, better function) - 10 weeks		The mean change in arm function - 10 weeks in the intervention groups was 0.6 higher (0.61 lower to 1.81 higher)		78 (1 study)	Very low[1,2,4]
Change in arm function (higher score, better function) - 6 months		The mean change in arm function - 6 months in the intervention groups was 1.9 higher (0.66 to 3.14 higher)		78 (1 study)	Very low[1,2,3]
Change in QuickDASH (higher score, greater limitation)- 10 weeks		The mean change in QuickDASH - 10 weeks in the intervention groups was 2.4 lower (7.75 lower to 2.95 higher)		78 (1 study)	Very low[1,2,3]
Change in QuickDASH (higher score, greater limitation)- 6 months		The mean change in QuickDASH - 6 months in the intervention groups was 3.5 lower (8.69 lower to 1.69 higher)		78 (1 study)	Very low[1,2,3]
Change in level of pain (higher score, greater pain) - 10 weeks		The mean change in level of pain - 10 weeks in the intervention groups was 0.5 lower (1.14 lower to 0.14 higher)		78 (1 study)	Very low[1,2,3]
Change in level of pain (higher score, greater pain) - 6 months		The mean change in level of pain - 6 months in the intervention groups was 1.4 lower (2.09 to 0.71 lower)		78 (1 study)	Very low[1,2,3]
Change in oxford shoulder score (higher scores, greater disability) - 10 weeks		The mean change in oxford shoulder score - 10 weeks in the intervention groups was 0.4 higher (1.98 lower to 2.78 higher)		78 (1 study)	Very low[1,2,3]
Change in oxford shoulder score (higher scores, greater disability) - 6 months		The mean change in oxford shoulder score - 6 months in the intervention groups was 1.4 lower (3.79 lower to 0.99 higher)		78 (1 study)	Very low[1,2,3]
Change in FACT-B score (higher score better quality of life) - 10 weeks		The mean change in FACT-B score - 10 weeks in the intervention groups was 1.3 lower (6.53 lower to 3.93 higher)		78 (1 study)	Very low[1,2,3]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Exercise alone	Corresponding risk Yoga plus exercise			
Change in FACT-B score (higher score better quality of life) - 6 months		The mean change in FACT-B score - 6 months in the intervention groups was 1.3 higher (3.61 lower to 6.21 higher)		78 (1 study)	Very low[1,2,3]

CI: confidence interval; DASH: disability of shoulder, arm and hand questionnaire; FACT-B: functional assessment of cancer therapy for breast cancer; RR: risk ratio
[1]Harder 2015 - unblinded participants
[2]Harder 2015 - participants in both arms received exercises
[3] 95%CI crossed null effect and one boundary of default MID; N<400
[4] N<400

Table 13: Summary clinical evidence profile: Comparison 6. Education versus no education

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Without education	Corresponding risk With education			
Lymphoedema - Any stage	500 per 1000	490 per 1000 (330 to 735)	RR 0.98 (0.66 to 1.47)	356 (1 study)	Very low[1,2,3]
Lymphoedema - Stage 1	545 per 1000	644 per 1000 (502 to 829)	RR 1.18 (0.92 to 1.52)	178 (1 study)	Very low[1,4]
Lymphoedema - Stage 2 or 3	455 per 1000	355 per 1000 (250 to 509)	RR 0.78 (0.55 to 1.12)	178 (1 study)	Very low[1,4]
Change in upper arm girth (greater arm girth, worsening lymphedema) at 3 months		The mean change in upper arm girth at 3 months in the intervention groups was 0.31 higher (0.48 lower to 1.09 higher)		149 (1 study)	Very low[4,6,7]
Change in upper arm girth (greater arm girth, worsening lymphedema) at 3 months - ALND		The mean change in upper arm girth at 3 months - ALND in the intervention groups was 0.7 higher (0.2 to 1.2 higher)		69 (1 study)	Very low[4,6]
Change in upper arm girth (greater arm girth, worsening lymphedema) at 3 months - SLNB		The mean change in upper arm girth at 3 months - SLNB in the intervention groups was 0.1 lower (0.63 lower to 0.43 higher)		80 (1 study)	Very low[6,9]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Without education	Corresponding risk With education			
Reported frequencies of lymphoedema-related symptoms (lower score, lower incidence of lymphedema symptoms)		The mean reported frequencies of lymphoedema-related symptoms in the intervention groups was 1.68 lower (2.61 to 0.75 lower)		136 (1 study)	Very low[4,5]
DASH Disability scores (higher score, greater disability) - 3 months		The mean DASH disability scores (higher score, greater disability) - 3 months in the intervention groups was 0.96 higher (1.83 lower to 3.76 higher)		149 (1 study)	Very low[4,6]
DASH Disability scores (higher score, greater disability) - 3 months - ALND		The mean DASH disability scores (higher score, greater disability) - 3 months in the intervention groups was 0.1 higher (3.88 lower to 4.08 higher)		69 (1 study)	Very low[4,6]
DASH Disability scores (higher score, greater disability) - 3 months - SLNB		The mean DASH disability scores (higher score, greater disability) - 3 months in the intervention groups was 1.80 higher (2.13 lower to 5.73 higher)		80 (1 study)	Very low[4,6]
Change in flexion shoulder (º) at 3 months		The mean change in flexion shoulder at 3 months in the intervention groups was 2.8 higher (0.81 lower to 6.41 higher)		149 (1 study)	Very low[4,6]
Change in flexion shoulder (º) at 3 months - ALND		The mean change in flexion shoulder at 3 months - ALND in the intervention groups was 3.5 higher (1.21 lower to 8.21 higher)		69 (1 study)	Very low[4,6]
Change in flexion shoulder (º) at 3 months - SLNB		The mean change in flexion shoulder at 3 months - SLNB in the intervention groups was 1.8 higher (3.83 lower to 7.43 higher)		80 (1 study)	Very low[4,6]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Without education	Corresponding risk With education			
Change in abduction shoulder (°) at 3 months		The mean change in abduction shoulder at 3 months in the intervention groups was 1.42 higher (2.24 lower to 5.09 higher)		149 (1 study)	Very low[6,9]
Change in abduction shoulder (°) at 3 months - ALND		The mean change in abduction shoulder at 3 months - ALND in the intervention groups was 0.6 higher (4.37 lower to 5.57 higher)		69 (1 study)	Very low[4,6]
Change in abduction shoulder (°) at 3 months - SLNB		The mean change in abduction shoulder at 3 months - SLNB in the intervention groups was 2.4 higher (3.02 lower to 7.82 higher)		80 (1 study)	Very low[4,6]
Change in horizontal extension shoulder (°) at 3 months		The mean change in horizontal extension shoulder at 3 months in the intervention groups was 0.16 lower (1.9 lower to 1.58 higher)		149 (1 study)	Very low[6]
Change in horizontal extension shoulder (°) at 3 months - ALND		The mean change in horizontal extension shoulder at 3 months - ALND in the intervention groups was 0.1 lower (2.86 lower to 2.66 higher)		69 (1 study)	Very low[4,6]
Change in horizontal extension shoulder (°) at 3 months - SLNB		The mean change in horizontal extension shoulder at 3 months - SLNB in the intervention groups was 0.2 lower (2.43 lower to 2.03 higher)		80 (1 study)	Very low[6,9]
Change in grip strength' (greater scores, greater strength) at 3 months		The mean change in grip strength at 3 months in the intervention groups was 0.92 lower (2.89 lower to 1.03 higher)		149 (1 study)	Very low[4,6,8]

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk Without education	Corresponding risk With education			
Change in grip strength[ɬ] (greater scores, greater strength) at 3 months - ALND		The mean change in grip strength at 3 months - ALND in the intervention groups was 2 lower (3.8 to 0.2 lower)		69 (1 study)	Very low[4,6]
Change in grip strength[ɬ] (greater scores, greater strength) at 3 months - SLNB		The mean change in grip strength at 3 months - SLNB in the intervention groups was 0 higher (1.43 lower to 1.43 higher)		80 (1 study)	Very low[6]

ALND: axillary lymph node dissection; CI: confidence interval; DASH: disability of shoulder, arm and hand questionnaire; RR: risk ratio; SLNB: sentinel lymph node biopsy; (°) = degrees; ɬ= measured using a dynamometers (unit was not reported)
[1]Lu 2015 - allocation to treatment by the surgeon and no attempt to control confounders
[2]I2=71%
[3] 95%CI crossed null effect and two boundaries of default MID; <300 events
[4] 95%CI crossed null effect and one boundary of default MID; <N<400
[5] Fu 2010 - Retrospective study and group was formed by recalled memory of women regarding receipt of lymphoedema education from healthcare providers;
[6] Sato 2014 - group was formed by patients' preference; short follow-up period
[7] I2=78%
[8] I2=66%
[9]N<400

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: Exercise plus usual care versus usual care alone

Critical outcomes

Lymphoedema (incidence, time to on-set, function and severity)

Change in arm volume

- There is moderate quality evidence from 1 RCT (N=204) that there is no clinically important difference between exercise plus usual care and usual care alone on change in arm volume at 3 months and 6 months among women who had breast surgery with axillary intervention.
- There is low quality evidence from 2 RCTs (N=308) that there is no clinically important difference between exercise plus usual care compared to usual care alone on change in

arm volume at follow-up after 1 year among women who had breast surgery with axillary intervention.

Incidence of lymphoedema

- There is very low to low quality evidence from randomised studies that there is no clinically important difference between exercise plus usual care and usual care alone on incidence of lymphoedema defined by either exceeding BIS ratio at 8 weeks (1 RCT; N=151) or at 6 months (1RCT; N=141) OR defined by more than 2 cm of interlimb difference at 8 weeks (1 RCT; N=151) or 6 months (1 RCT; N=141) or 12 months (1 RCT; N=134) OR defined by more than or equal 10 percent difference from baseline at first assessment after intervention (3 RCTs; N=502) or at follow-up (2 RCTs; N=345) among women who had breast surgery with axillary intervention.

Function

- There is low quality evidence from 1 RCT (N=153) that there is no clinically important difference between exercise plus usual care and usual care alone on range of motion assessed by pound weight at leg press at 12 months whereas moderate quality evidence 1 RCT (N=122) reported a clinically significant beneficial effect of exercise plus usual care on range of motion assessed by pound weight at bench press at 12 months in comparison with usual care alone among women who had breast surgery with axillary intervention.
- There is very low to low quality evidence from 1 RCT that there is a clinically important beneficial effect of exercise plus usual care in comparison with usual care alone at 8 weeks (N=151) but no clinically significant difference at 6 months (n=141) on range of motion assessed by forward flexion among women who had breast surgery with axillary intervention.
- There is very low quality evidence from 1 RCT that there is a clinically important beneficial effect of exercise plus usual care in comparison with usual care alone at 8 weeks (N=151) and at 6 months (n=141) on range of motion assessed by abduction among women who had breast surgery with axillary intervention.
- There is low quality evidence from 1 RCT that there is no clinically important difference between exercise plus usual care and usual care alone on range of motion assessed by external rotation at 8 weeks (N=151) and 6 months (n=141) among women who had breast surgery with axillary intervention.
- There is very low to low quality evidence from 1 RCT that there is a clinically important beneficial effect of exercise plus usual care in comparison with usual care alone at 8 weeks (N=151) but no clinically important difference at 6 months (n=141) on range of motion assessed by horizontal extension among women who had breast surgery with axillary intervention.
- There is very low to low quality evidence from 1 RCT that there is a clinically important beneficial effect of exercise plus usual care in comparison with usual care alone at 8 weeks (N=151) and at 6 months (n=141) on strength assessed by abduction among women who had breast surgery with axillary intervention.
- There is very low quality evidence from 1 RCT that there is no clinically important difference between exercise plus usual care and usual care alone at 8 weeks (N=151) and at 6 months (n=141) on strength assessed by forward flexion among women who had breast surgery with axillary intervention.
- There is low quality evidence from 1 RCT that there is no clinically important difference between exercise plus usual care and usual care alone at 8 weeks (N=151) and at 6 months (n=141) on strength assessed by horizontal extension among women who had breast surgery with axillary intervention.
- There is very low to low quality evidence from 1 RCT that there is no clinically important difference between exercise plus usual care and usual care alone at 8 weeks (N=151) and at 6 months (n=141) on strength assessed by horizontal flexion among women who had breast surgery with axillary intervention.

- There is low quality evidence from 1 RCT (N=118) that there is a clinically significant beneficial effect of weight-lifting plus usual care in comparison with usual care alone on physical activity assessed by international physical activity questionnaires and presented as metabolic equivalent per week among women who had breast surgery with axillary intervention.
- There is very low quality evidence from 1 RCT (N=104) that there is a clinically important beneficial effect of exercise plus usual care in comparison with usual care alone on total metres walked in 6 minutes among women who had breast surgery with axillary intervention.

Symptoms of lymphoedema

- There is low quality evidence from 1 RCT (N=118) that there is a clinically significant harmful effect of no activity restriction (i.e., exercise) in comparison with restriction of activity of any kind on pain symptoms reported as '0' VAS score (i.e, no pain) at 3 months and 6 months but no clinically important difference at 2 years follow-up among women who had breast surgery with axillary intervention.
- There is low quality evidence from 1 RCT (N=147) that there is no clinically important difference between exercise plus usual care and usual care alone on the change in the number of symptoms reported OR change in symptom severity at 12 months among women who had breast surgery with axillary intervention.

Health-related quality of life

- There is very low to low quality evidence from randomised studies that there is no clinically important difference between exercise plus usual care and usual care alone on health-related quality of life assessed by FACT-B total score (1 RCT; n= 104) OR by BR23 breast symptoms at 8 weeks post-intervention (1 RCT; N=151) and 6 months follow-up (1 RCT; n=141) OR BR23 arm symptoms at 8 weeks post-intervention (1 RCT; N=151) and 6 months follow-up (1 RCT; n=141) among women who had breast surgery with axillary intervention.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Arm and shoulder function

- No evidence was found for this outcome.

Psychological morbidity

- No evidence was found for this outcome.

Comparison 2: Physiotherapy versus control

Critical outcomes

Lymphoedema (incidence, time to on-set, function and severity)

Incidence of lymphoedema

- There is very low quality evidence from 2 RCTs (N=173) that there is no clinically important difference between with and without physiotherapy on the incidence of lymphoedema among women who had breast surgery with axillary intervention.
- Moderate quality evidence from 1 RCT (N=120) reported a clinical significant beneficial effect of physiotherapy in comparison with control on incidence of lymphoedema

assessed by change in volume ratio from baseline (higher change, more lymphoedema) whereas low quality evidence from 1 RCT (N=57) reported no clinically important difference between physiotherapy and control on incidence of lymphoedema assessed by change in circumferential difference among women who had breast surgery with axillary intervention.

Function

- There is very low quality evidence from 1 RCT (N=57) that there is a clinically significant beneficial effect of physiotherapy in comparison with control on flexion, abduction and external rotation but no clinically significant difference on extension, internal rotation and adduction at 6 months follow-up among women who had breast surgery with axillary intervention.

Health-related quality of life

- There is very low quality evidence from 1 RCT (N=57) that there is a clinically important beneficial effect of physiotherapy in comparison with control on health-related quality of life assessed by physical activity questionnaires at 6 months follow up among women who had breast surgery with axillary intervention.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Arm and shoulder function

- No evidence was found for this outcome

Psychological morbidity

- No evidence was found for this outcome.

Comparison 3: Manual lymph drainage versus usual care

Critical outcomes

Lymphoedema (incidence, time to on-set, function and severity)

- There is very low quality evidence from 1 RCT (N=158) that there is no clinically important effect of manual lymph drainage compared to usual care on the incidence of lymphoedema (>/= 200mL increase), the incidence of lymphoedema (>/= 2cm increase), or change in arm volume (mL) at 3 months, 6 months, or 12 months follow up in adults treated with axillary intervention.
- There is very low quality evidence from 1 RCT (N=225) that there is no clinically important effect of manual lymph drainage compared to usual care on change in arm volume (mL) at 3 months or 6 months follow up in adults treated with axillary intervention.
- There is very low quality evidence from 1 RCT (N=154) that there is no clinically important effect of manual lymph drainage compared to usual care on change in arm volume (mL) at 12 months follow up in adults treated with axillary intervention.

Health-related quality of life

- There is very low quality evidence from 1 RCT (N=158) that there is no clinically important effect of manual lymph drainage compared to usual care on physical health quality of life at 3 months or 6 months follow up in adults treated with axillary intervention.

- There is very low quality evidence from 1 RCT (N=154) that there is no clinically important effect of manual lymph drainage compared to usual care on physical health quality of life at 12 months follow up in adults treated with axillary intervention.
- There is very low quality evidence from 1 RCT (N=158) that there is no clinically important effect of manual lymph drainage compared to usual care on mental health quality of life at 3 months follow up in adults treated with axillary intervention.
- There is very low quality evidence from 1 RCT (N=158) that there is no clinically important effect of manual lymph drainage compared to usual care on mental health quality of life at 6 months follow up in adults treated with axillary intervention.
- There is very low quality evidence from 1 RCT (N=154) that there is no clinically important effect of manual lymph drainage compared to usual care on mental health quality of life 12 months follow up in adults treated with axillary intervention.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Arm and shoulder function

- No evidence was found for this outcome.

Psychological morbidity

- No evidence was found for this outcome.

Comparison 4: Compression corset versus no compression corset

Critical outcomes

Lymphoedema (incidence, time to on-set, function and severity)

Symptoms of lymphoedema

- There is very low quality evidence from 1 RCT (N=39) that there is no clinically important difference between use of a compression corset and no compression corset on the number of women with pain reduction among those who had breast surgery with axillary intervention.

Health-related quality of life

- No evidence was found for this outcome.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Arm and shoulder function

- No evidence was found for this outcome.

Psychological morbidity

- No evidence was found for this outcome.

Comparison 5: Yoga plus exercise versus exercise alone

Critical outcomes

Lymphoedema (incidence, time to on-set, function and severity)

Function

- Very low quality evidence from one RCT (N=78) reported that there is no clinically significant difference between yoga plus exercise in comparison with exercise alone on the change in arm function at 10 weeks but a clinically important beneficial effect of yoga plus exercise observed at 6 months follow-up among women who had breast surgery with axillary intervention.
- There is very low quality evidence from 1 RCT (N=78) that there is no clinically significant difference between yoga plus exercise and exercise alone on arm functionality assessed by QuickDASH score at 10 weeks OR at 6 months follow-up among women who had breast surgery with axillary intervention.

Symptoms of lymphoedema

- There is very low quality evidence from 1 RCT (N=78) that there is no clinically significant difference between yoga plus exercise in comparison with exercise alone on the change in level of pain at 10 weeks but a clinically important beneficial effect of yoga plus exercise observed at 6 months follow-up among women who had breast surgery with axillary intervention.

Health-related quality of life

- There is very low quality evidence from 1 RCT (N=78) that there is no clinically important difference between yoga plus exercise and exercise alone on health-related quality of life assessed by FACT-B health-related quality of life scores OR assessed by Oxford shoulder score at 10 weeks or 6 months among women who had breast surgery with axillary intervention.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Arm and shoulder function

- No evidence was found for this outcome.

Psychological morbidity

- No evidence was found for this outcome.

Comparison 6: Education versus no education

Critical outcomes

Lymphoedema (incidence, time to on-set, function and severity)

Incidence of lymphoedema

- There is very low quality evidence from 1 retrospective cohort study that there is no clinically important difference between with and without patient-centred education program on the incidence of lymphoedema of any stage (N=356) OR stage 1 (n=178) OR stage 2 or 3 (n=178). Moreover, very low quality evidence from 1 non-randomised controlled trial reported that there is no clinically important difference between with and without

educational program on change in upper arm girth at 3 months in any type of axillary intervention (N=149) OR ALND (n=69) OR SLNB (n=80).

Symptoms of lymphoedema

- There is very low quality evidence from 1 retrospective cohort study (N=136) that there is a clinically important beneficial effect in women who received information about breast cancer related lymphoedema in comparison with women who did not on the reported frequencies of lymphoedema-related symptoms.

Disability due to lymphoedema

- There is very low quality evidence from 1 non-randomised controlled trial that there is no clinically important difference between with and without educational program on disability measured by the DASH disability scores at 3 months in any type of axillary intervention (N=149) OR ALND (n=69) OR SLNB (n=80).

Function

- There is very low quality evidence from 1 non-randomised controlled trial that there is no clinically important difference between with and without educational program on functionality of arm assessed by change in flexion shoulder, abduction shoulder, horizontal extension and grip strength at 3 months in any type of axillary intervention (N=149) OR ALND (n=69) OR SLNB (n=80).

Health-related quality of life

- No evidence was found for this outcome.

Important outcomes

Intervention related morbidity

- No evidence was found for this outcome.

Arm and shoulder function

- No evidence was found for this outcome.

Psychological morbidity

- No evidence was found for this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

This review was concerned with onset of lymphoedema following axillary intervention; therefore critical outcomes were lymphoedema (measured by incidence, function, severity and time to onset, in order of importance) and health-related quality of life, on which lymphoedema can have a serious impact. Intervention-related morbidity was selected as an important outcome in order to help balance the benefits and harms associated with interventions. Finally, arm and shoulder function, and psychological morbidity, were selected as important outcomes as they may be affected by lymphoedema.

The quality of the evidence

The quality of the evidence for this review was assessed using GRADE. RCT evidence for lymphoedema outcomes (incidence, time to on-set, function and severity) was measured in a number of ways and ranged from moderate to very low quality; the main reason evidence

was downgraded was due to imprecision around the estimate due to wide confidence intervals and risk of bias due to lack of blinding and allocation concealment. The only evidence examining the effect of education on lymphoedema was from a retrospective cohort study and was therefore low quality; this was further downgraded to very low quality due to lack of controlling for confounding factors between arms.

Health-related quality of life evidence all came from RCTs and was low to very low quality due to risk of bias and imprecision. There was no evidence for intervention-related morbidity, arm psychological morbidity; the arm and should function evidence was included under lymphoedema outcomes.

The recommendation was based on evidence that there was no effect of exercise on the majority of lymphoedema outcomes reported and no clinically important difference in health-related quality of life.

No recommendations were made for physiotherapy despite the potential clinical benefit observed as the committee agreed that this aspect was covered by existing recommendations that were part of the previous guideline CG80 (NICE 2009), regarding arm mobility and functional exercises (see recommendations 1.12.5 to 1.12.8 in the short guideline).

No recommendations were made regarding manual lymph drainage, compression corsets or yoga as there was no evidence of clinical benefit or harm.

No recommendations were made regarding education as there was mixed, low quality evidence of a clinical benefit and the intervention was too complex to determine which aspect may be effective for prevention of lymphoedema.

Benefits and harms

There were no benefits demonstrated by the evidence as there was no clinically important effect of any of the interventions on lymphoedema outcomes or health-related quality of life. Therefore, the committee agreed that the main benefits associated with the recommendation would be to minimise the number of people unnecessarily avoiding exercise; this may in turn improve health-related quality of life by improving physical and mental health.

There were no harms associated with any of the interventions; the recommendations are unlikely to produce any harm as they will result in levels of exercise being maintained, rather than increased.

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 did not identify any costs or changes in resource use associated with the recommendations as advice for the prevention of lymphoedema is already being provided as part of routine practice.

Other factors the committee took into account

The committee were aware of a systematic review of precautions for breast-cancer related lymphoedema (Asdourian, 2016). None of the studies in this review met the inclusion criteria as they were non-comparative cohort and case-control studies. However, as there was an absence of any evidence that met the review protocol criteria, the committee used their expertise in conjunction with this systematic review to make a statement that there was no consistent evidence of increased risk of lymphoedema relating to a number of activities: there was no evidence of an association between lymphoedema and trauma to the hand or arm on the side of the cancer, air travel, travel to hot countries and sunburn, manicures, hot-

tub use, alcohol intake or sports injury. There was mixed evidence of association between lymphoedema and compression sleeve use, infection or injury and medical procedures (blood tests, injections, intravenous medication and blood pressure measurement), and some low quality evidence of an association between lymphoedema and sauna use. The committee were also aware of recommendations from an expert panel (McLaughlin, 2017) that using the ipsilateral arm for intravenous medication or blood pressure is not contraindicated.

Trauma to the hand or arm was not included in this recommendation as it is covered by existing recommendations to prevent infection and trauma and would be considered good practice even in the absence of a specific risk of lymphoedema; similarly, sunburn was not included due to the associated skin cancer risk in the whole population. Alcohol intake was not mentioned in the recommendation to avoid conflicting with lifestyle recommendations in this guideline; compression sleeve use was not mentioned as this is only used in the UK as treatment, rather than as a preventative measure. As above, the main benefits associated with this recommendation would be to minimise the number of people unnecessarily restricting activities.

Further, the committee recommended that people with breast cancer are advised that there is no consistent evidence of increased risk of lymphoedema associated with medical procedures on the treated side. This recommendation should lead to a reduction in people being declined immunisations or elective procedures due to venous access and improve access to standard care, such as blood tests at their local GP surgery.

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Schmitz, K. H., Ahmed, R. L., Troxel, A. B., Cheville, A., Lewis-Grant, L., Smith, R., Bryan, C. J., Williams-Smith, C. T., Chittams, J. (2010) Weight lifting for women at risk for breast cancer-related lymphedema: A randomized trial. JAMA - Journal of the American Medical Association, 304, 2699-270.

Torres Lacomba 2010

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Zimmermann 2012

Zimmermann, A., Wozniewski, M., Szklarska, A., Lipowicz, A., Szuba, A. (2012) Efficacy of manual lymphatic drainage in preventing secondary lymphedema after breast cancer surgery. Lymphology, 45, 103-11.

Appendices

Appendix A – Review protocols

Review protocol for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Field (based on PRISMA-P)	Content
Review question	Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?
Type of review question	Intervention review
Objective of the review	The aim of this review is to determine whether axillary treatment (further surgery or radiotherapy) can be safely omitted in some patients with tumour deposits greater than 0.2 mm. Recommendations will aim to cover in which groups this option should be discussed.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with invasive breast cancer and axillary lymph node metastasis but no distant metastases (M0) following sentinel node biopsy or axillary node sampling or radiological biopsy.
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	No axillary treatment (axillary RT or ANC)
Eligibility criteria – comparator(s)/control or reference (gold) standard	Axillary treatment (axillary RT or ANC)
Outcomes and prioritisation	Critical (up to 3 outcomes) Locoregional recurrence (MID: any statistically significant difference) Treatment-related morbidity (e.g., lymphoedema [MID: GRADE default values], arm and shoulder function [MID: GRADE default values], surgical complications [MID: GRADE default values]) HRQoL (MID: values from the literature where available, otherwise GRADE default values) Important but not critical Overall survival (MID: any statistically significant difference) Breast cancer specific survival (MID: any statistically significant difference) Rate of adjuvant therapy (MID: GRADE default values) 5 and 10 year follow-up periods will be prioritised when multiple time points are reported.

Field (based on PRISMA-P)	Content
	MIDs: HRQoL MID values from the literature: 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 and/or meta-analyses of RCTs RCTs
Other inclusion exclusion criteria	Foreign language studies, conference abstracts, and narrative reviews will not routinely be included. Studies will be excluded if participants have received neoadjuvant systemic therapy.
Proposed sensitivity/sub-group analysis, or meta-regression	Subgroups (critical outcomes only – excluding treatment related morbidity): Extent of lymph node metastasis (micro metastases, macro metastases [1 node involved], macro metastases [>1 node involved] Systemic therapy (including hormone therapy; yes/no) Type of surgery (conservation [followed by whole breast RT]/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 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. As additional methods of axillary treatment and diagnosing positive axilla are in common use since the review question in the previous guideline CG80 (NICE 2009), the searches will be undertaken from 1996 when the first studies using SLNB were published, rather than from 2008 when the

Field (based on PRISMA-P)	Content
	previous search was undertaken. 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 question: What are the indications for completion axillary clearance when the axilla has been found by biopsy to contain metastasis? Date of search: 28/02/2008 Relevant recommendation(s) from previous guideline: 1) Offer further axillary treatment to patients with early invasive breast cancer who: • have macrometastases or micrometastases shown in a sentinel lymph node • have a preoperative ultrasound guided needle biopsy with histologically proven metastatic cancer. The preferred technique is axillary lymph node dissection (ALND) because it gives additional staging information. 2) Do not offer further axillary treatment to patients found to have only isolated tumour cells in their sentinel lymph nodes. These patients should be regarded as lymph node-negative.
Author contacts	For details 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).
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.

Field (based on PRISMA-P)	Content
Rationale/context – what is known	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee https://www.nice.org.uk/guidance/cg80/historydeveloped 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 Developing NICE guidelines: the manual.
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

ANC, axillary node clearance; BCS, breast cancer subscale; 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; M0, no distant metastases; 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; RT, radiotherapy; SLNB, sentinel lymph node biopsy; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Review protocol for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Field (based on PRISMA-P)	Content
Review question	What are the best strategies to prevent lymphoedema following axillary intervention?
Type of review question	Intervention review
Objective of the review	The objective of this review is to clarify which strategies for the prevention of lymphoedema are evidence based. Recommendations might include what information could be provided to patients about lifestyle factors, whether specific interventions are effective prevention tools and the safety of medical interventions such as blood pressure measurement, venepuncture and injections.
Eligibility criteria – population/disease/condition/issue/domain	Adults (18 or over) with breast cancer who have undergone axillary intervention without established lymphoedema
Eligibility criteria – intervention(s)/exposure(s)/prognostic factor(s)	Any strategy with the aim of preventing lymphoedema, e.g.,: Advice on interventions to avoid e.g., venepuncture, flu jab, blood pressure Active management of infection and injury (antibiotic) Compression garments Education Diet/Exercise Simple lymph drainage massage Skin care Physiotherapy
Eligibility criteria – comparator(s)/control or reference (gold) standard	No strategies aimed at preventing lymphoedema
Outcomes and prioritisation	Critical (up to 3 outcomes) Lymphoedema (incidence, time to on-set, function and severity; MID: GRADE default values; order of importance: incidence, function, severity, time to on-set) HRQoL (MID: values from the literature where available; GRADE default value for FACT-G & FACT-B) Important but not critical Intervention-related morbidity (Infection, arm pain and sensation; MID: GRADE default values) Arm and shoulder function (active range of motion, function in activities of daily living; MID GRADE default values) Psychological morbidity (e.g., anxiety/depression measures; MID: GRADE default values)

Field (based on PRISMA-P)	Content
	1 year (early onset) and 5 year (longer term) follow-up will be prioritised if multiple time points are reported. Little information available after 5 years as not part of routine follow-up. 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 and/or meta-analyses of RCTs RCTs Controlled, non-randomised studies (only if RCTs unavailable or insufficient data to inform decision making) Cohort studies (minimum no. of participants 100)
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	N/A
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 it may be difficult to distinguish between preventative and treatment strategies at title/abstract level; 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.

Field (based on PRISMA-P)	Content
	Searches will be undertaken from 2008 onwards as it is an update from the previous version of this guideline. The current question has a narrower focus than the previous guideline (limited to those who have received axillary intervention) so only a subset of previously included studies may be relevant.
Identify if an update	Previous question: In patients with breast cancer which strategies are effective in preventing arm lymphoedema? Date of search: 27/02/2008 Relevant recommendation(s) from previous guideline: 1) Inform all patients with early breast cancer about the risk of developing lymphoedema and give them relevant written information before treatment with surgery and radiotherapy. 2) Give advice on how to prevent infection or trauma that may cause or exacerbate lymphoedema to patients treated for early breast cancer. 3) Ensure that all patients with early breast cancer who develop lymphoedema have rapid access to a specialist lymphoedema service.
Author contacts	For authors please see the guideline in development 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) of the guideline.
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 of the guideline.
Meta-bias assessment – publication bias, selective reporting bias	For details please see Section 6.2 of Developing NICE guidelines: the manual.

Field (based on PRISMA-P)	Content
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 in the full guideline.
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; 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; M0, no distant metastases; 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; RT, radiotherapy; TOI, Trial outcome index; WHOQOL, World Health Organization quality of life

Appendix B – Literature search strategies

Literature search strategies for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

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: 26 September 2017

#	Searches
1	exp Breast Neoplasms/
2	exp "Neoplasms, Ductal, Lobular, and Medullary"/
3	exp Fibrocystic Breast Disease/
4	or/1-3
5	exp Breast/
6	breast.tw.
7	5 or 6
8	(breast adj milk).ti,ab,sh.
9	(breast adj tender$).ti,ab,sh.
10	8 or 9
11	7 not 10
12	exp Neoplasms/
13	11 and 12
14	exp Lymphedema/
15	14 and 11
16	(breast adj25 neoplasm$).ti,ab,sh.
17	(breast adj25 cancer$).ti,ab,sh.
18	(breast adj25 tumour$).ti,ab,sh.
19	(breast adj25 tumor$).ti,ab,sh.
20	(breast adj25 carcinoma$).ti,ab,sh.
21	(breast adj25 adenocarcinoma$).ti,ab,sh.
22	(breast adj25 sarcoma$).ti,ab,sh.
23	(breast adj50 dcis).ti,ab,sh.
24	(breast adj25 ductal).ti,ab,sh.
25	(breast adj25 infiltrating).ti,ab,sh.
26	(breast adj25 intraductal).ti,ab,sh.
27	(breast adj25 lobular).ti,ab,sh.
28	(breast adj25 medullary).ti,ab,sh.
29	or/16-28
30	4 or 13 or 15 or 29

#	Searches
31	exp Mastectomy/
32	30 or 31
33	(mammary adj25 neoplasm$).ti,ab,sh.
34	(mammary adj25 cancer$).ti,ab,sh.
35	(mammary adj25 tumour$).ti,ab,sh.
36	(mammary adj25 tumor$).ti,ab,sh.
37	(mammary adj25 carcinoma$).ti,ab,sh.
38	(mammary adj25 adenocarcinoma$).ti,ab,sh.
39	(mammary adj25 sarcoma$).ti,ab,sh.
40	(mammary adj50 dcis).ti,ab,sh.
41	(mammary adj25 ductal).ti,ab,sh.
42	(mammary adj25 infiltrating).ti,ab,sh.
43	(mammary adj25 intraductal).ti,ab,sh.
44	(mammary adj25 lobular).ti,ab,sh.
45	(mammary adj25 medullary).ti,ab,sh.
46	or/33-45
47	32 or 46
48	exp Breast Self-Examination/
49	(breast adj25 self$).ti,ab,sh.
50	(breast adj25 screen$).ti,ab,sh.
51	exp Mammography/
52	or/47-51
53	mammograph$.tw.
54	53 and 11
55	52 or 54
56	exp Sentinel Lymph Node Biopsy/
57	(sentinel adj2 node).mp.
58	(SN or SNB or SLN or SLNB).mp.
59	exp Axilla/
60	exp Neoplasm Staging/
61	exp Lymph Node Excision/
62	lymphadenectomy.mp.
63	(axill$ adj3 (surg$ or sampl$ or stag$)).mp.
64	((block or lymph node or axillary) adj dissection).mp.
65	((block or lymph node or axillary) adj clearance).mp.
66	or/56-65
67	55 and 66
68	Meta-Analysis/
69	Meta-Analysis as Topic/
70	(meta analy* or metanaly* or metaanaly*).ti,ab.
71	((systematic* or evidence*) adj2 (review* or overview*)).ti,ab.

#	Searches
72	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
73	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
74	(search* adj4 literature).ab.
75	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
76	cochrane.jw.
77	68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78	randomized controlled trial.pt.
79	controlled clinical trial.pt.
80	randomized controlled trials.sh.
81	random allocation.sh.
82	double-blind method.sh.
83	single-blind method.sh.
84	or/78-83
85	clinical trial.pt.
86	exp Clinical Trials/
87	(clin$ adj25 trial$).ti,ab.
88	((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab.
89	placebos.sh.
90	placebo$.ti,ab.
91	random$.ti,ab.
92	research design.sh.
93	or/85-92
94	84 or 93
95	67 and 94
96	(animals not humans).sh.
97	95 not 96
98	67 and 77
99	97 or 98
100	(2015* or 2016* or 2017*).dc,ed,yr.
101	99 and 100 [Then general exclusions filter applied]

Database: Embase

Last searched on **Embase Classic+Embase** 1947 to 2017 September 25.

Date of last search: 26 September 2017.

#	Searches
1	exp breast cancer/
2	exp breast carcinoma/
3	exp medullary carcinoma/
4	exp intraductal carcinoma/

#	Searches
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$)).tw.
20	15 or 16 or 17 or 18 or 19
21	6 or 20
22	exp sentinel lymph node biopsy/
23	(sentinel adj2 node).mp.
24	(SN or SNB or SLN or SLNB).mp.
25	exp axilla/
26	exp cancer staging/
27	exp lymph node dissection/
28	lymphadenectomy.mp.
29	(axill$ adj3 (surg$ or sampl$ or stag$)).mp.
30	((block or lymph node or axillary) adj dissection).mp.
31	((block or lymph node or axillary) adj clearance).mp.
32	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
33	21 and 32
34	systematic review/
35	meta-analysis/
36	(meta analy* or metanaly* or metaanaly*).ti,ab.
37	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
38	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
39	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
40	(search* adj4 literature).ab.
41	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.

#	Searches
42	((pool* or combined) adj2 (data or trials or studies or results)).ab.
43	cochrane.jw.
44	34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45	random*.ti,ab.
46	factorial*.ti,ab.
47	(crossover* or cross over*).ti,ab.
48	((doubl* or singl*) adj blind*).ti,ab.
49	(assign* or allocat* or volunteer* or placebo*).ti,ab.
50	crossover procedure/
51	single blind procedure/
52	randomized controlled trial/
53	double blind procedure/
54	45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55	33 and 44
56	33 and 54
57	55 or 56
58	(2015* or 2016* or 2017*).dd,em,yr.
59	57 and 58 [Then general exclusions filter applied]

Database: Cochrane Library via Wiley Online

Date of last search: 26 September 2017

#	Searches
#1	MeSH descriptor: [Breast Neoplasms] explode all trees
#2	breast near cancer*:ti,ab,kw (Word variations have been searched)
#3	breast near neoplasm*:ti,ab,kw (Word variations have been searched)
#4	breast near carcinoma*:ti,ab,kw (Word variations have been searched)
#5	breast near tumour*:ti,ab,kw (Word variations have been searched)
#6	breast near tumor*:ti,ab,kw (Word variations have been searched)
#7	#1 or #2 or #3 or #4 or #5 or #6
#8	MeSH descriptor: [Sentinel Lymph Node Biopsy] explode all trees
#9	sentinel lymph node biopsy or SLNB or SNB or SLN or (sentinel near node):ti,ab,kw (Word variations have been searched)
#10	MeSH descriptor: [Axilla] explode all trees
#11	axilla* near (surg* or sampl* or stag*):ti,ab,kw (Word variations have been searched)
#12	MeSH descriptor: [Neoplasm Staging] explode all trees
#13	MeSH descriptor: [Lymph Node Excision] explode all trees
#14	"lymphadenectomy":ti,ab,kw (Word variations have been searched)
#15	(block or lymph node or axillary) near dissection:ti,ab,kw (Word variations have been searched)
#16	(block or lymph node or axillary) near clearance:ti,ab,kw (Word variations have been searched)
#17	#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#	Searches
#18	#7 and #17 Publication Year from 2015 to 2017

Literature search strategies for 2.2 What are the best strategies for preventing lymphoedema after axillary intervention?

Database: Medline & Embase (Multifile)

Last searched on **Embase** 1974 to 2017 October 10, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R)** 1946 to Present.

Date of last search: 11 October 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

#	Searches
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$)).tw.
31	23 or 24 or 25 or 26 or 27 or 28 or 29 or 30
32	11 or 31
33	exp Lymphedema/ use prmz
34	exp lymphedema/ use oemezd
35	arm edema/ use oemezd
36	(arm$ adj4 (morbid$ or swell$ or swollen or pain$ or oedem$ or edem$)).mp.
37	(upper limb$ adj4 (morbid$ or swell$ or swollen or pain$ or oedem$ or edem$)).mp.
38	(lymph$ adj4 (oedem$ or edem$)).tw.
39	(lymph?ed$ or elephantiasis).mp.
40	Edema/ use prmz
41	edema/ use oemezd
42	(upper limb$ or arm$).mp.
43	40 or 41
44	42 and 43
45	33 or 34 or 35 or 36 or 37 or 38 or 39 or 44
46	32 and 45
47	limit 46 to yr="2008 -Current" [Then general exclusions filter applied]

Database: Cochrane Library via Wiley Online

Date of last search: 11 October 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

#	Searches
#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: [Lymphedema] explode all trees
#23	(lymphed* or lymphoed* or elephantiasis):ti,ab,kw (Word variations have been searched)
#24	(arm* near/4 (morbid* or swell* or swollen or pain* or oedem* or edem*)):ti,ab,kw (Word variations have been searched)
#25	(upper limb* near/4 (morbid* or swell* or swollen or pain* or oedem* or edem*)):ti,ab,kw (Word variations have been searched)
#26	(lymph* near/4 (oedem* or edem*)):ti,ab,kw (Word variations have been searched)
#27	MeSH descriptor: [Edema] explode all trees
#28	(upper limb* or arm*):ti,ab,kw (Word variations have been searched)
#29	#27 and #28
#30	#22 or #23 or #24 or #25 or #26 or #29
#31	#21 and #30 Publication Year from 2008 to 2017

Database: Cinahl Plus

Date of last search: 11 October 2017

#	Searches
S8	S3 AND S6 [Limiters - Publication Year: 2008-2017]
S7	S3 AND S6
S6	S4 OR S5
S5	((TI lymphoedema or AB lymphoedema) or (TI lymphedema or AB lymphedema) or (TI lymph* edema or AB lymph* edema)) or (TI elephantiasis or AB elephantiasis))
S4	(MM "Lymphedema")
S3	S1 OR S2
S2	((TI breast cancer* or AB breast cancer*) or (TI breast tumor* or AB breast tumor*)) or ((TI breast tumour* or AB breast tumour*) or (TI mammary neoplasm* or AB mammary neoplasm*) or (TI mammary carcinoma* or AB mammary carcinoma*) or (TI breast neoplasm* or AB breast neoplasm*) or (TI breast carcinoma* or AB breast carcinoma*))
S1	(MM "Breast Neoplasms")

Database: AMED

Last searched on **OVID AMED (Allied and Complementary Medicine)** 1985 to present.

Date of last search: 11 October 2017

#	Searches
1	exp breast neoplasms/
2	(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.
3	(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.
4	(paget$ and (breast$ or mammary or nipple$)).tw.
5	1 or 2 or 3 or 4
6	exp Lymphedema/
7	(lymph?ed$ or elephantiasis).tw.
8	(arm$ adj4 (morbid$ or swell$ or swollen or pain$ or oedem$ or edem$)).tw.
9	(upper limb$ adj4 (morbid$ or swell$ or swollen or pain$ or oedem$ or edem$)).tw.
10	(lymph$ adj4 (oedem$ or edem$)).tw.
11	Edema/
12	(upper limb$ or arm$).tw.
13	11 and 12
14	6 or 7 or 8 or 9 or 10 or 13
15	5 and 14
16	limit 15 to yr="2008 -Current"

Database: PsycINFO

Last searched on **OVID PsycINFO 1806 to present.**

Date of last search: 11 October 2017

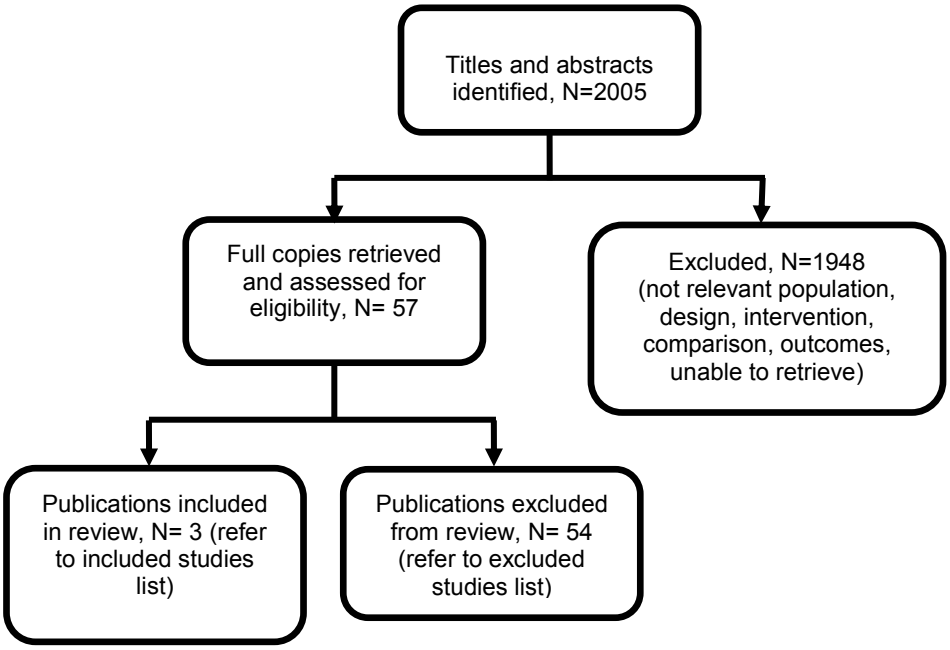
#	Searches
1	exp breast neoplasms/
2	(breast$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
3	(mammar$ adj5 (neoplasm$ or cancer$ or tumo?r$ or carcinoma$ or adenocarcinoma$ or sarcoma$ or leiomyosarcoma$ or dcis or duct$ or infiltrat$ or intraduct$ or lobul$ or medullary or tubular)).tw.
4	(paget$ and (breast$ or mammary or nipple$)).tw.
5	1 or 2 or 3 or 4
6	exp Lymphedema/
7	(lymph?ed$ or elephantiasis).tw.
8	(arm$ adj4 (morbid$ or swell$ or swollen or pain$ or oedem$ or edem$)).tw.
9	(upper limb$ adj4 (morbid$ or swell$ or swollen or pain$ or oedem$ or edem$)).tw.
10	(lymph$ adj4 (oedem$ or edem$)).tw.
11	Edema/
12	(upper limb$ or arm$).tw.
13	11 and 12

#	Searches
14	6 or 7 or 8 or 9 or 10 or 13
15	5 and 14
16	limit 15 to yr="2008 -Current"

Appendix C – Clinical evidence study selection

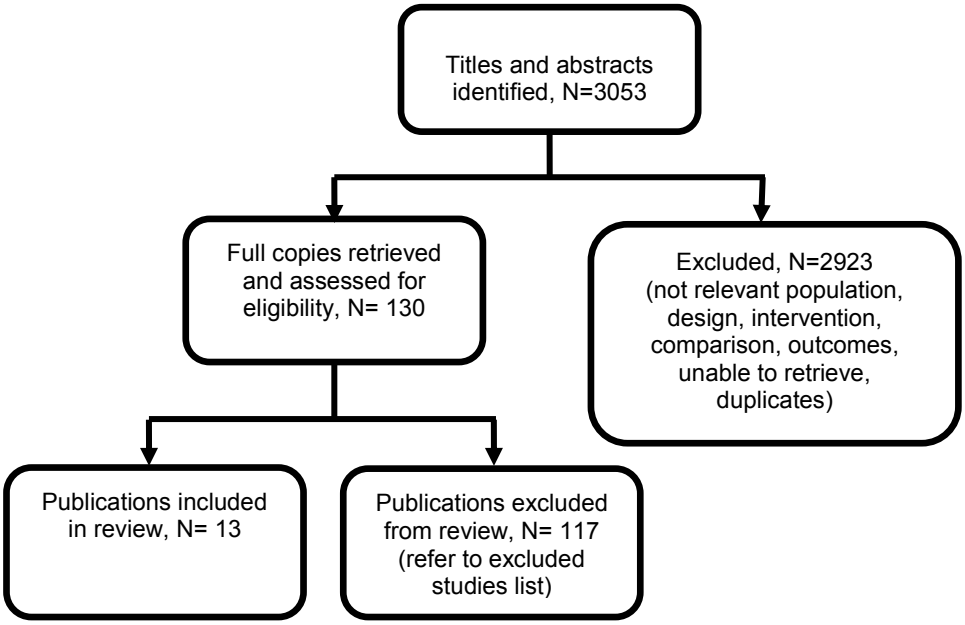
Clinical evidence study selection for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Figure 1: Flow diagram of clinical article selection for axillary treatment when the axilla has been found to contain metastatic disease review.



Clinical evidence study selection for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Figure 2: Flow diagram of clinical article selection for prevention of lymphoedema



Appendix D – Clinical evidence tables

Clinical evidence tables for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Table 14: Studies included in the evidence review for axillary treatment

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Schmidt-Hansen, M., Bromham, N., Hasler, E., Reed, M. W., Axillary surgery in women with sentinel node-positive operable breast cancer: a systematic review with meta-analyses, Springerplus, 5, 85, 2016 **Ref Id** 566824 **Country/ies where the study was carried out** Europe, USA. South America, Australia, Spain, Hungary **Study type** Systematic review of randomised trials **Aim of the study** To assess in a systematic review conducted and reported according to the PRISMA guidelines (Moher 2009) the benefits and harms of alternative approaches to axillary surgery (including omitting such surgery altogether) in terms of: overall survival; disease-free survival; local, regional and distant recurrences; short-term adverse events; and long-term complications in women with	**Sample size** Five RCTs (N=3919) **Inclusion criteria** Randomised controlled trials in women with clinically-defined operable primary breast cancer with positive sentinel lymph node(s).	**Interventions** ALND versus no axillary surgery; and ALND versus axillary radiotherapy without ALND	**Details** Five studies (N=3919) were included in the review. Three randomised trials compared ALND following sentinel lymph node dissection (SLND) to SLND alone (ACOSOG-Z0011; ATTRM-048-13-2000 and IBCSG-23-01). Two randomised trials compared ALND to axillary RT (AMAROS and OTOASOR) following SLND. The ATTRM-048-13-2000 and IBCSG-23-01 trials included only patients with micro-metastatic disease in sentinel lymph nodes, whereas ACOSOG-Z0011 included patients with 1 or 2 positive sentinel lymph nodes	**Results** See GRADE tables and forest plots for results extracted from this review	**Limitations** See GRADE tables for risk of bias assessments from this review

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
pathologically-confirmed sentinel node-positive operable breast cancer. **Study dates** Literature search date was 12 March 2015. **Source of funding** No funding received					
Full citation Savolt, A., Peley, G., Polgar, C., Udvarhelyi, N., Rubovszky, G., Kovacs, E., Gyorffy, B., Kasler, M., Matrai, Z., Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial, European Journal of Surgical OncologyEur J Surg Oncol, 43, 672-679, 2017 **Ref Id** 682568 **Country/ies where the study was carried out** Hungary **Study type** RCT **Aim of the study** To evaluate survival, morbidity and locoregional control for patients with axillary lymph node metastasis on SLNB treated with RNI or cALND. **Study dates** 2002-2009	**Sample size** 474 **Characteristics** Mean age, 55 years. Surgery: BCT 83%, mastectomy 17% Clinical T stage: T1 66%, T2 34% Histology: ductal 81%, lobular 14%, other 5% Mutlifocal disease: 10% ER status: 83% positive PR status: 73% positive **Inclusion criteria** Tumour size < 3 cm. Women were randomised before surgery to the treatment they would receive if their sentinel lymph node biopsy (SLNB) proved positive.	**Interventions** Breast-conserving surgery or mastectomy + ALND (level I and II; at least 6 nodes) (N=244) Breast-conserving surgery or mastectomy + aRT including the contents of all three levels of the axilla and the supraclavicular fossa; 25 fractions of 2 Gy (N=230). Radiotherapy received: ALND: Postoperative RT to the regional nodes when ≥ 4 positive nodes (pN2a-3a) or 1-3 positive nodes (pN1a) with other high-risk characteristics. 232 patients received RT to the breast/chest wall, 76 patients received RT to the axillary/supraclavicular nodes. aRT: 208 patients received RT to the breast/chest wall, 230 patients received RT to the axillary/supraclavicular nodes.	**Details** Mean follow-up = 8.1 years (inter-quartile range 6.7 – 10 years)	**Results** See forest plots	**Limitations** See risk of bias assessment in Schmidt-Hansen (2016). **Other information** Equivalence trial

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding One author was supported by the OTKA K 108655 grant.	**Exclusion criteria** Patients were excluded for protocol violation or chose to leave the study(N=52), if no sentinel node was found (N=33).	Chemotherapy: 190 ALND; 159 aRT Endocrine therapy: 213 ALND; 204 aRT Both chemo and endocrine therapy: 159 ALND; 133 aRT			
Full citation Giuliano, A. E., Ballman, K. V., McCall, L., Beitsch, P. D., Brennan, M. B., Kelemen, P. R., Ollila, D. W., Hansen, N. M., Whitworth, P. W., Blumencranz, P. W., Leitch, A. M., Saha, S., Hunt, K. K., Morrow, M., Effect of Axillary Dissection vs No Axillary Dissection on 10-Year Overall Survival Among Women With Invasive Breast Cancer and Sentinel Node Metastasis: The ACOSOG Z0011 (Alliance) Randomized Clinical Trial, JAMAJama, 318, 918-926, 2017 **Ref Id** 682599 **Country/ies where the study was carried out** USA **Study type** RCT **Aim of the study** To determine whether overall survival of patients with sentinel lymph node metastases treated with breast-conserving therapy and sentinel lymph node dissection (SLND) alone without	**Sample size** 891 **Characteristics** Median age, 55 years. Surgery: BCT 100%, Clinical T stage: T1 68%, T2 30% Histology: ductal 82%, lobular 7%, other 11% Mutlifocal disease: NR **Inclusion criteria** Age ≥ 18 years ;Tumour size < 5cm, clinical N0; Breast conservation therapy; 1-2 sentinel lymph node metastases and ECOG status ≤ 2. **Exclusion criteria** Not reported in the 2017 publication.	**Interventions** Breast conserving surgery + SLND + ALND consisting of removal of all level I and II nodes on affected side with at least 10 identified nodes per surgical specimen (N=420) . In this group 37.5% had SN micrometastasis and 62.5% SN macro-metastasis Breast conserving surgery + SLND alone: After the blue or hot nodes were removed any remaining axillary nodes were palpated and removed as SLNs if suggestive of disease (N=436). In this group 44.8% had SN micrometastasis and 55.2% SN macro-metastasis Radiotherapy: Whole breast RT. Some patients also received RT to the supraclavicular area (total N = 89). Chemotherapy: 243 ALND; 253 SLND alone	**Details** Median follow-up = 9.3 (IQR 6.3–10.34) years	**Results** See forest plots	**Limitations** See risk of bias assessment in Schmidt-Hansen (2016). **Other information** Non-inferiority trial. Closed early

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
axillary lymph node dissection (ALND) is non-inferior to that of women treated with axillary dissection. **Study dates** 1999-2004 **Source of funding** Supported by grants U10CA180821 and U10CA180882 (awarded to the Alliance), U10CA047559, U10CA077651, U10CA180791, U10CA180838, U10CA180858, and U10CA180870 from the National Cancer Institute.		Endocrine therapy: 195 ALND; 203 SLND alone			

ACOSOG-Z011, American College of Surgeons Oncology Group-Z0011; ALND, axillary lymph node dissection; AMAROS, After mapping of the axilla: radiotherapy or surgery; ECOG, Eastern Cooperative Oncology Group; ER, oestrogen receptor; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IBCSG-23-01, International Breast Cancer Study Group-23-01; NR, not reported; OTOASOR, The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy; PR, progesterone receptor; PRISMA, Preferred Reporting Items for Systematic reviews and Meta-Analyses; RCT, randomised controlled trial; SLNB, sentinel lymph node biopsy; SLND, sentinel lymph node dissection; SN, sentinel node

Clinical evidence tables for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Table 15: Studies included in the evidence review for prevention of lymphoedema

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Anderson, R. T., Kimmick, G. G., McCoy, T. P., Hopkins, J., Levine, E., Miller, G., Ribisl, P., Mihalko, S. L., A randomized trial of exercise on well-being and function following breast cancer surgery: The RESTORE trial, Journal of cancer survivorship, 6, 172-181, 2012 **Ref Id** 632564 **Country/ies where the study was carried out** USA **Study type** Randomised controlled single-blind trial **Aim of the study** To examine the role of exercise program on	**Sample size** 104 **Characteristics** Gender: 100% female Age: 17% ≥65 Ethnicity: 89% Caucasian **Inclusion criteria** Women with newly diagnosed stage I-III breast cancer with axillary or sentinel lymph node dissection who can take part in moderate exercise training **Exclusion criteria** Women with disability, dementia, existing lymphoedema or any other chronic condition	**Interventions** Women were randomised 4-12 weeks after surgery. Intervention: the RESTORE program consisted of individualised exercise, methods to prevent lymph oedema, and education including diet and counselling **Control:** Usual care (patient education) only	**Details** **Intervention (exercise):** moderate exercise program with "lymphedema prevention module"(LPM). The LPM was delivered by a certified therapist and it was education about lymphedema and preventive use of compression sleeve and daily breathing exercises, mild arm and head exercises to enhance lymph flow. Centre based exercise program started at 3 months and ended at 9months follow-up. There were two exercise sessions every week at centre. Each included aerobic for 5 mins, moderate to hard walking for 30 mins, upper and lower body strength training for 20 mins and 10 min stretching and this was aimed to obtain baseline levels of strength and function of each participant. The exercise started with 50% of their baseline levels for first 1-2 weeks and increased weekly as	**Results** **Change in arm volume at 18 months (mm):** exercise: N=52, M=33.5, SE=29; usual care: N=52, M=60.4, SE=32.5 **Metres walked in 6 minutes:** Exercise versus usual care: beta(SE);(95%CI) 6-min walk: 34.3 (12.8);(8.61, 60.08); p=0.01 **HRQoL – FACT-B scores:** Exercise versus usual care: beta(SE);(95%CI): 1.38(2.44) ; (-3.50, 6.26); p=0.573	**Selection bias: random sequence generation** using randomisation database which was accessed electronically **Selection bias: allocation concealment** Not clear **Selection bias: overall judgement** Unclear/Low **Performance bias** Not clear; unlikely **Detection bias** The investigator was unblinded. **Attrition bias** Good adherence and ITT analysis **Selective reporting** All outcomes in method session were reported **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
lymphoedema, arm morbidity and quality of life among women after operation for non-metastatic breast cancer **Study dates** The study finished in 2007 with 18-month follow-up **Source of funding** US Army			appropriate. The exercises were targeted to upper, core and lower body parts. American college of sports and science guidelines was also recommended throughout. **Control (usual care):** were provided with information about lymphedema awareness and American cancer society (ACS) prevention exercises, quarterly newsletter about nutrition and physical activity. The primary outcome was function at 6-min walk (total metres walked in 6 minutes) and FACT-B.		None **Limitations** **Other information**
Full citation Cinar, N., Seckin, U., Keskin, D., Bodur, H., Bozkurt, B., Cengiz, O., The effectiveness of early rehabilitation in patients with modified radical mastectomy, Cancer nursing, 31, 160-165, 2008 **Ref Id** 632665	**Sample size** 57 **Characteristics** Gender: NR Age: intervention mean 52.6, SD 12.2; control mean 51, SD 13 Ethnicity: NR **Inclusion criteria**	**Interventions** **Intervention arm:** 15 sessions of an individual rehabilitation program and home-based activity program **Control arm**: received a form with the exercises to perform at home	**Details** **Intervention arm:** The shoulder was positioned at various degrees of flexion, abduction, and internal rotation on a wedge pillow on the 1st postoperative day and the exercise scheme prescribed active hand and elbow ROM exercises under supervision of a physiotherapist. On the 2nd postoperative day,	**Results** **Shoulder movement at 6 months – flexion:** intervention N=27, M=176.94, SD=5.16; control N=30, M=161.56, SD=11.73 **Shoulder movement at 6 months – abduction:** intervention N=27, M=174.93, SD=11.32; control: N=30, M=153.64, SD=19.66 **Shoulder movement at 6 months – internal rotation:**	**Selection bias: random sequence generation** Randomisation procedure not reported - Unclear **Selection bias: allocation concealment** Allocation concealment procedure not reported - Unclear **Selection bias: overall judgement**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Turkey **Study type** RCT **Aim of the study** To assess the effects of an early onset rehabilitation program on shoulder mobility, functional status, lymphedema, and the incidence of postoperative complications in women who had modified radical mastectomy **Study dates** Not reported **Source of funding** No sources reported	Not reported **Exclusion criteria** Not reported		hand and forearm exercises were started. On the 3rd and 4th days, the exercises included active assistive and active flexion, abduction, and internal and external rotation ROM exercises of the shoulder joint. In the following days, passive stretching exercises were performed. When the drains were removed, the patients in TG received individual 15 sessions of physiotherapy program in physical medicine and rehabilitation department, which the patients performed the exercises at home in the following 8 weeks. **Control arm:** The control group received a form that instructed participants on how to perform the exercises by themselves after removal of the drains. Both treatment groups were informed about skin care and issues that they should take care during daily living activities.	intervention N=27, M=90, SD=0; control N=30, M=84.45, SD=18.45 **Shoulder movement at 6 months – external rotation:** intervention N=27, M=90, SD=0; control N=30, M=81.76, SD=18.39 **Shoulder movement at 6 months – adduction:** intervention N=27, M=54.93, SD=7.09; control N=30, M=55, SD=6.51 **Shoulder movement at 6 months – extension:** intervention N=27, M=77.17, SD=6.87; control N=30, M=74.54, SD=8.23 **Shoulder movement at 6 months – functional questionnaire form:** intervention N=27, M=0.21, SD=0.97; control N=30, M=1.45, SD=1.77 **Incidence of mild-moderate lymphedema:** Intervention, n (%): 5/27 (19%); Control, n (%): 6/30 (20%) **Circumferential difference between operated and unoperated extremity, cm** **Baseline**	Unclear **Performance bias** Did not state whether patients were blinded **Detection bias** Assessors were blinded to group assignment **Attrition bias** Did not report attrition rate or how attrition was managed **Selective reporting** All stated outcomes reported **Indirectness** Control did not meet criteria specified in protocol i.e. that the control contain no strategy to prevent lymphedema - High **Limitations** Study did not report a power calculation, limited follow up period of 6 months as lymphedema can develop a year after intervention

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Intervention, mean (SD): 0.67 (1.77) Control, mean (SD): 0.30 (2.34) **Fifth day** Intervention, mean (SD): 0.13 (1.82) Control, mean (SD):0.52 (2.52) **First month** Intervention, mean (SD): 1.14 (1.59) Control, mean (SD):1.15 (2.16) **Third month** Intervention, mean (SD): 0.95 (2.64) Control, mean (SD): 1.56 (2.17) **Sixth month** Intervention, mean (SD): 0.97 (2.36) Control, mean (SD): 1.8 (2.15)	**Other information**
Full citation Devoogdt, N., Christiaens, M. R., Geraerts, I., Truijen, S., Smeets, A., Leunen, K., Neven, P., Van	**Sample size** 160 **Characteristics** Gender: 99% female	**Interventions** **Intervention arm**: prevention guidelines, exercise therapy, and manual lymph drainage	**Details** **Intervention arm:** All patients received guidelines about the prevention of arm lymphoedema: lift the arm	**Results** **Cumulative incidence rate of arm lymphoedema (increase of 200 mL)** **3 months after surgery**	**Selection bias: random sequence generation** Randomisation procedure not reported - Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Kampen, M., Effect of manual lymph drainage in addition to guidelines and exercise therapy on arm lymphoedema related to breast cancer: randomised controlled trial, BMJ, 343, d5326, 2011 **Ref Id** 565932 **Country/ies where the study was carried out** Belgium **Study type** RCT **Aim of the study** To assess the preventive efficacy of manual lymph drainage (MLD) on the development of secondary lymphoedema related to breast cancer **Study dates** October 2007 to February 2009	Age: intervention mean 56, SD 13; control mean 55, SD 11 Ethnicity: NR **Inclusion criteria** Patients with operable breast cancer who unilateral surgery with axillary lymph node dissection **Exclusion criteria** No additional criteria reported	**Control arm:** prevention guidelines and exercise therapy	in case of heaviness, avoid lifting heavy objects and performing repetitive movements, use the arm as normally as possible, avoid limb constriction, avoid extremes of temperature, apply skin care, wear a sleeve during a flight, and avoid an increase in weight. The exercise therapy consisted of different treatment modalities. Each session was individual and took half an hour. At the start of the treatment, patients had to come twice a week. Later, when the difference in shoulder mobility compared with the value before surgery was less than 20°, frequency was reduced to once a week, and then, if the patient was able to start maintenance treatment, to once every two weeks. Patients in the intervention group also received standardised manual lymph drainage. Firstly, lymph nodes of neck and axilla were emptied. Secondly, axillary anastomoses at the breast and back and	Intervention, n (%): 8/77 (24) Control, n (%): 6/81 (19) **6 months after surgery** Intervention, n (%): 11/77 (24) Control, n (%): 12/81 (19) **12 months after surgery** Intervention, n (%): 18/75 (24) Control, n (%): 15/79 (19) **Change in arm volume at 3 months (ml):** intervention N=77, M=29, SD=82; control N=81, M=18, SD=101 **Change in arm volume at 6 months (ml):** intervention N=77, M=58, SD=104; control N=81, M=31, SD=114 **Change in arm volume at 12 months (ml):** intervention N=75, M=34, SD=158; control N=79, M=45, SD=111 **Mental HRQoL at 3 months:** intervention N=77, M=72, SD=34; control N=81, M=69, SD=38 **Mental HRQoL at 6 months:** intervention N=77, M=74,	**Selection bias: allocation concealment** Allocation procedure not reported - Unclear **Selection bias: overall judgement** Unclear **Performance bias** Participants were not blinded **Detection bias** Assessors who performed the measurements were blinded **Attrition bias** Good adherence and use of ITT analysis **Selective reporting** All stated outcomes were reported **Indirectness** Six patients developed lymphoedema soon after axillary surgery and before the start of the 20

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Innovation by Science and Technology, Applied Biomedical Research			lymphatics at the lateral side of the shoulder (Mascagni pathway) were stimulated. Thirdly, the arm and hand were drained from proximal to distal. One session took half an hour. Patients were scheduled to receive 40 sessions of manual lymph drainage, with an increase in frequency from once a week to three times a week, and then a decrease to once a week, to create a gradual adaptation of the lymph system and not to end too abruptly. **Control arm:** Patients in the control group received the same intervention, minus the manual lymph drainage If a patient in either group developed arm lymphoedema, defined as an increase of the arm volume of 200 mL or more, she or he had to wear an inelastic bandage until the lymphoedema was maximally diminished and thereafter had to wear a custom-made sleeve.	SD=42; control N=81, M=68, SD=33 **Mental HRQoL at 12 months:** intervention N=75, M=79, SD=36; control N=79, M=81, SD=32 **Physical HRQoL at 3 months:** intervention N=77, M=56, SD=27; control N=81, M=56, SD=38 **Physical HRQoL at 6 months:** intervention N=77, M=63 SD=40; control N=81, M=58, SD=36 **Physical HRQoL at 12 months:** intervention N=75, M=74, SD=37; control N=79, M=77, SD=35	week treatment period - High **Limitations** Six patients developed lymphoedema after axillary surgery and before the start of the 20 week treatment period. Participants may not have been representative of the larger population. The experience of the therapists differed, which could have affected the delivery of the MLD procedures. Patients did not receive the planned 40 MLD sessions because of illness related to chemotherapy; up to 85% of the patients received 30+ sessions. **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Full citation Hansdorfer-Korzon, R., Teodorczyk, J., Gruszecka, A., Wydra, J., Lass, P., Relevance of low-pressure compression corsets in physiotherapeutic treatment of patients after mastectomy and lymphadenectomy, Patient preference & adherence, 10, 1177-87, 2016 **Ref Id** 567932 **Country/ies where the study was carried out** Poland **Study type** RCT **Aim of the study** To determine whether compression corsets therapy with a class I compression garment can prevent truncal	**Sample size** 37 **Characteristics** Gender: 100% female Age: intervention mean 62, SD 13; control mean 63, SD 12 Ethnicity: NR **Inclusion criteria** Breast cancer patients classified by the oncologist as candidates for surgery **Exclusion criteria** Patients who experienced serious illness after chemotherapy, severe viral infection, or reoperation	**Interventions** **Intervention arm:** Compression corset **Control arm:** No physiotherapeutic treatment	**Details** **Intervention arm:** After baseline measurements after surgery and randomisation, women randomly assigned to the intervention group received a properly fitted compression corset, which they had to wear through the study (7 months total). Low-pressure compression corsets were used **Control arm:** After baseline measurements after surgery and randomisation, women randomly assigned to the control group were not given a compression corset	**Results** **Number of women with pain reduction:** Intervention 11/19 Control: 6/18	**Selection bias: random sequence generation** Not reported: Unclear **Selection bias: allocation concealment** Not reported: Unclear **Selection bias: overall judgement** Unclear **Performance bias** Not reported if participants were blinded **Detection bias** Not reported if assessors and researchers were blinded **Attrition bias** Attrition rates were not reported, nor was whether ITT analysis or other methods for handling attrition **Selective reporting** Outcomes for the size of truncal lymphedema and

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
lymphedema on the female patient's operated side for those who underwent mastectomy and additional radiotherapy and whether class I compression garments could be used for pain reduction strategies **Study dates** Not reported **Source of funding** No sources reported					average thickness ratios of the subcutaneous tissue of the chest wall were not reported in sufficient detail for analysis **Indirectness** None **Limitations** Short follow-up period **Other information**
Full citation Harder, H., Langridge, C., Solis-Trapala, I., Zammit, C., Grant, M., Rees, D., Burkinshaw, L., Jenkins, V., Post-operative exercises after breast cancer surgery: Results of a RCT evaluating standard care versus standard care plus additional yoga exercise, European Journal of Integrative Medicine, 7, 202-210, 2015	**Sample size** 92 **Characteristics** Gender: 100% female Age: intervention mean 55, SD 11; control mean 56, SD 12 Ethnicity: NR **Inclusion criteria** Women between the ages of 18 and 80,	**Interventions** **Intervention arm:** standard care post-operative exercises plus a 10-week self-practice general yoga programme (yoga DVD) **Control arm:** standard care post-operative exercises	**Details** **Intervention arm:** Participants in the intervention arm received standard care plus a self-practice yoga DVD. The DVD incorporated 16 postures that were covered in a 10-week course of general yoga. The DVD consisted of 2 parts- 1) Disc 1 including an introduction to yoga and a demonstration of the 16 poses; and 2) Disc 2 featuring a 1 hour yoga class. Participants were	**Results** **Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy-Breast+4 (FACT-B+4) (high FACT-B+4 scores indicate better QOL)** **Post-surgery (baseline)** Intervention (mean, SD): 74.3 (16.1) Control (mean, SD): 72.5 (13.6) **10 weeks post-surgery** Intervention (mean, SD): 84.0 (21.1)	**Selection bias: random sequence generation** Randomisation was conducted using a computer-generated programme - low **Selection bias: allocation concealment** Randomisation was undertaken by an independent researcher - low **Selection bias: overall judgement**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Ref Id 632808 **Country/ies where the study was carried out** UK **Study type** RCT **Aim of the study** To determine whether a specially developed self-practice yoga DVD affects QoL and arm and shoulder morbidity in women who had breast cancer surgery **Study dates** Not reported **Source of funding** This study did not receive any financial support	have early-stage breast cancer (stages I-III) **Exclusion criteria** No additional criteria reported		shown how to use the DVD and practice the poses and were given yoga materials to use during the intervention program. Participants were asked to use the DVD at least once a week. **Control arm:** Standard care included post-operative exercise materials given out by the hospital before surgery. Materials include written instructions for arm and shoulder mobilisation, an exercise leaflet, poster, or DVD. Women randomised to the control arm were offered the yoga-DVD after the last follow-up assessment.	Control (mean, SD): 83.5 (18.0) **6-months post-surgery** Intervention (mean, SD): 88.7 (19.7) Control (mean, SD): 85.6 (17.1) **Arm function (5 items)** **Post-surgery (baseline)** Intervention (mean, SD): 12.2 (4.7) Control (mean, SD): 12.0 (4.1) **10 weeks post-surgery** Intervention (mean, SD): 17.5 (3.7) Control (mean, SD): 16.7 (4.2) **6-months post-surgery** Intervention (mean, SD): 17.5 (3.1) Control (mean, SD): 15.4 (4.3) **QuickDASH (higher scores represent greater limitations)**	Low **Performance bias** "A home-visit was arranged to obtain informed consent, demographics, level of previous yoga experience, and details of the hospital post-operative exercises. After this visit participants were randomised and informed about group-allocation." **Detection bias** "Participants were asked not to reveal their group allocation to the physiotherapists" **Attrition bias** Adherence was good (attrition rate was 15%), but method to manage attrition, such as intention-to-treat analysis was not reported **Selective reporting** All outcomes stated were reported **Indirectness**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Post-surgery (baseline) Intervention (mean, SD): 41.2 (20.4) Control (mean, SD): 43.2 (18.3) **10 weeks post-surgery** Intervention (mean, SD): 10.8 (15.8) Control (mean, SD): 15.2 (19.1) **6-months post-surgery** Intervention (mean, SD): 9.9 (17.2) Control (mean, SD): 15.4 (16.3) **Level of pain (10-point scale with 0 representing no pain and 10 worst possible pain)** **Post-surgery (baseline)** Intervention (mean, SD): 3.0 (2.6) Control (mean, SD): 2.9 (2.0) **10 weeks post-surgery** Intervention (mean, SD): 1.0 (2.0) Control (mean, SD): 1.4 (2.1)	Control group involved exercise i.e. did not match protocol stating comparator needed to have no strategy to prevent lymphedema - high **Limitations** The study was underpowered, there was no pre-surgery baseline assessment of arm and shoulder function, treatment group may have performed more exercise than the control group **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				6-months post-surgery Intervention (mean, SD): 1.5 (1.7) Control (mean, SD): 2.8 (2.5) **Oxford Shoulder Score (OSS) (higher scores represent greater disability)** **Post-surgery (baseline)** Intervention (mean, SD): 25.7 (9.1) Control (mean, SD): 27.0 (8.6) **10 weeks post-surgery** Intervention (mean, SD): 16.1 (6.8) Control (mean, SD): 17.0 (7.7) **6-months post-surgery** Intervention (mean, SD): 15.0 (6.1) Control (mean, SD): 17.7 (7.3)	
Full citation Kilbreath, S. L., Refshauge, K. M.,	**Sample size** 160	**Interventions** Women were randomised 4-6	**Details** **Exercise group:** consisted of home program of	**Results** **EORTC breast module mean (SD)**	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Beith, J. M., Ward, L. C., Lee, M., Simpson, J. M., Hansen, R., Upper limb progressive resistance training and stretching exercises following surgery for early breast cancer: A randomized controlled trial, Breast Cancer Research and Treatment, 133, 667-676, 2012 **Ref Id** 616667 **Country/ies where the study was carried out** Australia **Study type** Randomised controlled trial **Aim of the study** To examine the effectiveness of early passive stretch and resistance exercise program of shoulder joint among women with operated breast cancer on arm	**Characteristics** Gender: 100% female Age: mean 53 **Inclusion criteria** Women who had surgery for stage I-III breast cancer with either biopsy or dissection of axillary node **Exclusion criteria** Women with history of lymphoedema; bilateral breast cancer or metastatic breast cancer; pre-existing restricted arm movement	weeks after surgery and the program lasted for 8 weeks and the physiotherapist or occupational therapist did not attend the follow-up. All the women received information about postoperative arm exercises (brief, active-assisted, active overhead movements in frontal and sagittal planes) and prevention of lymphoedema such as avoiding lifting heavy stuff and prolonged activities, etc.	resistance training and stretches and weekly supervised free weight training and follow-up. Resistance training at home - women did two sets of 8-15 repetitions for each exercise and were suggested to target scale of 15 (Hard) on the Borg Effort Scale. Stretching at home - performed daily in supine position ")shoulder flexion in which the arm was elevated overhead in the sagittal plane; (ii) arm abduction to 135 with horizontal extension to target pectoralis major, and (iii) abduction to 90 and with horizontal extension to target pectoralis minor " each stretch maintaining for 5 to 15 minutes **Control group:** were seen every two weeks to check lymphoedema. If lymphoedema (+), patients were referred to occupational therapist for compression garment.	**Post-baseline (after 8 weeks):** Exercise: 13(17) Control: 10 (14) **Follow-up (at 6 month)** Exercise:12(20) Control:8 (16) **BR23 breast symptoms - mean (SD)** **Post-baseline:** Exercise: 8(15) Control: 7 (18) **Follow-up** Exercise:10(17) Control: 6(20) **Post-baseline - mean (SD)** **Range of motion** **Forward Flexion** Exercise: 19.5(16.4) Control: 13.1(13.1) **Abduction** Exercise: 19.2(15.9) Control: 14.0(16.4) **External rotation** Exercise: 27.1(14.1) Control: 25(12.8) **Horizontal extension** Exercise: 9.2 (14.6) Control: 6.8(14.4) **Strength** **Abduction**	Unclear (did not assess protocol) **Selection bias: allocation concealment** Unclear (did not assess protocol) **Selection bias: overall judgement** Unclear (did not assess protocol) **Performance bias** Unclear (did not assess protocol) **Detection bias** Unclear (did not assess protocol) **Attrition bias** Low risk **Selective reporting** None **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
morbidity including oedema **Study dates** Not reported - likely to between 2006 (protocol publication date) and 2012 (study publication date) **Source of funding** NSW Cancer Council; National Breast Cancer Foundation				Exercise: 25.9(32.3) Control: 15.7(28.6) **Forward flexion** Exercise: 21.5(26) Control: 14.3(24.7) **Horizontal extension** Exercise: 17.9(26.1) Control: 13.7(26.2) **Horizontal flexion** Exercise: 17.4(35.4) Control: 14.6(29.2) **Follow-up - mean (SD)** **Range of motion** **Forward Flexion** Exercise: 16.5(17.7) Control: 14.6(20.3) **Abduction** Exercise: 20.1(16.7) Control: 10.1(21.6) **External rotation** Exercise: NR Control: NR **Horizontal extension** Exercise: 7.5(15.9) Control: 1.7(15.4) **Strength** **Abduction** Exercise: 23.4(38.4) Control: 20.4 (31.5)	Published protocol available at: Kilbreath SL, Refshauge KM, Beith JM, Ward LC, Simpson JM, Hansen RD (2006) Progressive resistance training and stretching following surgery for breast cancer: study protocol for a randomised controlled trial. BMC Cancer 6:273

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				Forward flexion Exercise: 18.1(30.1) Control: 14.3(27.7) **Horizontal extension** Exercise: 17.3(25.8) Control: 14.3(28.1) **Horizontal flexion** Exercise: 14.4(30.6) Control: 18.2 (26.0) **Lymphoedema - Exceeds BIS ratio (post-baseline)** Exercise: 5(7%) Control: 11(15%) **Interlimb circumference difference: 2 or more measure > 2 cm (post-baseline)** Exercise: 6(8%) Control: 5(5%) **Interlimb arm volume >/=10% difference (post-baseline)** Exercise: 8(11%) Control: 8(10%) **Lymphoedema - Exceeds BIS ratio (at follow-up)** Exercise: 6(8%) Control: 9(13%) **Interlimb circumference difference: 2 or more measure**	

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				> 2 cm (at follow-up) Exercise: 5(7%) Control: 4(6%) **Interlimb arm volume >/=10% difference (at follow-up)** Exercise: 6(8%) Control: 9(13%)	
Full citation Sagen, A., Karesen, R., Risberg, M. A., Physical activity for the affected limb and arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with two years follow-up, Acta Oncologica, 48, 1102-1110, 2009 **Ref Id** 551615 **Country/ies where the study was carried out** Norway **Study type**	**Sample size** 204 **Characteristics** Gender: NR Age: mean 55 **Inclusion criteria** Early stage breast cancer and had removal of breast or breast conserving surgery with dissection of axillary nodes **Exclusion criteria** Age > 75 years; too ill to undertake the exercise program; metastasis; cancer other than breast	**Interventions** **Intervention arm:** No activity restriction (NAR **Control arm:** Activity restriction (AR) Anyone who developed arm lymphoedema received treatment by a physical therapist.	**Details** Women were randomised 2 days after surgery and the study lasted for 6 months. **Intervention (NAR)**: Participants were encouraged to use the affected limb with no restrictions. And, they also received physical therapy program (moderate progressive resistance exercise training of 45 min for 2-3 times/week) at outpatient under supervision. The program aimed to improve muscular strength and resistance and each lasts for 45 min and repeated 2-3 times per week. The program consisted of at least 15 repetitions per each exercise with 0.5 kg	**Results** **Difference in volume between affected and control arm at 3 months:** intervention N=104, M=20, SD=120; control N=100, M=49, SD=125 **Difference in volume between affected and control arm at 6 months:** intervention N=104, M=32, SD=129; control N=100, M=64, SD=158 **Difference in volume between affected and control arm at 24 months:** intervention N=104, M=52, SD=153; control N=100, M=82, SD=165 **Incidence of arm lymphoedema at 3 months:** intervention 4%; control 7%	**Selection bias: random sequence generation** simple randomisation in blocks of 10 using a computer-generated program **Selection bias: allocation concealment** "the assignment scheme was given in sealed envelopes in a series of consecutive numbers" **Selection bias: overall judgement** low risk **Performance bias** participants received sealed envelope but unlikely investigators;

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Randomised controlled trial **Aim of the study** To examine the effects of activity restriction among women with operated breast cancer on physical morbidity and oedema of the affected limb **Study dates** 1993 to 2003 **Source of funding** Health and Rehabilitation, the Norwegian Cancer Society; Norwegian Women's Public Health Association	cancer; injury or decreased movement of the arms		resistance for initial 2 weeks, then the resistance was increased depending on individuals' durability. **Control (AR)**: Participants were suggested to limit the movement of the affected limb. The emphasis was given to abstain from heavy or strenuous physical activities of any type including aerobics or work and to stop carrying any items or > 3 kg. They also took part in the weekly standard care physical therapy program at outpatient. This program focused on flexibility and gentle massage of the affected arm and shoulder including scar using 6 different usual passive manual techniques. Anyone who developed arm lymphoedema received treatment by a physical therapist.	**Incidence of arm lymphoedema at 24 months:** intervention 13%; control 13% **No pain as measured by visual analogue scale at 3 months:** intervention 22%; control 55% **No pain as measured by visual analogue scale at 6 months:** intervention 40%; control 64% **No pain as measured by visual analogue scale at 24 months:** intervention 61%; control 64%	**Detection bias** outcome assessors were not blinded **Attrition bias** had prior sample size of 65 patients in each arm; ITT analysis **Selective reporting** outcomes mentioned in methods session were reported **Indirectness** None **Limitations** **Other information**
Full citation Sato, F., Ishida, T., Ohuchi, N., The perioperative educational program	**Sample size** 162 **Characteristics**	**Interventions** **Intervention arm:** An educational program to prevent or improve arm	**Details** **Intervention arm:** The intervention was a program that was designed to educate participants on the	**Results** **ALND:** **Lymphoedema symptoms – upper arm girth at 3 months:**	**Selection:** All patients who met the inclusion criteria during the study duration (January 2010 to April

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
for improving upper arm dysfunction in patients with breast cancer: A controlled trial, Tohoku journal of experimental medicine, 232, 115-122, 2014 **Ref Id** 633095 **Country/ies where the study was carried out** Japan **Study type** Controlled. non-randomised trial **Aim of the study** The aim of the study was to assess the effectiveness of intervention at up to 3 months after operation to prevent or improve upper arm function after breast cancer surgery **Study dates** January 2010 - July 2012	Gender: 100% female Age: intervention mean ALDN 53, SD 10; control mean ALND 52, SD 13; intervention mean SLNB 54, SD 11; control mean SLNB 54, SD 10 **Inclusion criteria** Eligible participants were greater than or equal to 20 years of age, able to answer a self-administered questionnaire, had no diagnosis or treatment for a mental illness; could provide written informed consent to participate in the study. **Exclusion criteria** Ineligible participants were patients with bilateral breast cancer or recurrence	morbidity outcomes in breast cancer patients post-surgery **Control arm:** No educational program	prevention or improvement of swelling post-operation, pain, decreased shoulder range of motion, numbness, decreased muscle strength in the arm, or feelings of pulling in the skin of the arm. Another goal was to change the knowledge of the participants in regards to the sciences of ecology and health, as well as self-care strategies, thereby changing the symptoms of impairment of upper limb function and quality of life. Methods for arm monitoring, exercises for preventing restricted shoulder range of motion or lymphoedema, and massaging methods were also taught during the intervention. Participants were asked to practice the skills and activities after they left the hospital. **Control arm:** Routine care from hospital staff and received information about the results of upper extremity function determined in the measurements in the treatment arm	intervention N=39, M=0.6, SD=1.1; control N=30, M=-0.1, SD=1 **Lymphoedema symptoms – forearm girth at 3 months:** intervention N=39, M=0.3, SD=1.1; control N=30, M=0.2, SD=1.2 **Arm function – SPOFIA score at 3 months:** intervention N=39, M=2.5, SD=1.9; control intervention N=30, M=3.2, SD=2.6 **Arm function – DASH score at 3 months:** intervention N=39, M=10.5, SD=8.7; control N=30, M=10.4, SD=8.1 **Shoulder function – flexion at 3 months:** intervention N=39, M=11.3, SD=16.7; control N=30, M=2.9, SD=10.1 **Shoulder function – abduction at 3 months:** intervention N=39, M=11.4, SD=14.8; control N=30, M=3.0, SD=10.4 **Shoulder function – horizontal extension at 3 months:** intervention N=39, M=2.0, SD=4.4; control N=30, M=0.6, SD=5.3	2012) at the study hospital; "Patients were allocated to the intervention or control group according to their wishes after receiving full information about the study protocols and providing informed consent" **Comparability:** Not reported **Indirectness** Low risk **Limitations** -Short follow up period (symptoms of lymphedema can appear one year after surgery) -Small sample size **Other information** Exposure Ascertainment of exposure- “methods were also demonstrated and implemented with the subject until learnt. And, at 1 months and 3 months, patients were assessed for ……and

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Japan Society for the Promotion of Science				**Arm function – grip strength at 3 months:** intervention N=39, M=0.2, SD=1.2; control N=30, M=1.2, SD=3.6 **SLNB** **Lymphoedema symptoms – upper arm girth at 3 months:** intervention N=51, M=0.1, SD=0.9; control N=29, M=0.1, SD=1.3 **Lymphoedema symptoms – forearm girth at 3 months:** intervention N=51, M=0.0, SD=1.0; control N=29, M=-0.1, SD=1.1 **Arm function – SPOFIA score at 3 months:** intervention N=51, M=1.1, SD=1.7; control intervention N=29, M=1.1, SD=1.4 **Arm function – DASH score at 3 months:** intervention N=51, M=7.4, SD=11.8; control N=29, M=5.6, SD=6.1 **Shoulder function – flexion at 3 months:** intervention N=51, M=3.8, SD=14.8; control N=29, M=2.0, SD=10.7 **Shoulder function – abduction at 3 months:** intervention N=51, M=3.7,	individual support was provided" Non-response rate- In the intervention group 6 patients dropped out and in the control group 7 patients dropped out

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
				SD=11.5; control N=29, M=1.3, SD=12.1 **Shoulder function – horizontal extension at 3 months:** intervention N=51, M=0.2, SD=4.9; control N=29, M=0.4, SD=4.9 **Arm function – grip strength at 3 months:** intervention N=51, M=-0.2, SD=2.4; control N=29, M=-0.2, SD=3.5	
Full citation Schmitz, K. H., Ahmed, R. L., Troxel, A. B., Cheville, A., Lewis-Grant, L., Smith, R., Bryan, C. J., Williams-Smith, C. T., Chittams, J., Weight lifting for women at risk for breast cancer-related lymphedema: A randomized trial, JAMA - Journal of the American Medical Association, 304, 2699-2705, 2010 **Ref Id** 633103 **Country/ies where the study was carried out**	**Sample size** 154 **Characteristics** Gender: NR Age: mean 55 Ethnicity: 71% Caucasian **Inclusion criteria** History of non-metastatic unilateral breast cancer diagnosis 1 to 5 years ago; </=50 BMI; minimum removal of 2 lymph nodes **Exclusion criteria**	**Interventions** **Intervention arm:** Weight-lifting **Control arm:** No exercise	**Details** "Lymphoedema was defined as an interlimb difference of at least 10% as measured by water volumetric, greatest circumferential difference or per the common toxicity criteria version 3.0 adverse events criteria, swelling, or obscuration of anatomic architecture or pitting oedema." All participants (intervention and control) had 1-hour education about lymphedema and exercise recommended by National lymphedema Network. **Weight-lifting:** received 1 year membership to a community fitness centre;	**Results** **Incidence of lymphoedema at 12 months - ≥5% increase:** intervention 8/72; control 13/75 **Incidence of lymphoedema at 12 months – clinically defined:** intervention 1/66; control 3/68 **Change in number of symptoms reported:** intervention N=72, M=-0.51, SD=1.57; control N=75, M=-0.42, SD=2.26 **Change in symptom severity:** intervention N=72, M=-0.27, SD=0.97; control, N=75, M=-0.28, SD=0.86 **Strength at 12 months – bench press (lb):** intervention	**Selection bias: random sequence generation** Computerised minimisation process (balancing age, number of lymph nodes removed, obesity and radiation Rx) **Selection bias: allocation concealment** concealed from research staff **Selection bias: overall judgement** low risk **Performance bias** participants were not blinded **Detection bias**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
USA **Study type** Randomised controlled non-inferiority trial **Aim of the study** To examine the role of weight-lifting among breast cancer survivors **Study dates** 1 October 2005 to February 2007 **Source of funding** National Cancer Institute; National Institutes of Health; equipment provided by BSN medical	History of lymphoedema; planned surgery; away for greater than 1 month during study		first 12 weeks - women were trained two times each week for safe exercise in groups (2 to 6) for 90 minutes, led by certified professionals. It included upper body exercises using resistance machine like dumbbells, lower body exercises with variable resistance machines. After 13 weeks, continue unsupervised exercises twice weekly and weight was increased by "smallest possible increment after 2 sessions of completing 3 sets of 10 repetitions with no change in arm symptoms". If missed the class two consecutive times, the weight was reduced. The trainers also received training course and education on lymphoedema. Anyone who had lymphedema were treated with custom-fitted compression garment and women in weightlifting group continued exercises with this fitted. The primary outcome was onset of lymphedema - 5%	N=59, M=54, SD=12; control N=63, M=43, SD=11 **Strength at 12 months – leg press (lb):** intervention N=61, M=213, SD=5-; control N=63, M=192, SD=53 **Physical activity (metabolic equivalent per week) at 12 months:** intervention N=58, M=3041.2, SD=2.29; control N=60, M=2440.6, SD=3.10	staff who measured the outcomes were blinded to treatment allocation **Attrition bias** 87% follow-up rate and reasons were justifiable between groups **Selective reporting** All outcomes in method session were reported **Indirectness** None **Limitations** **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
			or more increase in arm swelling. Or, clinician defined onset= certified lymphedema therapist used standardised method based on Common Toxicity Criteria version 3.0 criteria which assessed inter limb differences, change in symptoms or tissues. The prior sample size calculation had 80% power with type I error of 0.5.		
Full citation Torres Lacomba, M., Yuste Sanchez, M. J., Zapico Goni, A., Prieto Merino, D., Mayoral del Moral, O., Cerezo Tellez, E., Minayo Mogollon, E., Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: randomised, single blinded, clinical trial, BMJ, 340, b5396, 2010 **Ref Id** 633174	**Sample size** 120 **Characteristics** Gender: 100% female Age: mean 53, SD=12 Ethnicity: NR **Inclusion criteria** Women who had had unilateral breast cancer surgery with axillary lymph node dissection **Exclusion criteria**	**Interventions** **Intervention arm:** Early physiotherapy and an educational strategy **Control arm:** Educational strategy only	**Details** **Intervention arm:** Participants received manual lymph drainage, stretching exercises for levator scapulae, upper trapezius, pectoralis major, and medial and lateral rotators muscles of the shoulder, and progressive active and action assisted shoulder exercises. Functional activities and proprioceptive neuromuscular facilitation exercises without resistance. Those in the treatment group also received the standard educational intervention	**Results** **Development of lymphoedema** Intervention (n=59), n (%): 4 (7) Control (n=57), n (%): 14 (25) **Change in volume ratio (%) from baseline to 12-month follow up** Intervention group, mean (SD): 1.6 (5.6) Control group, mean (SD): 5.1 (7.6)	**Selection bias: random sequence generation** Random sequence generation performed by a computer - Low **Selection bias: allocation concealment** Random allocation completed by computer - Low **Selection bias: overall judgement** Low **Performance bias** Did not report - Unclear

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out Spain **Study type** RCT **Aim of the study** To assess the effectiveness of early physiotherapy in decreasing the risk of secondary lymphoedema after surgery for breast cancer **Study dates** May 2005 to June 2007 **Source of funding** Health Institute Carlos III, Spanish Health Ministry	Women were excluded if they had not had axillary lymph node dissection or who had had bilateral breast cancer, systemic disease, locoregional recurrence, or any contraindication to physiotherapy		**Control arm:** Both studies received the same educational intervention. The educational strategy included printed materials on the lymphatic system, causes of secondary lymphoedema, the identification of possible precipitating factors, and four types of interventions to prevent secondary lymphoedema, along with strategies for implementing these four interventions	**Maximum difference measured between two adjacent points (cm)** Intervention, mean (SD): 0.68 (0.91) Control, mean (SD): 1.15 (1.21)	**Detection bias** Did not report - Unclear **Attrition bias** Adherence was good and power calculations were reported **Selective reporting** All stated outcomes were reported **Indirectness** Low **Limitations** External validity to other regions or developed countries; criterion for diagnosing lymphoedema could have affected the results **Other information**
Full citation Zimmermann, A., Wozniewski, M., Szklarska, A.,	**Sample size** 67 **Characteristics**	**Interventions** **Intervention arm**: Standard program of physiotherapy plus	**Details** **Intervention arm:** MLD included massage strokes applied to the side of the	**Results** **Presence of lymphedema post-surgery on operated side**	**Selection bias: random sequence generation**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Lipowicz, A., Szuba, A., Efficacy of manual lymphatic drainage in preventing secondary lymphedema after breast cancer surgery, Lymphology, 45, 103-112, 2012 **Ref Id** 552359 **Country/ies where the study was carried out** Germany **Study type** RCT **Aim of the study** To determine the effectiveness of manual lymphatic drainage in the prevention of secondary lymphedema of the upper limb after treatment for breast cancer. **Study dates** Not reported	Gender: 100% female Age: mean 59, SD 10 Ethnicity: NR **Inclusion criteria** Women who had undergone breast surgery for primary breast cancer **Exclusion criteria** Not reported	manual lymph drainage (MLD) **Control arm:** Standard program of physiotherapy	oedematous limb, starting at the base of the neck and then progressing to the affected limb. The massage was always directed proximally from the upper arm to the axilla, and then from the hand to the elbow. Finally, the whole limb was massaged from the distal to the proximal extremity. MLD was applied 5-times a week for the first 2 weeks, and twice a week from the third week to 6th month post-surgery **Control arm:** Standard program of physiotherapy included exercises of limb and chest physical therapy, as well as applied self-drainage	Intervention: 0/33 (0%) Control: 24/34 (70.6%) **Lymphoedema – arm volume at 3 months (ml):** intervention N=33, M=2115, SD=506; control N=34, M=2036, SD=391 **Lymphoedema – arm volume at 6 months (ml):** intervention N=33, M=2108, SD=502; control N=34, M=2124, SD=470	Randomisation procedure not reported- Unclear **Selection bias: allocation concealment** Allocation procedure not reported- Unclear **Selection bias: overall judgement** Unclear **Performance bias** Concealment was not reported **Detection bias** Concealment was not reported **Attrition bias** Attrition rate was not reported **Selective reporting** All stated outcomes were reported **Indirectness** High - control did not meet protocol criteria (i.e. that the control involve no

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding Not reported					strategy for prevention of lymphedema) **Limitations** Lymphedema normally occurs within the first year after treatment, yet the follow-up was limited to only 6 months. The study was also not adequately powered, with only 67 participants included in the sample **Other information**
Full citation Fu, M. R., Chen, C. M., Haber, J., Guth, A. A., Axelrod, D., The effect of providing information about lymphedema on the cognitive and symptom outcomes of breast cancer survivors, Annals of Surgical Oncology, 17, 1847-1853, 2010 **Ref Id** 633733	**Sample size** 136 **Characteristics** Gender: 100% female Age: mean 54, Ethnicity: 74% Caucasian **Inclusion criteria** Women with treated breast cancer **Exclusion criteria**	**Interventions** **Intervention arm:** Women who received information about breast cancer related lymphedema (BCRL) **Control arm:** Women who did not receive information about breast cancer related lymphedema (BCRL)	**Details** **Intervention arm:** Women who received or were offered information regarding risk of lymphedema and how to prevent it from healthcare providers **Control arm:** Women who did not receive or were not offered information regarding risk of lymphedema and how to prevent it from healthcare provider Lymphedema and breast cancer questionnaire - was	**Results** **Lymphoedema symptoms:** intervention N=77, M=2.58, SD=2.38; control N=59, M=4.26; SD=3.0 **Impaired should mobility:** intervention 13/77; control 19/59 **Arm weakness:** intervention 16/77; control 12/59	**Indirectness** Low risk **Limitations** Of 157 responded to participation, 141 (89.8%) were eligible and 136 (96.5%) participated. (Justified reasons for those 5 women who did not participate) **Other information**

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Country/ies where the study was carried out USA **Study type** Retrospective cohort **Aim of the study** To examine the effects of lymphedema information provision among women with operated breast cancer **Study dates** August 2006 to May 2007 **Source of funding** Avon Foundation; Hartford Institute for Geriatric Nursing; NYU Pless centre of Nursing Research	No additional criteria reported		used to detect the presence of lymphedema-related symptoms and scores were calculated for total symptom reported.		
Full citation Lu, S. R., Hong, R. B., Chou, W., Hsiao, P. C., Role of physiotherapy and patient education	**Sample size** 1087 **Characteristics**	**Interventions** The intervention consisted of a patient-centred education program	**Details** The patient-centred educational program was led by a specialized physiotherapist who	**Results** **Incidence of lymphedema, n (%)** Intervention: 101 (15.0)	**Selection:** Reference to a primary record source (cancer registry data and medical charts); all women from

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
in lymphedema control following breast cancer surgery, Therapeutics and Clinical Risk Management, 11, 319-327, 2015 **Ref Id** 634142 **Country/ies where the study was carried out** Taiwan **Study type** Retrospective cohort study **Aim of the study** The aim of this study was to assess the effect of early post-operative education in reducing the occurrence of secondary upper-limb lymphoedema in who had breast cancer surgery and axillary lymph node dissection (ALND) **Study dates** 2002-2006	Gender: 100% female Age: intervention mean 53, SD 11; control mean 52, SD 12 Ethnicity: NR **Inclusion criteria** Women diagnosed with Stage 0-3 breast cancer for the first time between January 1, 2007 and December 31, 2011; underwent tumour resection and axillary lymph node dissection (ALND) as their primary therapy **Exclusion criteria** Bilateral breast cancer; developed lymphedema before surgery; neurological diseases that affected the ipsilateral arm, shoulder, or axilla mobility		provided patients with instructions on printed materials. The educational program provided information on the lymphatic system, the symptoms and signs of lymphedema, and suggestions for preventing lymphedema, including engaging in postoperative exercise, modifying activities, massaging the scar tissue, maintaining a healthy body weight, and avoiding trauma to or infection or venepuncture of the limb.	Control: 77 (18.6) **Severity of lymphedema, n (%)** **Stage 1** Intervention: 65 (64.4) Control: 42 (54.5) **Stage 2 or 3** Intervention: 36 (35.6) Control: 35 (45.5)	the study centre who matched the study's inclusion criteria during the study period were included. Hospital controls derived from the hospitalised population in the study centre **Comparability:** Cases and controls were not matched; however, the results of the multivariate analysis were adjusted for all of the variables with a significant difference in the univariate analysis **Indirectness** Low risk **Limitations** Hospital-based retrospective comparative cohort study, which limits generalisability; the cancer registries may not have included all the variables of outcome significance, which could have confounded multivariate analyses;

Study details	Participants	Interventions	Methods	Outcomes and results	Comments
Source of funding No financial relationships to disclose					researchers were unable to access information from other hospitals; allocation to treatment groups was by determined by the surgeon instead of a randomised process **Other information** Exposure: Ascertainment of exposure- "A patient-centred educational program, if requested, was conducted in a consistent manner." Non-response rate: not reported

ACS, American Cancer Society; AR, activity restriction; BIS, Bioelectrical impedance spectroscopy; BR23, EORTC-BR23 quality of life questionnaire; DASH, Disabilities of the Arm, Shoulder and Hand; EORTC, European Organisation for Research and Treatment of Cancer; FACT-B, Functional assessment of cancer therapy – Breast cancer; HRQoL, health-related quality of life; LPM, lymphoedema prevention module; M, mean; NAR, no activity restriction; NR, not reported; OSS, Oxford should score; RCT, randomised controlled trial; SD, standard deviation; SE, standard error; SPOFIA, Subjective Perception of Post-Operative Functional Impairment of the Arm; TOI, Trial Outcome Index

Appendix E – Forest plots

Forest plots for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Comparison 1.1 Axillary lymph node (ALND) following sentinel lymph node dissection (SLND) vs SLND alone

Figure 3: Overall survival in women with breast cancer and sentinel lymph node metastases at median follow-up of 5 to 9.3 years

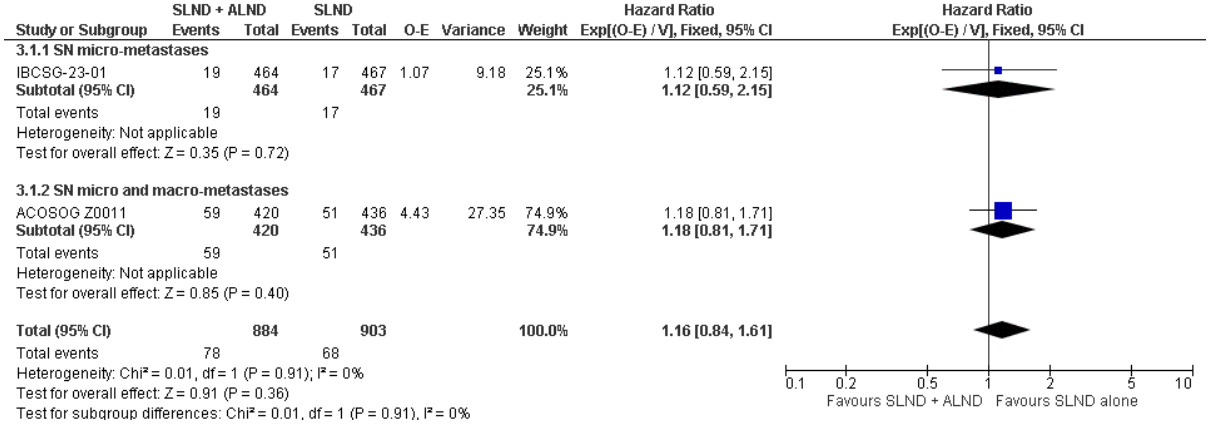


Figure 4: Disease-free survival in women with breast cancer and sentinel lymph node metastases at median follow-up of 5 to 9.3 years

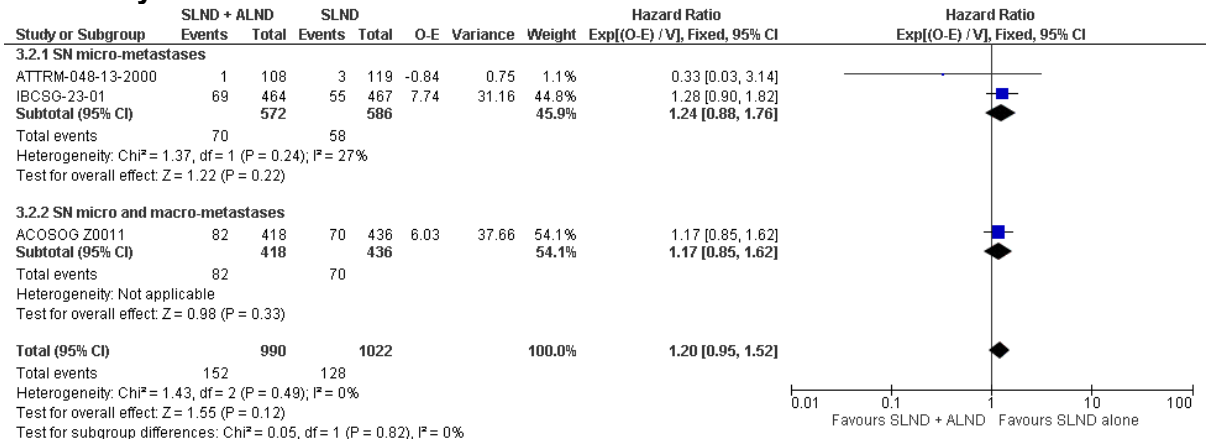


Figure 5: Breast cancer recurrence in the axilla in women with breast cancer and sentinel lymph node metastases at median follow-up of 5 to 9.3 years

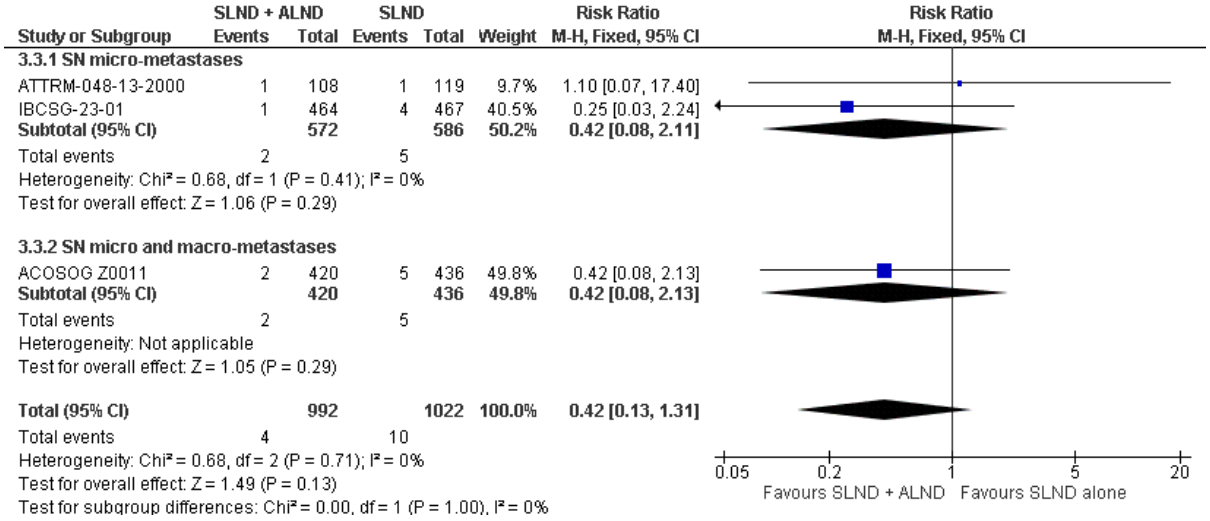


Figure 6: Local breast cancer recurrence in women with breast cancer and sentinel lymph node metastases at median follow-up of 5 to 9.3 years

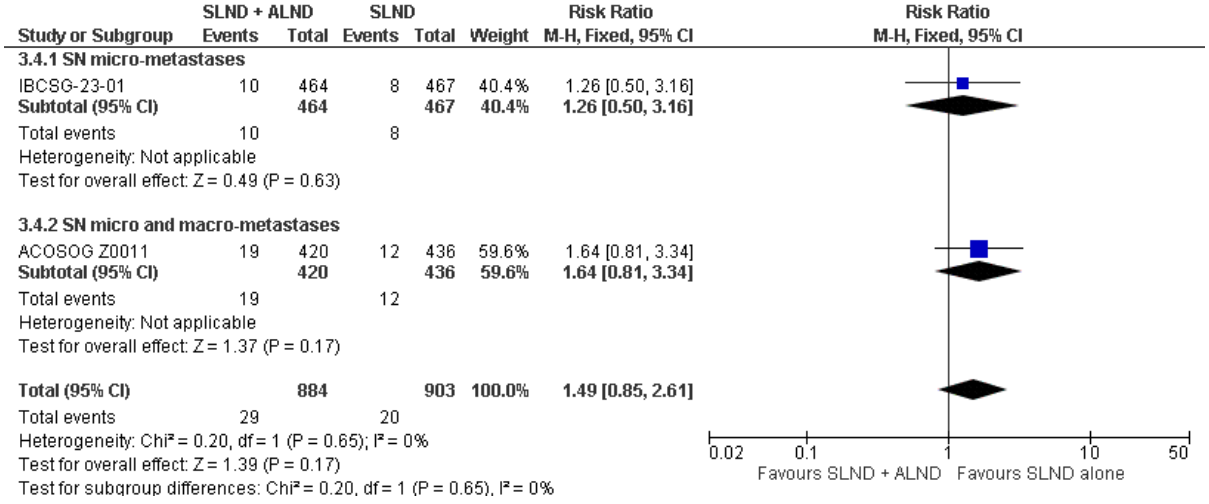


Figure 7: Distant breast cancer recurrence in women with breast cancer and sentinel lymph node metastases at median follow-up of 5 to 6 years

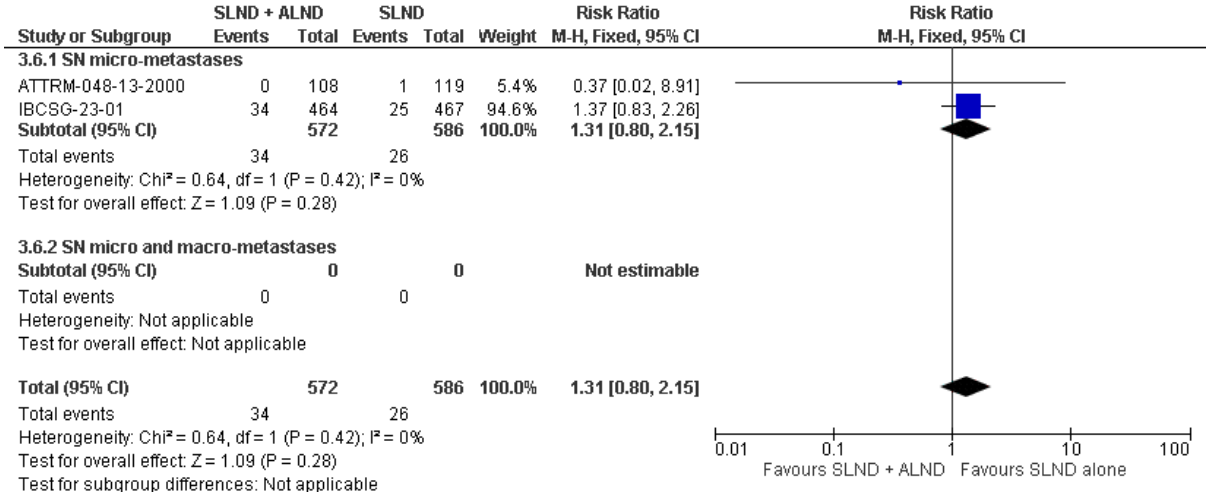


Figure 8: Short-term adverse events in women with breast cancer and sentinel lymph node micrometastases

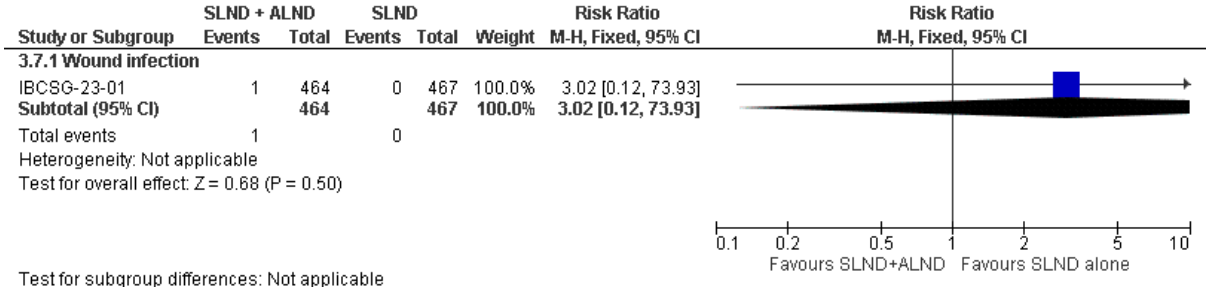


Figure 9: Short-term adverse events in women with breast cancer and sentinel lymph node micro or macro-metastases

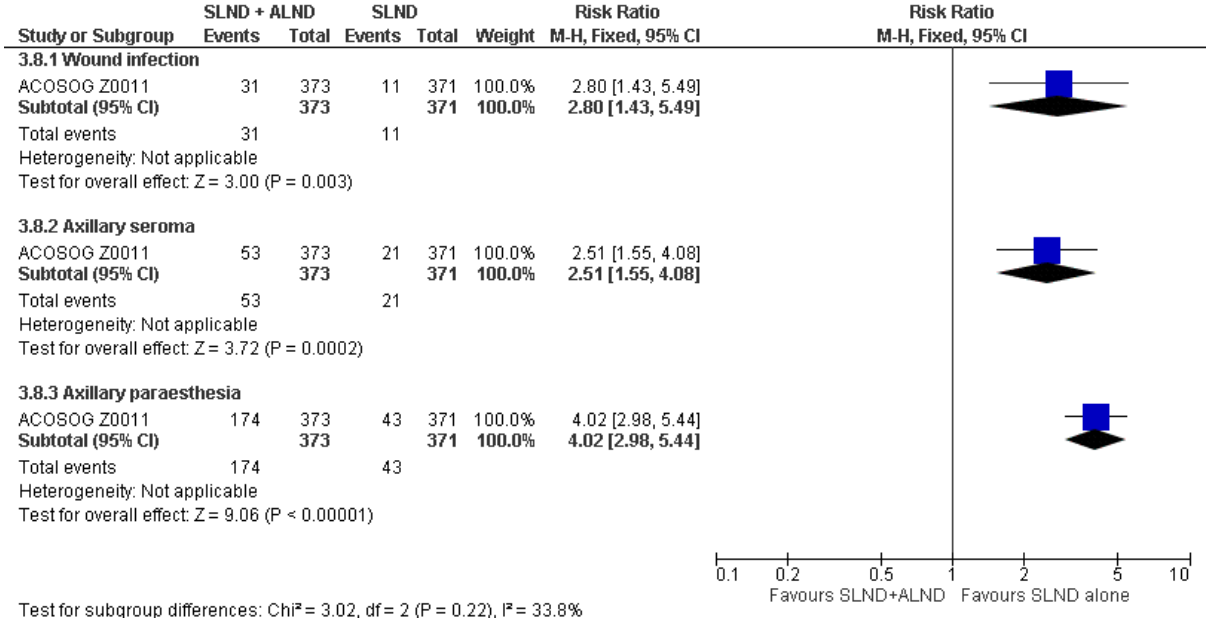


Figure 10: Long-term adverse events (at 12 or more months follow up) in women with breast cancer and sentinel lymph node micro-metastases

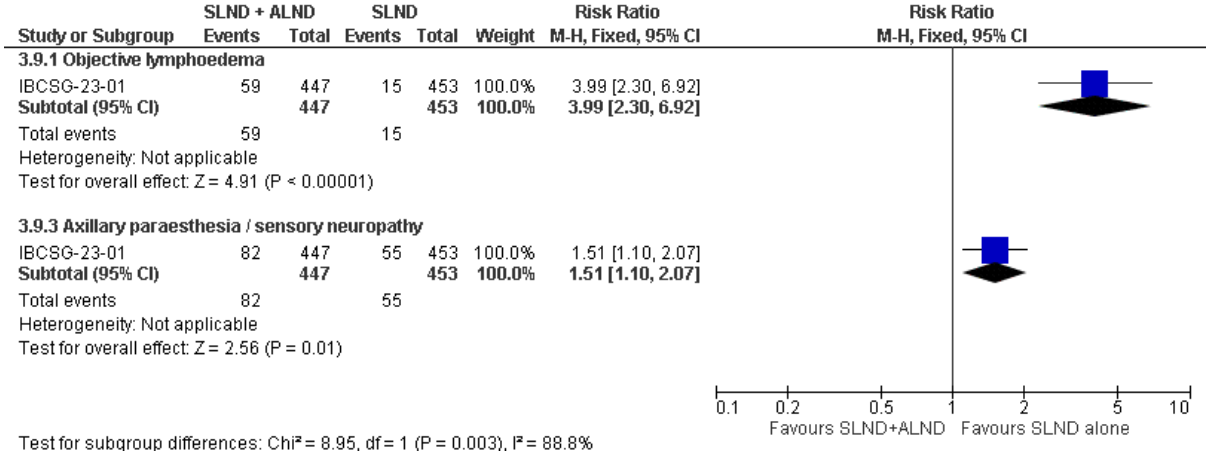


Figure 11: Long-term adverse events (at 12 or more months follow up) in women with breast cancer and sentinel lymph node micro or macro-metastases

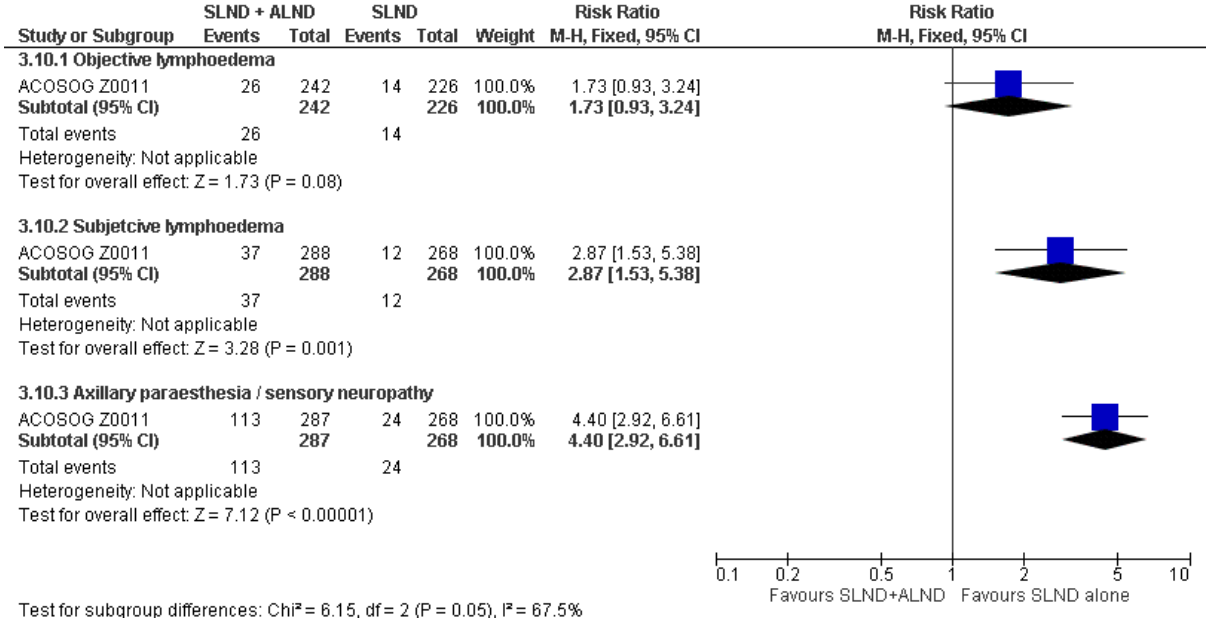


Figure 12: Disease-free survival in women with breast cancer and sentinel lymph node micro or macro-metastases at median follow-up 6 to 8 years

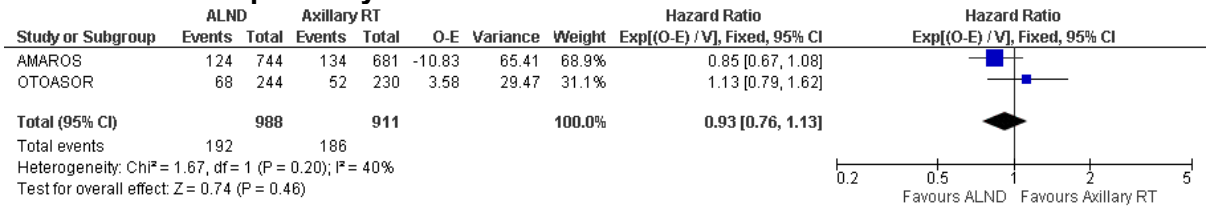
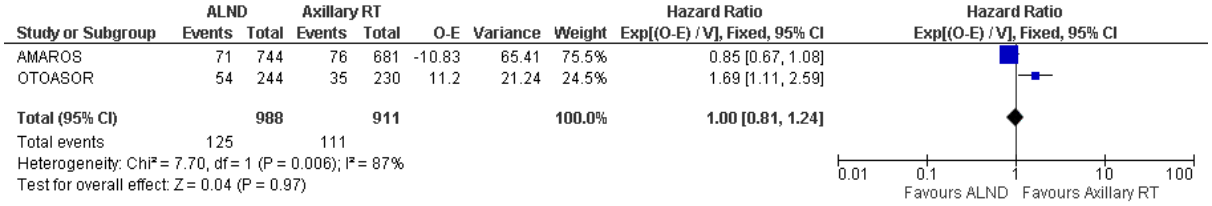


Figure 13: Axillary recurrence rates in women with breast cancer and sentinel lymph node micro or macro-metastases at median follow-up 6 to 8 years

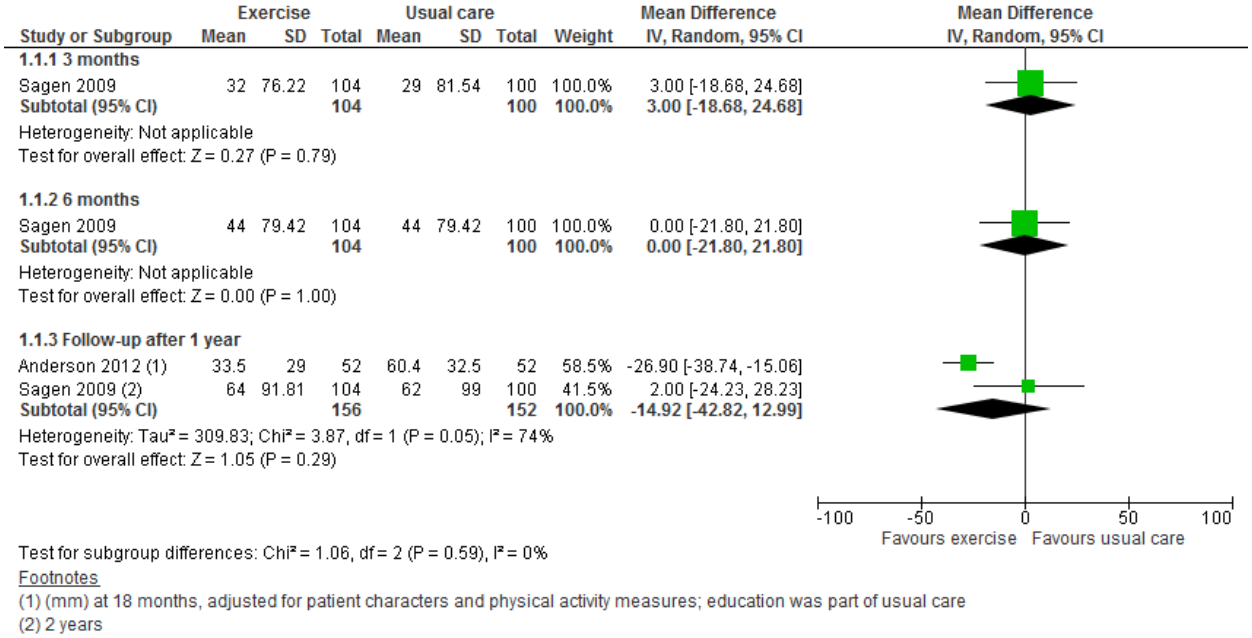
Figure 14: Overall survival in women with breast cancer and sentinel lymph node micro or macro-metastases at median follow-up 6 to 8 years



Forest plots for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Comparison 1: Exercise plus usual care versus usual care alone

Figure 15: Change in arm volume (ml)



Test for subgroup differences: Chi² = 1.06, df = 2 (P = 0.59), I² = 0%

Footnotes

(1) (mm) at 18 months, adjusted for patient characters and physical activity measures; education was part of usual care

(2) 2 years

Figure 16: Lymphoedema (exceeds BIS ratio)

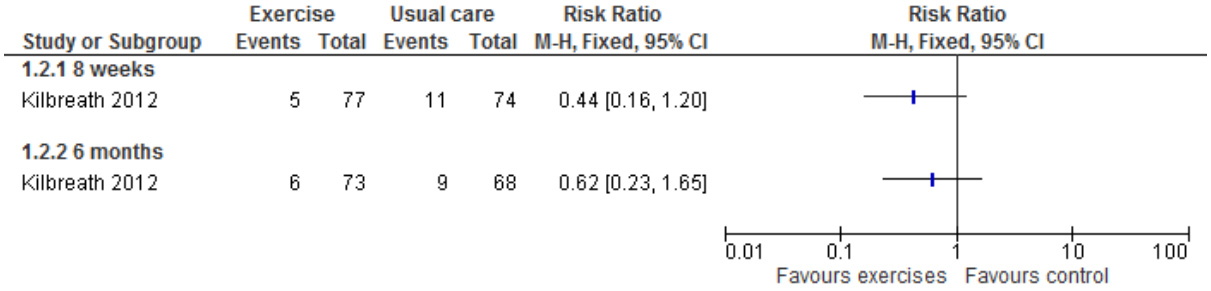
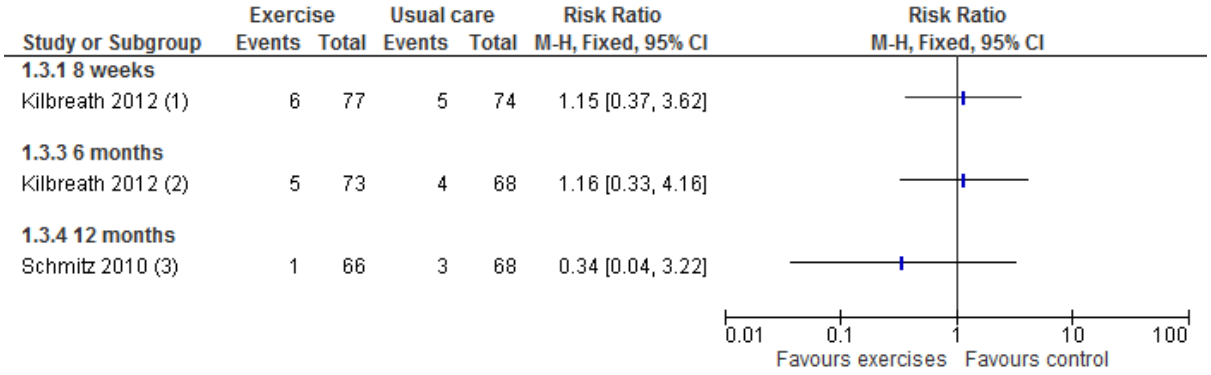
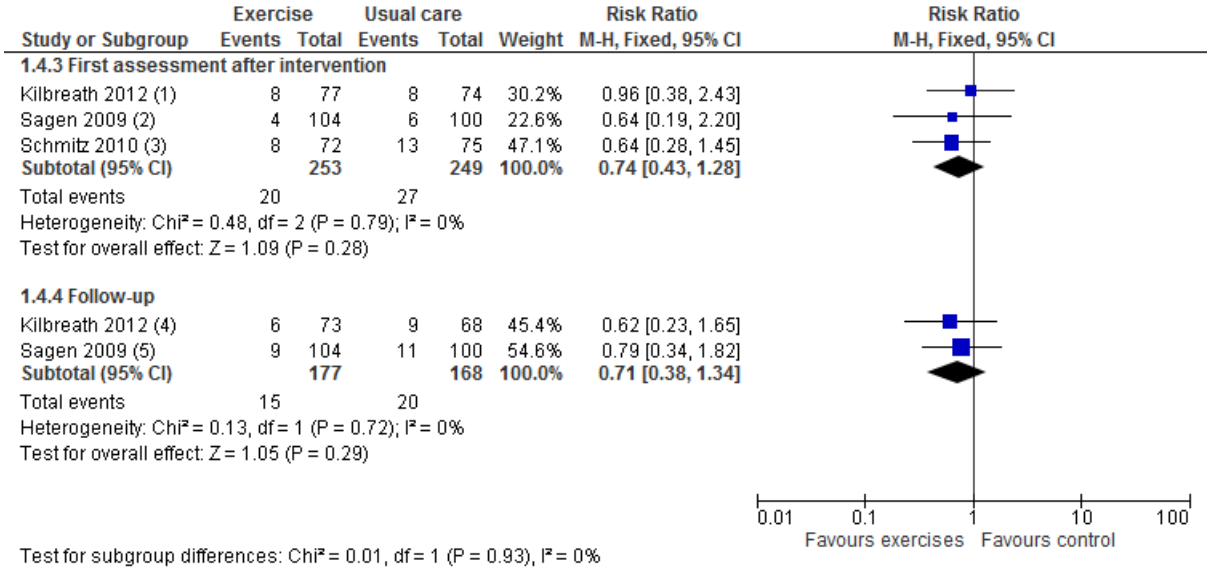


Figure 17: Lymphoedema (>2cm interlimb difference)



Footnotes
(1) post-intervention
(2) follow-up
(3) lymphedema assessed using Common Toxicity Criteria version 3.0 for interlimb differences, change in symptoms or...

Figure 18: Lymphoedema (≥10% difference)



Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%

Footnotes

(1) 8 weeks post-intervention
(2) 3 months (during intervention)
(3) >=5% change; post-intervention at 12 months
(4) 2 years follow-up
(5) 6 months follow-up

Figure 19: Function: leg press (lb)

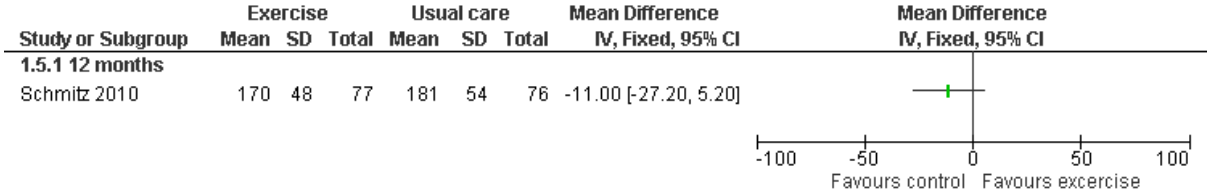


Figure 20: Function: bench press (lb)

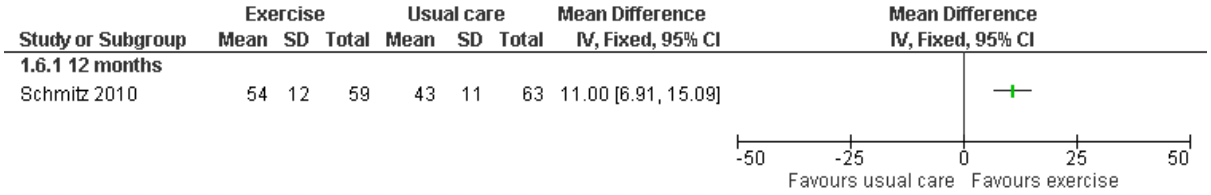


Figure 21: Forward flexion (range of motion, degrees) – change from baseline

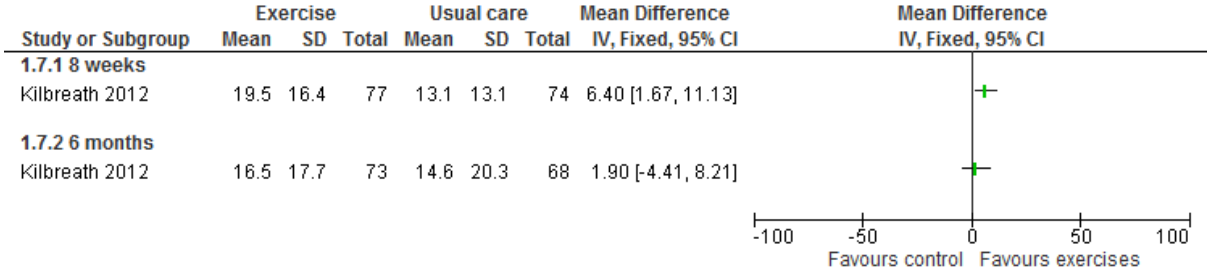


Figure 22: Abduction (range of motion, degrees) – change from baseline

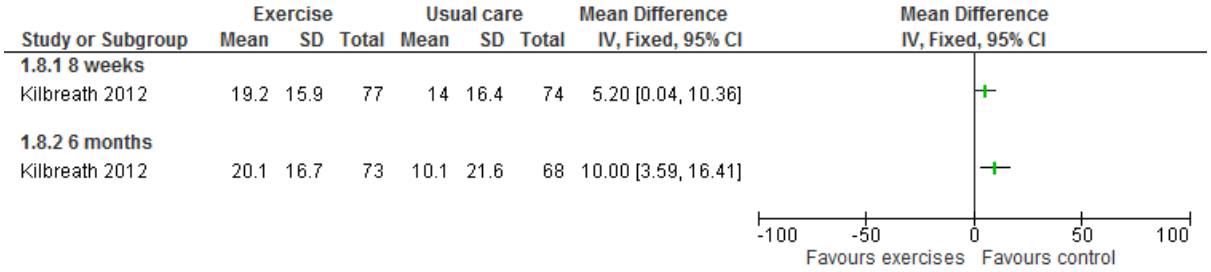
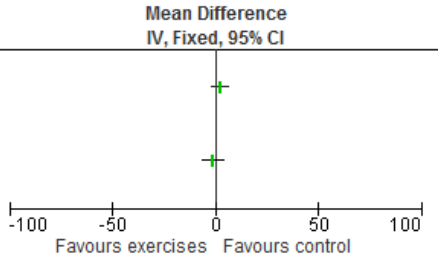


Figure 23: External rotation (range of motion, degrees) – change from baseline

Study or Subgroup	Exercise Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.9.1 8 weeks							
Kilbreath 2012	27.1	14.1	77	25	12.8	74	2.10 [-2.19, 6.39]
1.9.2 6 months							
Kilbreath 2012 (1)	0	15.1366	73	1.2	15.1366	68	-1.20 [-6.20, 3.80]



Footnotes
(1) mean and SD were imputated from provided MD with 95% CI

Figure 24: Horizontal extension (range of motion, degrees) – change from baseline

Study or Subgroup	Exercise Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.10.1 8 weeks							
Kilbreath 2012	9.2	14.6	77	6.8	14.4	74	2.40 [-2.23, 7.03]
1.10.2 6 months							
Kilbreath 2012	7.5	15.9	73	1.7	15.4	68	5.80 [0.63, 10.97]

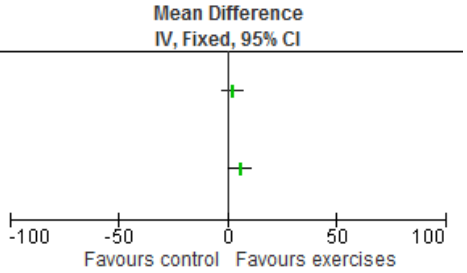


Figure 25: Abduction (strength, Newtons) – change from baseline

Study or Subgroup	Exercise Mean	SD	Total	Usual care Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.11.1 8 weeks							
Kilbreath 2012	25.9	32.3	77	15.7	28.6	74	10.20 [0.48, 19.92]
1.11.2 6 months							
Kilbreath 2012	23.4	38.4	73	20.4	31.5	68	3.00 [-8.56, 14.56]

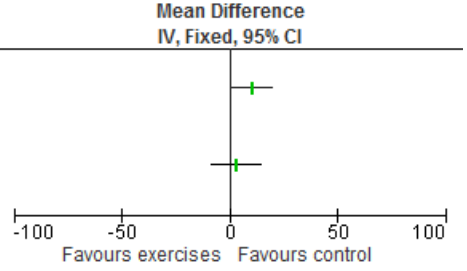


Figure 26: Forward flexion (strength, Newtons) – change from baseline

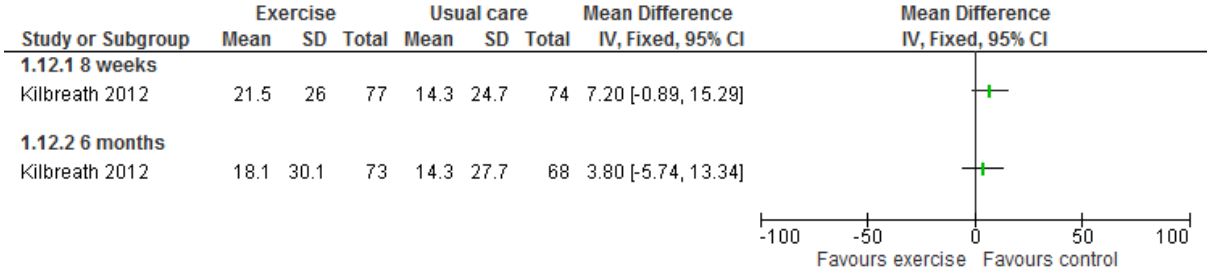


Figure 27: Horizontal extension (strength Newtons) – change from baseline

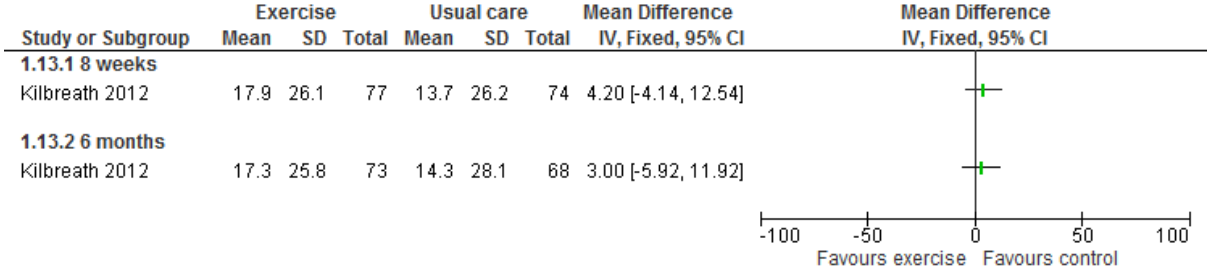


Figure 28: Horizontal flexion (strength Newtons) – change from baseline

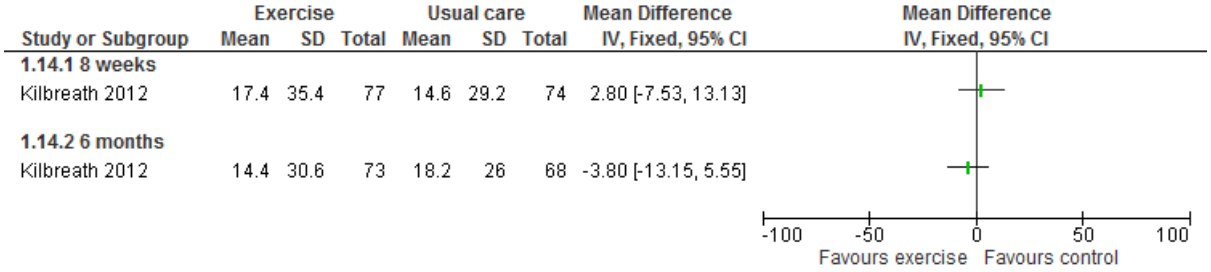
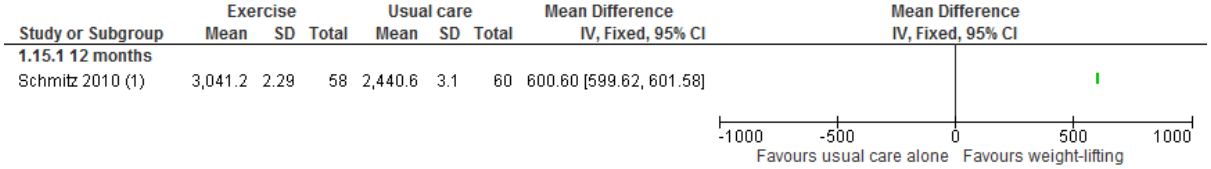
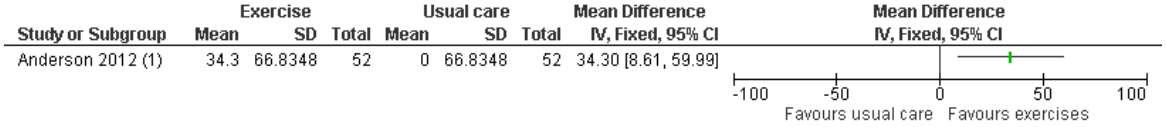


Figure 29: Physical activity (metabolic equivalent per week: MET-min/week)



Footnotes
(1) assessed by international physical activity questionnaires

Figure 30: Additional metres walked in 6 minutes



Footnotes
(1) Mean and SD were imputed from beta coefficient for execise group to give the additional meters walked compared to usual care

Figure 31: No pain (“0” VAS score)

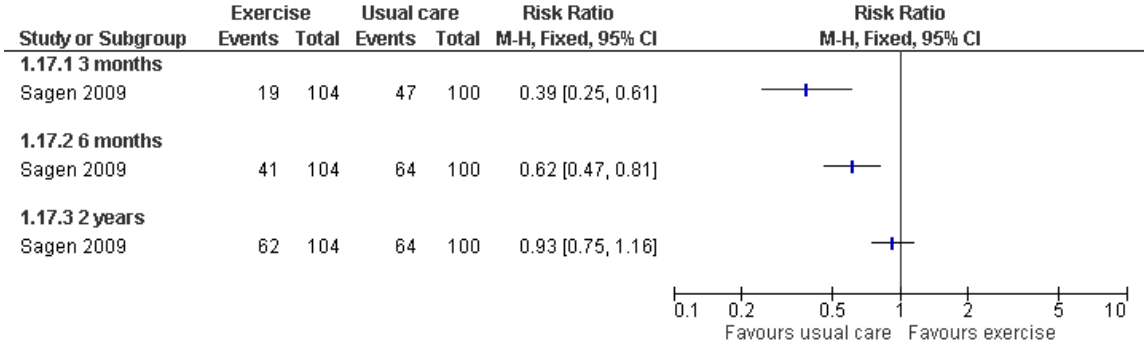


Figure 32: Change in number of symptoms reported

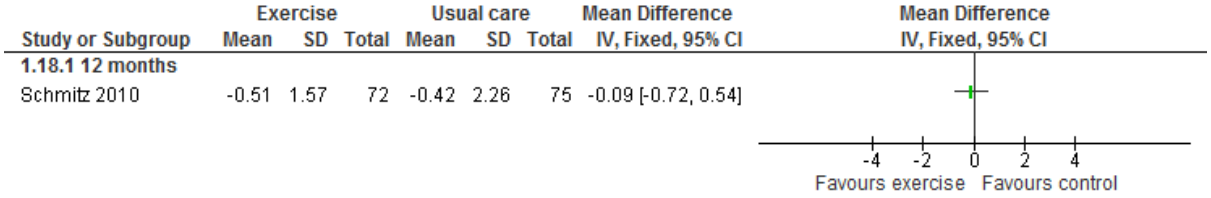


Figure 33: Change in symptom severity

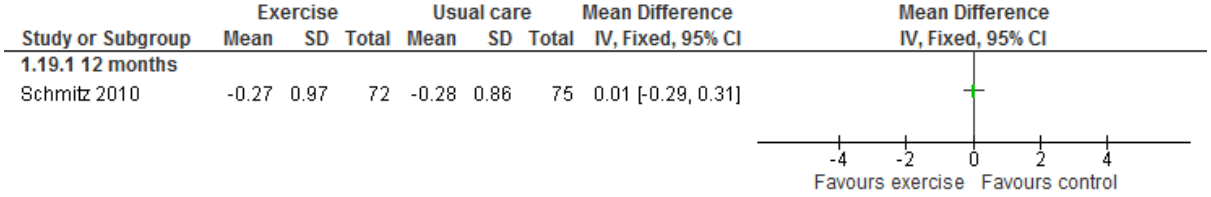
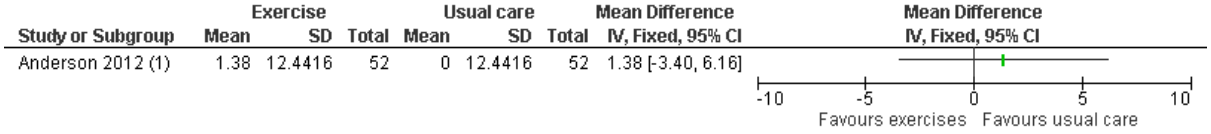


Figure 34: FACT-B score (effect of exercise)



Footnotes
(1) Mean and SD were imputed from given beta coefficent for the effect of excercise on FACT-B score

Figure 35: BR23 breast symptoms

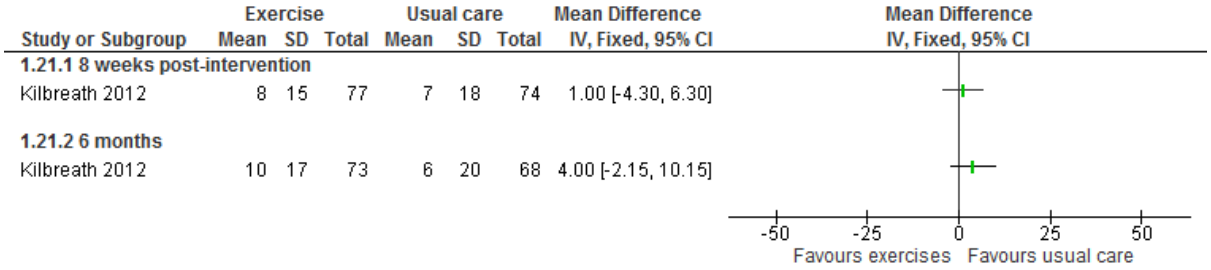
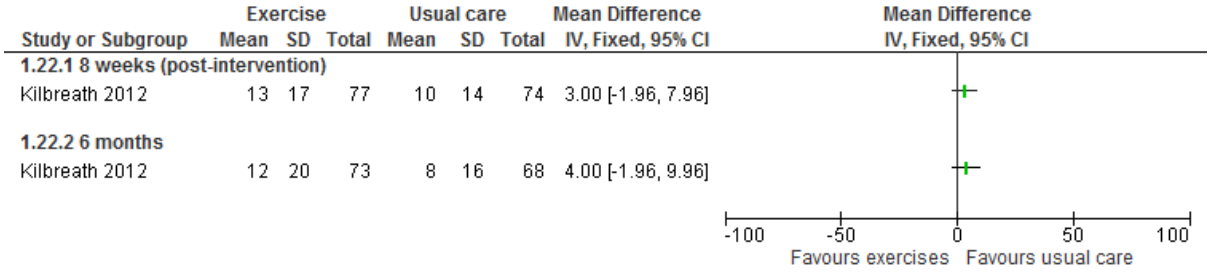
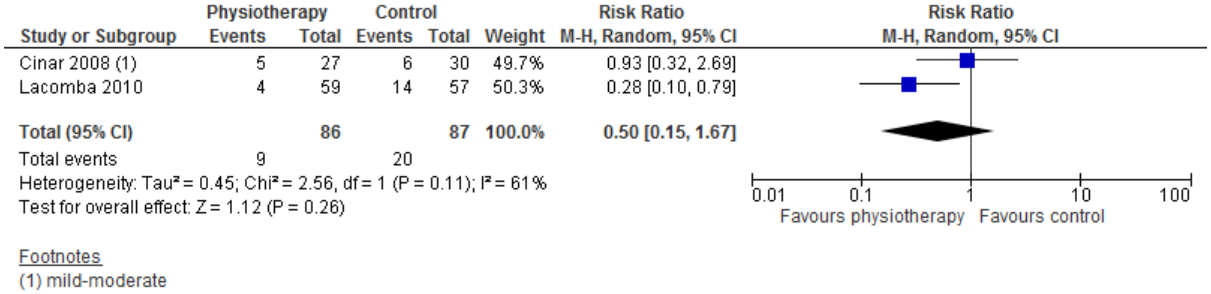


Figure 36: BR23 arm symptoms



Comparison 2: Physiotherapy versus control

Figure 37: Lymphoedema



Footnotes
(1) mild-moderate

Figure 38: Change in volume ratio (%) from baseline

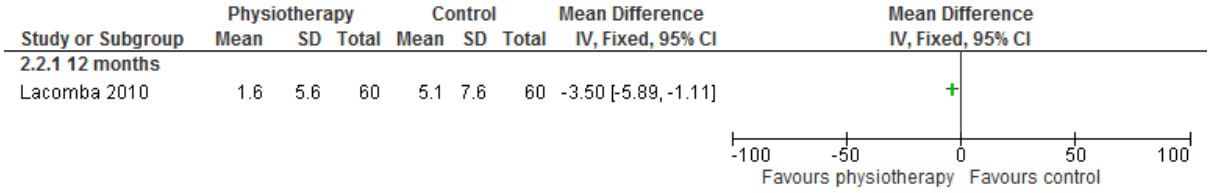


Figure 39: Change in circumferential difference (cm)

Study or Subgroup	Physiotherapy Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.3.1 6 months follow-up							
Cinar 2008	0.97	2.36	27	1.8	2.15	30	-0.83 [-2.01, 0.35]

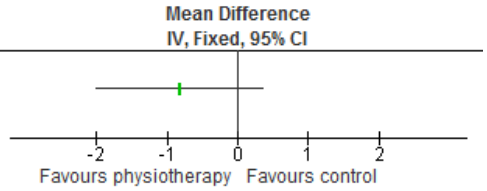


Figure 40: Arm function – flexion (degrees)

Study or Subgroup	Physiotherapy Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.4.1 6 months follow-up							
Cinar 2008	176.94	5.16	27	161.56	11.73	30	15.38 [10.75, 20.01]

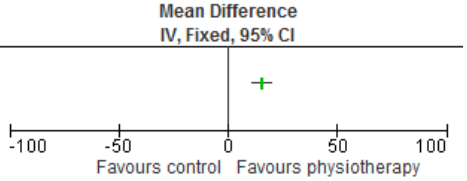


Figure 41: Arm function – extension (degrees)

Study or Subgroup	Physiotherapy Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.5.1 6 months follow-up							
Cinar 2008	77.17	6.87	27	74.54	8.23	30	2.63 [-1.29, 6.55]

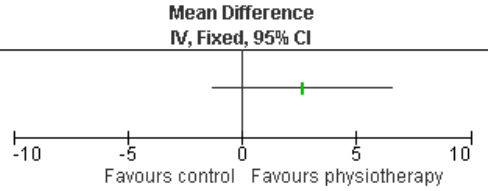
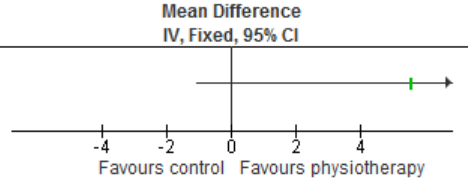


Figure 42: Arm function – internal rotation (degrees)

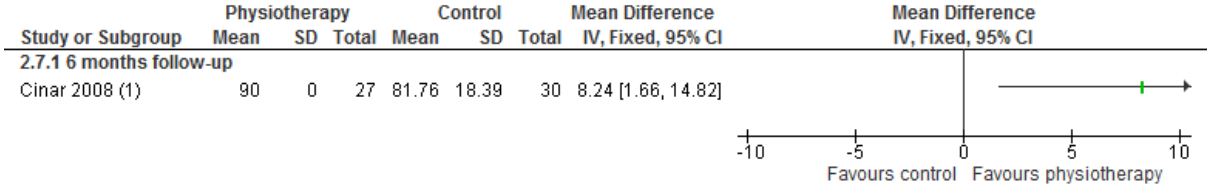
Study or Subgroup	Physiotherapy Mean	SD	Total	Control Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
2.6.1 6 months follow-up							
Cinar 2008 (1)	90	0.00001	27	84.45	18.54	30	5.55 [-1.08, 12.18]



Footnotes

(1) SD of intervention was "0" and 0.00001 was used for ease of interpretation.

Figure 43: Arm function – external rotation (degrees)



Footnotes
(1) SD of intervention was "0" and 0.00001 was used for ease of interpretation.

Figure 44: Arm function – adduction (degrees)

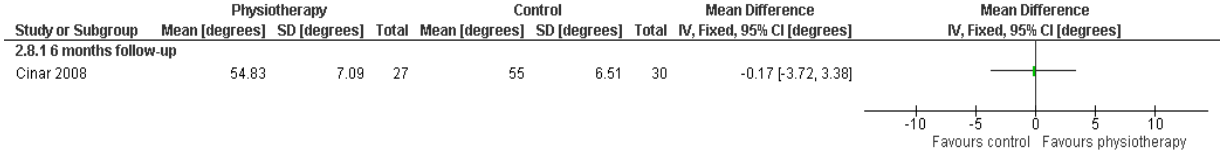


Figure 45: Arm function – abduction (degrees)

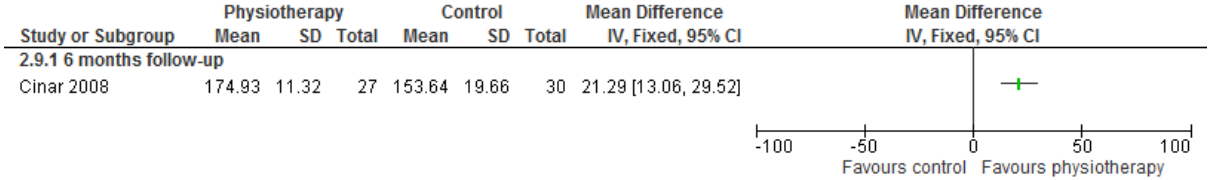
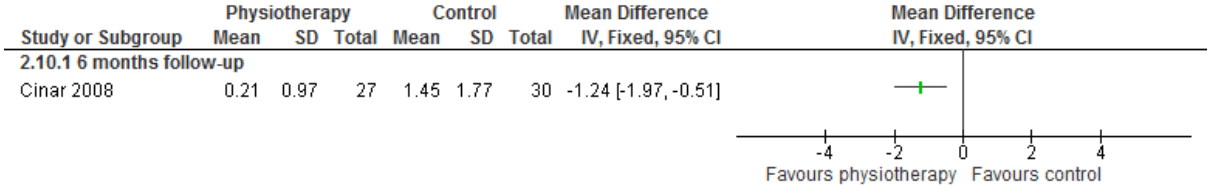
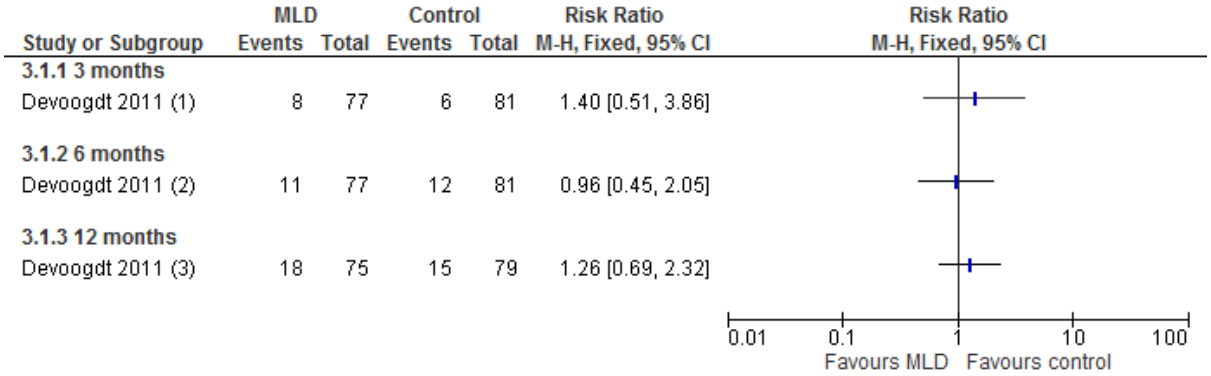


Figure 46: Arm function – functional questionnaire score



Comparison 3: Manual lymph drainage versus usual care

Figure 47: Lymphoedema (≥200ml increase)



Footnotes
(1) >=200 ml increase from baseline
(2) >=200 ml increase from baseline
(3) >=200 ml increase from baseline

Figure 48: Lymphoedema (≥2cm increase)

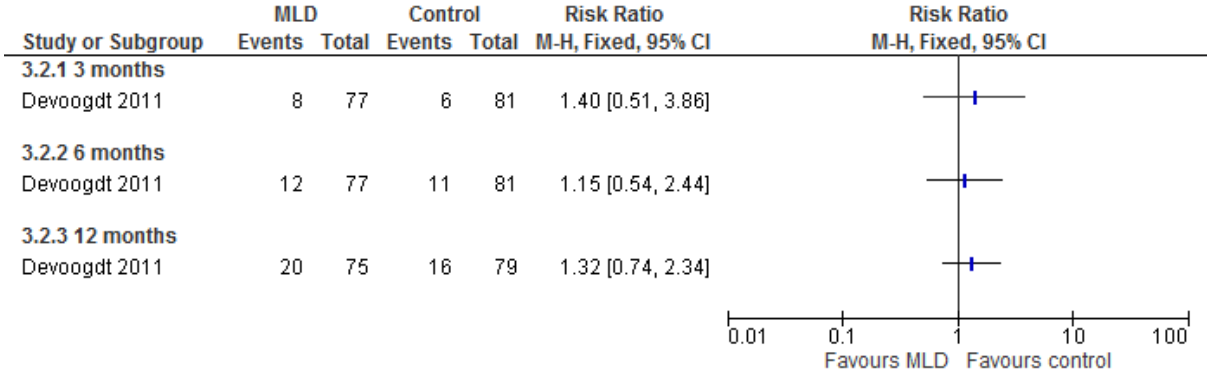


Figure 49: Change in arm volume (ml) – MLD plus prevention guidelines and exercise versus Prevention guidelines and exercise

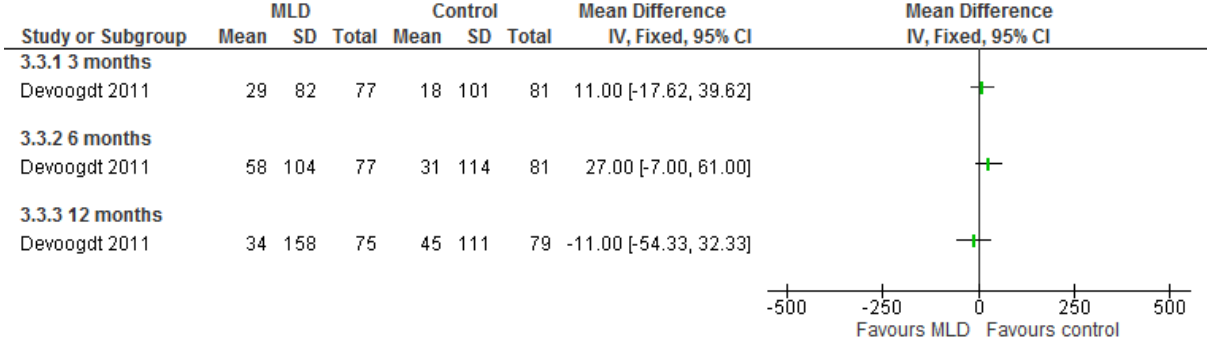


Figure 50: Change in arm volume (ml) – MLD plus physiotherapy versus Physiotherapy alone

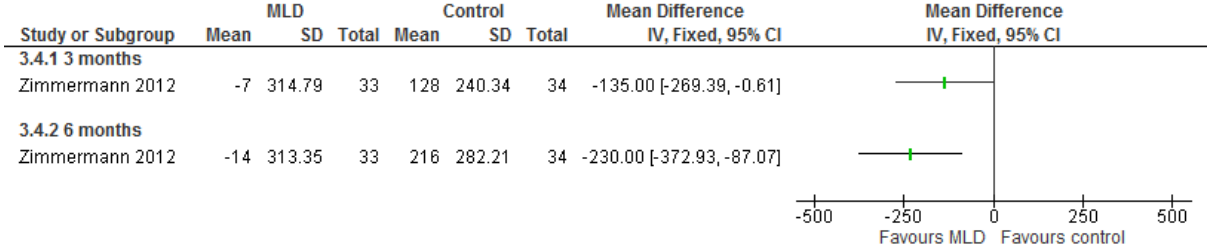


Figure 51: Mental HRQoL (scale 0 to 100, higher better)

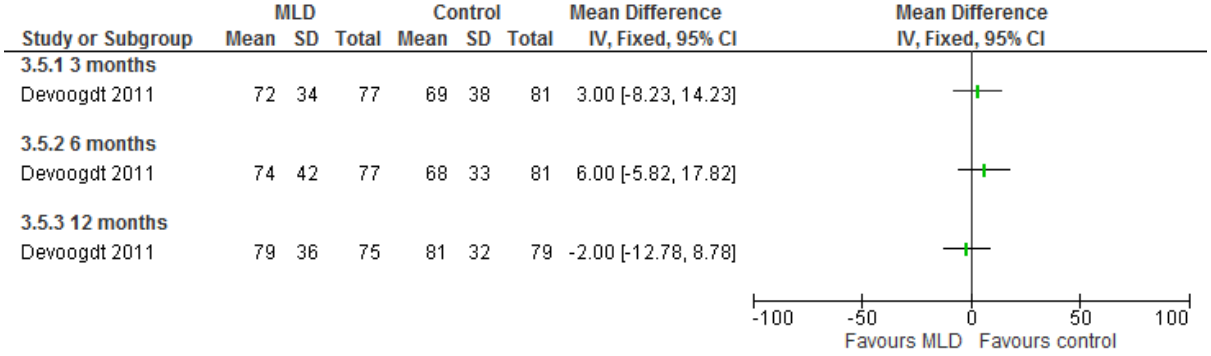
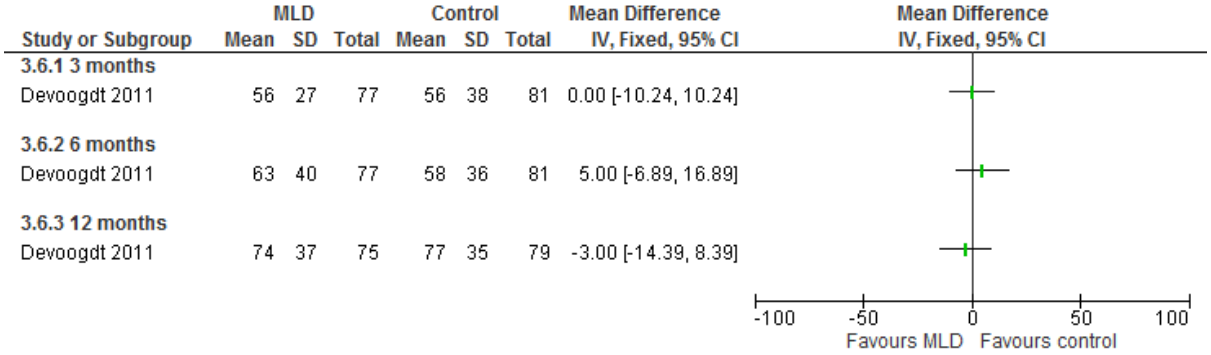
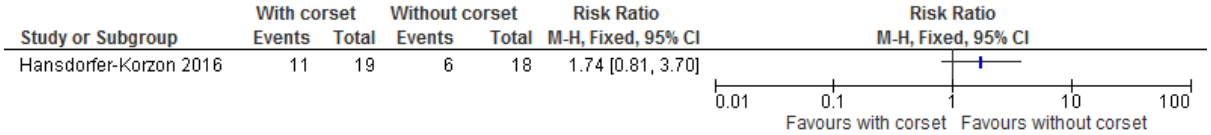


Figure 52: Physical HRQoL (scale 0 to 100, higher better)



Comparison 4: Compression corset versus no compression corset

Figure 53: Number of women with pain reduction



Comparison 5: Yoga plus exercise versus exercise alone

Figure 54: Change in arm function (FACT-B+4 arm subscale scored 0-20, higher better)

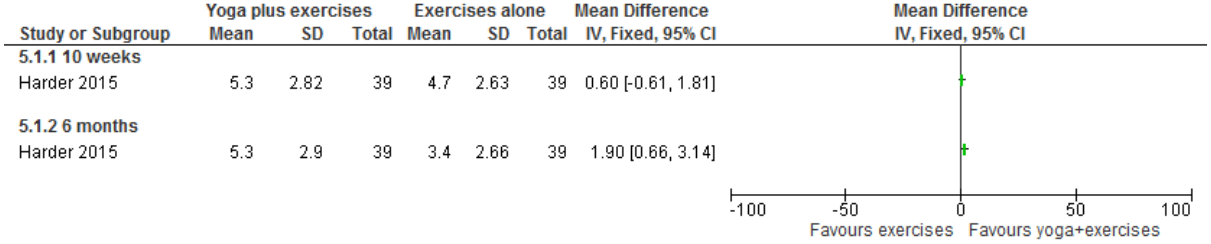


Figure 55: Change in QuickDASH score (QuickDASH is scored 0-100, lower better)

Study or Subgroup	Yoga plus exercises Mean	SD	Total	Exercises alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.2.1 10 weeks							
Harder 2015	-30.4	12.25	39	-28	11.85	39	-2.40 [-7.75, 2.95]
5.2.2 6 months							
Harder 2015	-31.3	12.27	39	-27.8	11.11	39	-3.50 [-8.69, 1.69]

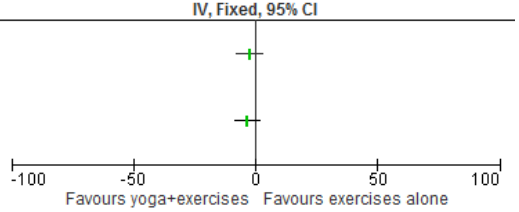


Figure 56: Change in level of pain (on a scale 0 to 10, lower better)

Study or Subgroup	Yoga plus exercises Mean	SD	Total	Exercises alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.3.1 10 weeks							
Harder 2015	-2	1.56	39	-1.5	1.3	39	-0.50 [-1.14, 0.14]
5.3.2 6 months							
Harder 2015	-1.5	1.61	39	-0.1	1.5	39	-1.40 [-2.09, -0.71]

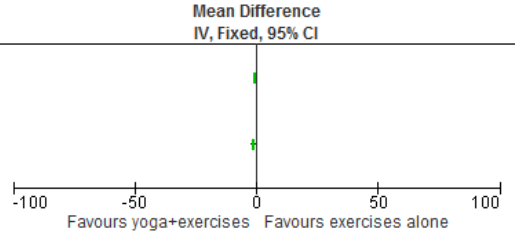


Figure 57: Change in Oxford shoulder score (on a scale 0 to 60, lower better)

Study or Subgroup	Yoga plus exercises Mean	SD	Total	Exercises alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.4.1 10 weeks							
Harder 2015	-9.6	5.48	39	-10	5.22	39	0.40 [-1.98, 2.78]
5.4.2 6 months							
Harder 2015	-10.7	5.59	39	-9.3	5.18	39	-1.40 [-3.79, 0.99]

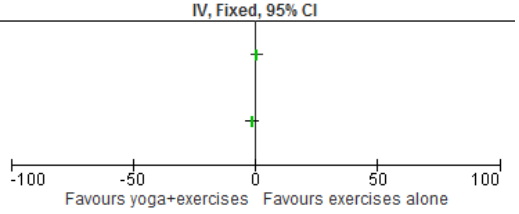
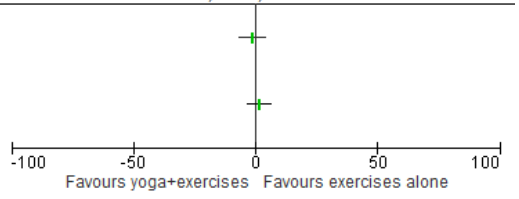


Figure 58: Change in FACT-B score (on a scale 0 to 112, lower better)

Study or Subgroup	Yoga plus exercises Mean	SD	Total	Exercises alone Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
5.5.1 10 weeks							
Harder 2015	9.7	12.68	39	11	10.83	39	-1.30 [-6.53, 3.93]
5.5.2 6 months							
Harder 2015	14.4	11.82	39	13.1	10.26	39	1.30 [-3.61, 6.21]



Comparison 6: Education versus no education

Figure 59: Lymphoedema (inter-limb circumference difference of 2cm or more)

Study or Subgroup	With education Events	Total	Without education Events	Total	Risk Ratio M-H, Random, 95% CI
6.1.1 Stage 1					
Lu 2015	65	101	42	77	1.18 [0.92, 1.52]
6.1.2 Stage 2 or 3					
Lu 2015	36	101	35	77	0.78 [0.55, 1.12]

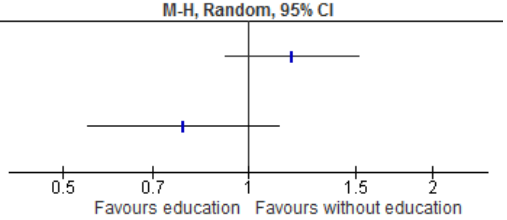
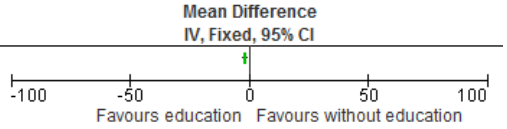


Figure 60: Frequency of self-reported lymphoedema symptoms

Study or Subgroup	With education Mean	SD	Total	Without education Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
Fu 2010 (1)	2.58	2.38	77	4.26	3	59	-1.68 [-2.61, -0.75]



Footnotes
(1) adjusted for mastectomy, lympectomy, radiation, chemotherapy and number of lymph nodes removed

Figure 61: DASH disability score (0 to 100, lower better)

Study or Subgroup	With education Mean	SD	Total	Without education Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
6.3.1 ALND							
Sato 2014	10.5	8.7	39	10.4	8.1	30	0.10 [-3.88, 4.08]
6.3.2 SLNB							
Sato 2014	7.4	11.8	51	5.6	6.1	29	1.80 [-2.13, 5.73]

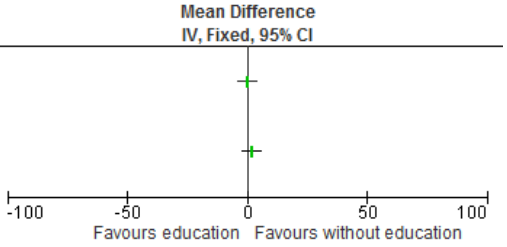


Figure 62: Change in upper arm girth at 3 months (difference between arms, cm)

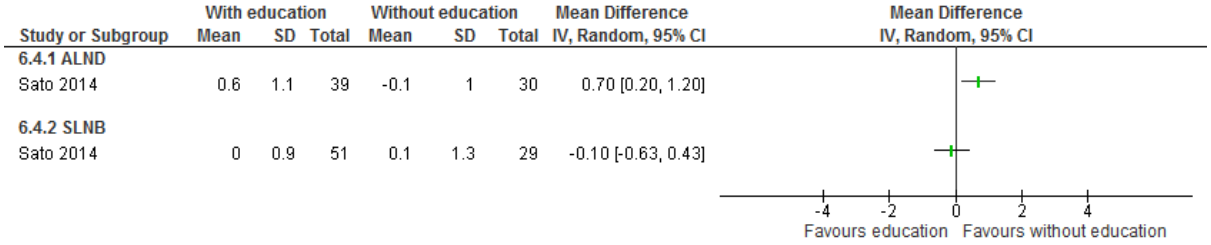


Figure 63: Change in shoulder at flexion (degrees) at 3 months

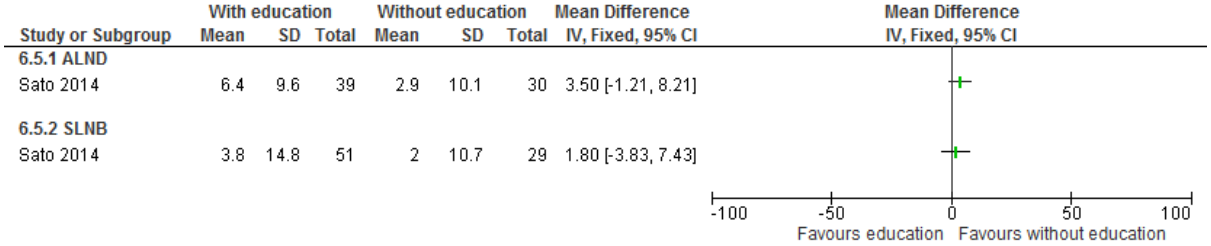


Figure 64: Change in shoulder abduction (degrees) at 3 months

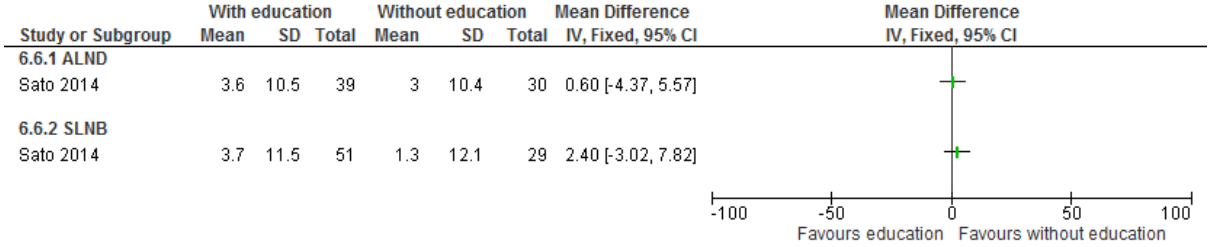


Figure 65: Change in horizontal shoulder extension (degrees) at 3 months

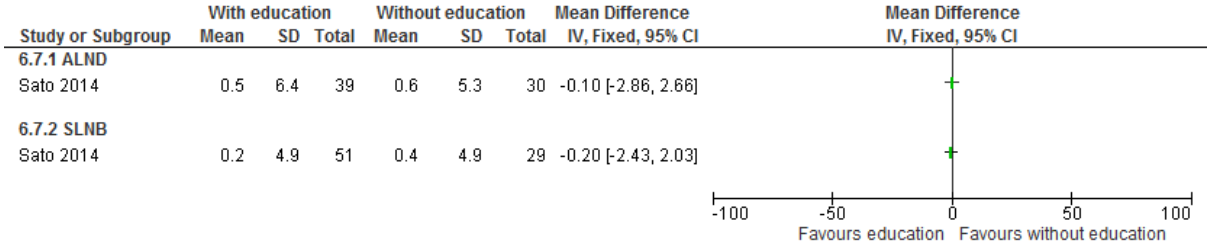
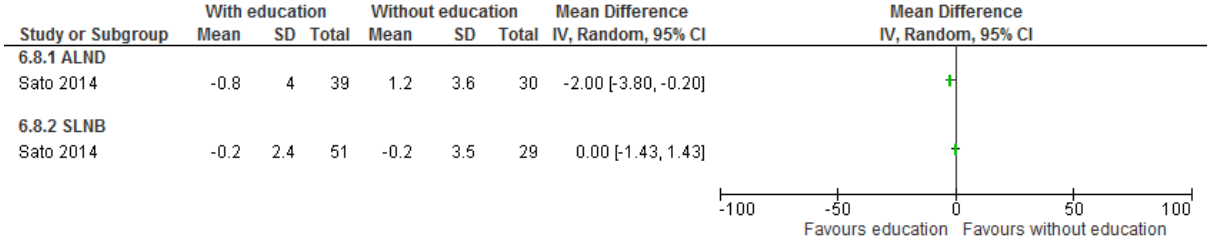


Figure 66: Change in grip strength at 3 months (difference between arms, Newtons)



Appendix F – GRADE tables

GRADE tables for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Table 16: Clinical evidence profile: Comparison 1.1. SLND + ALND versus SLND in people with breast cancer with sentinel lymph node micrometastases

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLND+ ALND	SLND	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (follow-up median 5 years; HR < 1 favours ALND)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	19/464 (4.1%)	17/467 (3.6%)	HR 1.12 (0.59 to 2.15)	SLND alone 98% OS at 5 years, with SLND+ALND 98% OS at 5 years (96% to 99%)	LOW	IMPORTANT
Disease-free survival (follow-up median 5 years; HR < 1 favours ALND)												
2	Randomised trials	Serious[1]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[3]	None	70/572 (12.2%)	58/586 (9.9%)	HR 1.24 (0.88 to 1.73)	SLND alone 88% DFS at 5 years, with SLND+ALND 85% DFS at 5 years (80% to 89%)	VERY LOW	IMPORTANT
Breast cancer recurrence in the axilla (follow-up median 5 years; RR < 1 favours ALND)												
2	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	2/572 (0.35%)	5/586 (0.85%)	RR 0.42 (0.08 to 2.11)	5 fewer per 1000 (from 8 fewer to 9 more)	VERY LOW	CRITICAL
Local breast cancer recurrence (follow-up median 5 years RR < 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	10/464 (2.2%)	8/467 (1.7%)	RR 1.26 (0.50 to 3.16)	4 more per 1000 (from 9 fewer to 37 more)	VERY LOW	CRITICAL
Distant breast cancer recurrence (follow-up median 5 years RR < 1 favours ALND)												
2	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	34/572 (5.9%)	26/586 (4.4%)	RR 1.31 (0.8 to 2.15)	14 more per 1000 (from 9 fewer to 51 more)	VERY LOW	IMPORTANT
Short-term adverse events - wound infection (follow-up 30 days RR < 1 favours ALND)												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLND+ ALND	SLND	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious imprecision[3,4]	None	1/464 (0.22%)	0/467 (0%)	RR 3.02 (0.12 to 73.93)	-	VERY LOW	CRITICAL
Long term adverse events - objective lymphoedema (follow-up 12 months RR < 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	59/447 (13.2%)	15/453 (3.3%)	RR 3.99 (2.30 to 6.92)	99 more per 1000 (from 43 more to 196 more)	VERY LOW	CRITICAL
Long term adverse events) - Axillary paraesthesia / sensory neuropathy (follow-up 12 months RR < 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	82/447 (18.3%)	55/453 (12.1%)	RR 1.51 (1.10 to 2.07)	62 more per 1000 (from 12 more to 130 more)	VERY LOW	CRITICAL

ALND, axillary lymph node clearance; HR, hazard ratio; RR, risk ratio; SLND, sentinel lymph node dissection
[1] Unclear or inadequate allocation concealment. Not blinded, but this is unlikely to influence survival outcomes.
[2] Unclear or inadequate allocation concealment. No blinding - potential risk of detection bias.
[3] <300 events.
[4] 95% confidence interval crosses boundary for no effect (1) and minimally important difference
[5] Downgraded one level for indirectness - disease free survival was a composite outcome defined as time to death or first recurrence of breast cancer

Table 17: Clinical evidence profile: Comparison 1.2. SLND + ALND versus SLND in people with breast cancer with sentinel lymph node micro or macro-metastases

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLND + ALND	SLND	Relative (95% CI)	Absolute	Quality	Importance
Overall survival (follow-up median 9.3 years; HR > 1 favours ALND)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	59/420 (14.0%)	51436 (11.7%)	HR 1.18 (0.81 to 1.61)	SLND 86% OS at 10 years; SLND+ALND 84% OS at 10 years (79% to 87%)	LOW	IMPORTANT
Disease-free survival (follow-up median 9.3 years; HR > 1 favours ALND)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLND + ALND	SLND	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[1]	No serious inconsistency	Serious indirectness[5]	Serious imprecision[3]	None	82/418 (19.6%)	73/435 (16.8%)	HR 1.17 (0.85 to 1.62)	SLND 80% DFS at 10 years; SLND+ALND 78% DFS at 5 years (74% to 82%)	VERY LOW	IMPORTANT
Breast cancer recurrence in the axilla (follow-up median 9.3 years; RR > 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	2/420 (0.48%)	5/436 (1.1%)	RR 0.42 (0.08 to 2.13)	7 fewer per 1000 (from 11 fewer to 13 more)	VERY LOW	CRITICAL
Local breast cancer recurrence (follow-up median 9.3 years; RR > 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	19/420 (4.5%)	12/436 (2.8%)	RR 1.64 (0.81 to 3.34)	18 more per 1000 (from 5 fewer to 64 more)	VERY LOW	CRITICAL
Short term adverse events - Wound infection (follow-up 30 days; RR > 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	31/373 (8.3%)	11/371 (3%)	RR 2.80 (1.43 to 5.49)	53 more per 1000 (from 13 more to 133 more)	VERY LOW	CRITICAL
Short term adverse events - Axillary seroma (follow-up 30 days; RR > 1 favours ALND)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	53/373 (14.2%)	21/371 (5.7%)	RR 2.51 (1.55 to 4.08)	85 more per 1000 (from 31 more to 174 more)	VERY LOW	CRITICAL
Short term adverse events - Axillary paraesthesia (follow-up 30 days)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	174/373 (46.6%)	43/371 (11.6%)	RR 4.02 (2.98 to 5.44)	350 more per 1000 (from 229 more to 515 more)	VERY LOW	CRITICAL
Long term adverse events - Objective lymphoedema (follow-up 12 months)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	SLND + ALND	SLND	Relative (95% CI)	Absolute		
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Very serious imprecision[3,4]	None	26/242 (10.7%)	14/226 (6.2%)	RR 1.73 (0.93 to 3.24)	45 more per 1000 (from 4 fewer to 139 more)	VERY LOW	CRITICAL
Long term adverse events - Subjective lymphoedema (follow-up 12 months)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	37/288 (12.8%)	12/268 (4.5%)	RR 2.87 (1.53 to 5.38)	84 more per 1000 (from 24 more to 196 more)	VERY LOW	CRITICAL
Long term adverse events) - Axillary paraesthesia / sensory neuropathy (follow-up 12 months)												
1	Randomised trials	Very serious[2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	113/287 (39.4%)	24/268 (9%)	RR 4.40 (2.92 to 6.61)	304 more per 1000 (from 172 more to 502 more)	VERY LOW	CRITICAL

ALND, axillary lymph node clearance; HR, hazard ratio; RR, risk ratio; SLND, sentinel lymph node dissection
[1] Unclear or inadequate allocation concealment. Not blinded, but this is unlikely to influence survival outcomes.
[2] Unclear or inadequate allocation concealment. No blinding - potential risk of detection bias.
[3] <300 events.
[4] 95% confidence interval crosses boundary for no effect (1) and minimally important difference
[5] Downgraded one level for indirectness - disease free survival was a composite outcome defined as time to death or first recurrence of breast cancer

Table 18: Clinical evidence profile: Comparison 2. ALND versus axillary radiotherapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALND	Axillary RT	Relative (95% CI)	Absolute		
Overall survival (median follow-up 6.1 to 8 years; HR < 1 favours ALND)												
2	Randomised trials	No serious risk of bias	Very serious inconsistency[5]	No serious indirectness	Serious imprecision[3]	None	125/988 (12.7%)	111/911 (12.2%)	HR 1.00 (0..81 to 1.24)	5yr OS 93% with art vs 93% (91% to	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ALND	Axillary RT	Relative (95% CI)	Absolute		
										94%) with ALND		
Disease free survival (median follow-up 6.1 years; HR < 1 favours ALND)												
2	Randomised trials	Serious[1]	No serious inconsistency	Serious indirectness[6]	Serious imprecision[3]	None	192/988 (19.4%)	186/911 (20.4%)	HR 0.93 (0..76 to 1.13)	5yr DFS 83% with art vs 84% (74% to 87%) with ALND	VERY LOW	IMPORTANT
Breast cancer recurrence in the axilla (median follow-up 6.1 years; RR < 1 favours ALND)												
2	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	9/988 (0.9%)	11/811 (1.4%)	RR 0.58 (0.24 to 1.42)	6 fewer per 1000 (from 10 fewer to 6 more)	LOW	CRITICAL
Long-term adverse events - lymphoedema (follow-up 12 months; assessed with: Arm circumference increase > 10%; RR < 1 favours ALND)												
1	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	32/410 (7.8%)	24/410 (5.9%)	RR 1.33 (0.80 to 2.22)	19 more per 1000 (from 12 fewer to 71 more)	VERY LOW	CRITICAL
Long-term adverse events - lymphoedema (follow-up 12 months; assessed with: clinical signs; RR < 1 favours ALND)												
1	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	Serious imprecision[3]	None	114/410 (28%)	62/410 (15%)	RR 1.84 (1.39 to 2.43)	127 more per 1000 (from 59 more to 216 more)	VERY LOW	CRITICAL
Long term adverse events - shoulder motion (follow-up 12 months; assessed with: Range of motion in 4 excursions compared between arms; RR < 1 favours ALND)												
1	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	-	LOW	CRITICAL
Quality of life (assessed with: EORTC-QLQ-C30 and QLQ-BR23)												
1	Randomised trials	Very serious[1,2]	No serious inconsistency	No serious indirectness	No serious imprecision	None	-	-	-	-	LOW	CRITICAL

ALND, axillary lymph node clearance; EORTC, European Organisation for Research and Treatment of Cancer; HR, hazard ratio; RR, risk ratio; RT, radiotherapy

[1] No blinding - risk of detection bias

[2] Progressively higher rates of attrition with longer follow up - risk of attrition bias

[3] *<300 events.*
[4] *95% confidence interval crosses boundary for no effect (1) and minimally important difference*
[5] *I2> 80%; random effects model not possible*
[6] *Downgraded one level for indirectness - disease free survival was a composite outcome defined as time to death or first recurrence of breast cancer*

GRADE tables for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Table 9: Clinical evidence profile: Comparison 1: Exercise plus usual care versus usual care alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute	Quality	Importance
Change in arm volume - 3 months (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[7]	None	104	100	-	MD 3 higher (18.68 lower to 24.68 higher)	MODERATE	CRITICAL
Change in arm volume - 6 months (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias[1]	No serious inconsistency	No serious indirectness	Serious[7]	None	104	100	-	MD 0 higher (21.8 lower to 21.8 higher)	MODERATE	CRITICAL
Change in arm volume - Follow-up after 1 year (Better indicated by lower values)												
2	Randomised trials	Serious[1,2]	No serious inconsistency	No serious indirectness	Serious[7]	None	156	152	-	MD 22.01 lower (32.8 to 11.22 lower)	LOW	CRITICAL
Lymphoedema (Exceeds BIS ratio) - 8 weeks												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[4]	None	5/77 (6.5%)	11/74 (14.9%)	RR 0.44 (0.16 to 1.2)	83 fewer per 1000 (from 125 fewer to 30 more)	VERY LOW	CRITICAL
Lymphoedema (Exceeds BIS ratio) - 6 months												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	6/73 (8.2%)	9/68 (13.2%)	RR 0.62 (0.23 to 1.65)	50 fewer per 1000 (from 102 fewer to 86 more)	VERY LOW	CRITICAL
Lymphoedema (>2 cm interlimb circumference) - 8 weeks												

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute	Quality	Importance
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	6/77 (7.8%)	5/74 (6.8%)	RR 1.15 (0.37 to 3.62)	10 more per 1000 (from 43 fewer to 177 more)	VERY LOW	CRITICAL
Lymphoedema (>2cm interlimb circumference) - 6 months												
1	Randomised trials	Serious3	No serious inconsistency	No serious indirectness	Very serious[5]	None	5/73 (6.8%)	4/68 (5.9%)	RR 1.16 (0.33 to 4.16)	9 more per 1000 (from 39 fewer to 186 more)	VERY LOW	
Lymphoedema (>2cm interlimb circumference) - 12 months												
1	Randomised trials	No serious risk of bias[6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	1/66 (1.5%)	3/68 (4.4%)	RR 0.34 (0.04 to 3.22)	29 fewer per 1000 (from 42 fewer to 98 more)	LOW	CRITICAL
Lymphoedema(>/=10% difference) - First assessment after intervention												
3	Randomised trials	Serious[1,3,6]	No serious inconsistency	No serious indirectness	Very serious[5]	None	20/253 (7.9%)	27/249 (10.8%)	RR 0.74 (0.43 to 1.28)	28 fewer per 1000 (from 62 fewer to 30 more)	VERY LOW	CRITICAL
Lymphoedema(>/=10% difference) - Follow-up												
2	Randomised trials	Serious[1,3]	No serious inconsistency	No serious indirectness	Very serious[5]	None	15/177 (8.5%)	20/168 (11.9%)	RR 0.71 (0.38 to 1.34)	35 fewer per 1000 (from 74 fewer to 40 more)	VERY LOW	CRITICAL
Leg press (lb) - 12 months (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias[6]	No serious inconsistency	No serious indirectness	Serious[8]	None	77	76	-	MD 11 lower (27.2 lower to	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute	Quality	Importance
										5.2 higher)		
Bench press (lb) - 12 months (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias6	No serious inconsistency	No serious indirectness	Serious[7]	None	59	63	-	MD 11 higher (6.91 to 15.09 higher)	MODERATE	CRITICAL
Forward flexion (range of motion) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	77	74	-	MD 6.4 higher (1.67 to 11.13 higher)	VERY LOW	CRITICAL
Forward flexion (range of motion) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	73	68	-	MD 1.9 higher (4.41 lower to 8.21 higher)	LOW	CRITICAL
Abduction (range of motion) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	77	74	-	MD 5.2 higher (0.04 to 10.36 higher)	VERY LOW	CRITICAL
Abduction (range of motion) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	73	68	-	MD 10 higher (3.59 to 16.41 higher)	VERY LOW	CRITICAL
External rotation (range of motion) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	77	74	-	MD 2.1 higher (2.19	LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute	Quality	Importance
										lower to 6.39 higher)		
External rotation (range of motion) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	73	68	-	MD 1.2 lower (6.2 lower to 3.8 higher)	LOW	CRITICAL
Horizontal extension (range of motion) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	77	74	-	MD 2.4 higher (2.23 lower to 7.03 higher)	LOW	CRITICAL
Horizontal extension (range of motion) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	73	68	-	MD 5.8 higher (0.63 to 10.97 higher)	VERY LOW	
Abduction (strength) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[8]	None	77	74	-	MD 10.2 higher (0.48 to 19.92 higher)	VERY LOW	CRITICAL
Abduction (strength) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	73	68	-	MD 3 higher (8.56 lower to 14.56 higher)	LOW	CRITICAL
Forward Flexion (strength) - 8 weeks (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	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	None	77	74	-	MD 7.2 higher (0.89 lower to 15.29 higher)	VERY LOW	CRITICAL
Forward Flexion (strength) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	None	73	68	-	MD 3.8 higher (5.74 lower to 13.34 higher)	VERY LOW	CRITICAL
Horizontal extension (strength) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	77	74	-	MD 4.2 higher (4.14 lower to 12.54 higher)	LOW	CRITICAL
Horizontal extension (strength) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	73	68	-	MD 3 higher (5.92 lower to 11.92 higher)	LOW	CRITICAL
Horizontal flexion (strength) - 8 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	77	74	-	MD 2.8 higher (7.53 lower to 13.13 higher)	LOW	CRITICAL
Horizontal flexion (strength) - 6 months (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	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	None	73	68	-	MD 3.8 lower (13.15 lower to 5.55 higher)	VERY LOW	CRITICAL
Physical activity (metabolic equivalent per week: MET-min/week) - 12 months (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	58	60	-	MD 600.6 higher (599.62 to 601.58 higher)	LOW	CRITICAL
Total metres walked in 6 minutes (Better indicated by lower values)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Very serious[8]	None	52	52	-	MD 34.3 higher (8.61 to 59.99 higher)	VERY LOW	CRITICAL
No pain ("0" VAS score) - 3 months												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[9]	None	19/104 (18.3%)	47/100 (47%)	RR 0.39 (0.25 to 0.61)	287 fewer per 1000 (from 183 fewer to 352 fewer)	LOW	CRITICAL
No pain ("0" VAS score) - 6 months												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	41/104 (39.4%)	64/100 (64%)	RR 0.62 (0.47 to 0.81)	243 fewer per 1000 (from 122 fewer to 339 fewer)	LOW	CRITICAL
No pain ("0" VAS score) - 2 years												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Serious[4]	None	62/104 (59.6%)	64/100 (64%)	RR 0.93 (0.75 to 1.16)	45 fewer per 1000 (from 160 fewer to	LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute		
										102 more)		
Change in number of symptoms reported - 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	72	75	-	MD 0.09 lower (0.72 lower to 0.54 higher)	LOW	CRITICAL
Change in symptom severity - 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[6]	No serious inconsistency	No serious indirectness	Serious[7]	None	72	75	-	MD 0.01 higher (0.29 lower to 0.31 higher)	LOW	CRITICAL
FACT-B total score (Better indicated by lower values)												
1	Randomised trials	Serious[2]	No serious inconsistency	No serious indirectness	Serious[7]	None	52	52	-	MD 1.38 higher (3.4 lower to 6.16 higher)	LOW	CRITICAL
BR23 breast symptoms - 8 weeks post-intervention (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Serious[7]	None	77	74	-	MD 1 higher (4.3 lower to 6.3 higher)	LOW	CRITICAL
BR23 breast symptoms - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	None	73	68	-	MD 4 higher (2.15 lower to 10.15 higher)	VERY LOW	CRITICAL
BR23 - Arm symptoms - 8 weeks (post-intervention) (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	Exercise plus usual care	Usual care alone	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	None	77	74	-	MD 3 higher (1.96 lower to 7.96 higher)	VERY LOW	CRITICAL
BR23 - Arm symptoms - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[3]	No serious inconsistency	No serious indirectness	Very serious[8]	None	73	68	-	MD 4 higher (1.96 lower to 9.96 higher)	VERY LOW	CRITICAL

BIS: bioelectrical impedance spectroscopy; BR23: EORTC-BR23 quality of life questionnaire; CI: confidence interval; FACT-B: functional assessment of cancer therapy for breast cancer; MET: metabolic equivalent of task; RR: risk ratio; VAS: visual analogue scale

[1] Sagen 2009 - outcome assessors and investigators were not blinded

[2] Anderson 2012 - unclear allocation concealment and unblinded trial.

[3] Kilbreath 2012 - Unclear randomisation, unclear blinding

[4] 95%CI crossed null effect and one boundary of default MID; <300 events

[5] 95%CI crossed null effect and two boundaries of default MID; <300 events

[6] Schmitz 2010 - participants were not blinded

[7] N<400

[8] 95%CI crossed null effect and one boundary of default MID; N<400

[9] <300 events

Table 10: Clinical evidence profile: Comparison 2: Physiotherapy versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physiotherapy versus control	Control	Relative (95% CI)	Absolute		
Lymphoedema												
2	Randomised trials	Serious[1,2]	No serious inconsistency	No serious indirectness	Very serious[3]	None	9/86 (10.5%)	20/87 (23%)	RR 0.50 (0.15 to 1.67)	115 fewer per 1000 (from 195	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physiotherapy versus control	Control	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 154 more)		
Change in volume ratio (%) from baseline - 12 months (Better indicated by lower values)												
1	Randomised trials	No serious risk of bias[2]	No serious inconsistency	No serious indirectness	Serious[5]	None	60	60	-	MD 3.5 lower (5.89 to 1.11 lower)	MODERATE	CRITICAL
Change in circumferential difference, cm - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	27	30	-	MD 0.83 lower (2.01 lower to 0.35 higher)	VERY LOW	CRITICAL
Flexion - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	27	30	-	MD 15.38 higher (10.75 to 20.01 higher)	VERY LOW	CRITICAL
Extension - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	27	30	-	MD 2.63 higher (1.29 lower to 6.55 higher)	VERY LOW	CRITICAL
Internal rotation - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	27	30	-	MD 5.55 higher (1.08 lower to 12.18 higher)	VERY LOW	CRITICAL
External rotation - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	27	30	-	MD 8.24 (1.66 to 14.82 higher)	VERY LOW	CRITICAL
Adduction - 6 months follow-up (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	Physiotherapy versus control	Control	Relative (95% CI)	Absolute		
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	27	30	-	MD 0.17 lower (3.72 lower to 3.38 higher)	VERY LOW	CRITICAL
Abduction - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[3]	None	27	30	-	MD 21.29 higher (13.06 to 29.52 higher)	VERY LOW	CRITICAL
Functional questionnaire score - 6 months follow-up (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	27	30	-	MD 1.24 lower (1.97 to 0.51 lower)	VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio
[1] Cinar 2008 - Unclear randomisation, unclear blinding, unclear attrition bias
[2] Torres Lacomba 2010 - Unclear blinding
[3] 95%CI crossed null effect and two boundaries of default MID; Optimal information size not met (events<300; N<400)
[4] 95%CI crossed null effect and one boundary of default MID; N<400
[5] N<400

Table 11: Clinical evidence profile: Comparison 3: Manual lymph drainage versus usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual lymph node drainage versus usual care	Control	Relative (95% CI)	Absolute		
Lymphoedema (>=200ml increase) - 3 months												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	8/77 (10.4%)	6/81 (7.4%)	RR 1.4 (0.51 to 3.86)	30 more per 1000 (from 36	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual lymph node drainage versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 212 more)		
Lymphoedema (>=200ml increase) - 6 months												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	11/77 (14.3%)	12/81 (14.8%)	RR 0.96 (0.45 to 2.05)	6 fewer per 1000 (from 81 fewer to 156 more)	VERY LOW	CRITICAL
Lymphoedema (>=200ml increase) - 12 months												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	18/75 (24%)	15/79 (19%)	RR 1.26 (0.69 to 2.32)	49 more per 1000 (from 59 fewer to 251 more)	VERY LOW	CRITICAL
Lymphoedema (>=2cm increase) - 3 months												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	8/77 (10.4%)	6/81 (7.4%)	RR 1.4 (0.51 to 3.86)	30 more per 1000 (from 36 fewer to 212 more)	VERY LOW	CRITICAL
Lymphoedema (>=2cm increase) - 6 months												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	12/77 (15.6%)	11/81 (13.6%)	RR 1.15 (0.54 to 2.44)	20 more per 1000 (from 62 fewer to 196 more)	VERY LOW	CRITICAL
Lymphoedema (>=2cm increase) - 12 months												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	20/75 (26.7%)	16/79 (20.3%)	RR 1.32 (0.74 to 2.34)	65 more per 1000 (from 53 fewer to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual lymph node drainage versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
										271 more)		
Change in arm volume (ml) - 3 months (MLD plus prevention guidelines plus exercise) (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	77	81	-	MD 11 higher (17.62 lower to 39.62 higher)	VERY LOW	CRITICAL
Change in arm volume (ml) - 6 months (MLD plus prevention guidelines plus exercise) (Better indicated by lower values)												
1	Randomised trials	Serious[1]	Very serious[6]	Serious[2]	Very serious[7]	None	77	81	-	MD 27 lower (7.0 lower to 61 higher)	VERY LOW	CRITICAL
Change in arm volume (ml) - 12 months (MLD plus prevention guidelines plus exercise) (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	75	79	-	MD 11 lower (54.33 lower to 32.33 higher)	VERY LOW	CRITICAL
Change in arm volume (ml) - 3 months (MLD plus physiotherapy) (Better indicated by lower values)												
1	Randomised trials	Serious[1]	Serious[5]	Serious[8]	Very serious[7]	None	33	34	-	MD 135 lower (269.39 to 0.61 lower)	VERY LOW	CRITICAL
Change in arm volume (ml) - 6 months (MLD plus physiotherapy) (Better indicated by lower values)												
1	Randomised trials	Serious[1]	Very serious[4]	Serious[8]	Very serious[7]	None	33	34	-	MD 230 lower (372.93 to 87.07 lower)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual lymph node drainage versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
Physical health (qol) - 3 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	77	81	-	MD 0 higher (10.24 lower to 10.24 higher)	VERY LOW	CRITICAL
Physical health (qol) - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	77	81	-	MD 5 higher (6.89 lower to 16.89 higher)	VERY LOW	CRITICAL
Physical health (qol) - 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	75	79	-	MD 3 lower (14.39 lower to 8.39 higher)	VERY LOW	CRITICAL
Mental Health qol - 3 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	77	81	-	MD 3 higher (8.23 lower to 14.23 higher)	VERY LOW	CRITICAL
Mental Health qol - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[7]	None	77	81	-	MD 6 higher (5.82 lower to 17.82 higher)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Manual lymph node drainage versus usual care	Control	Relative (95% CI)	Absolute	Quality	Importance
Mental Health qol - 12 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[9]	None	75	79	-	MD 2 lower (12.78 lower to 8.78 higher)	VERY LOW	CRITICAL

CI: confidence interval; qol: quality of life; RR: risk ratio
[1] Devoogdt 2011- Unclear randomisation and unblinded participants
2 Devoogdt 2011 – Prevention guidelines and exercise therapy were given in both arms - downgraded by 1 level
[3] 95%CI crossed null effect and two boundaries of default MID; <300 events
[4] Zimmermann 2012 - Unclear randomisation, blinding, and attrition
[5] I^2=77%
[6] I^2=91%
[7] 95%CI crossed one boundary of default MID; N<400
[8] Zimmerman 2012 – Physiotherapy was given in both arms - downgraded by 1 level
[9] N<400

Table 12: Clinical evidence profile: Comparison 4: Compression corset versus no compression corset

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With or Without compression corset	Control	Relative (95% CI)	Absolute	Quality	Importance
Number of women with pain reduction												
1	Randomised trials	Very serious[1]	No serious inconsistency	No serious indirectness	Very serious[2]	None	11/19 (57.9%)	6/18 (33.3%)	RR 1.74 (0.81 to 3.7)	247 more per 1000 (from 63 fewer to 900 more)	VERY LOW	CRITICAL

CI: confidence interval; RR: risk ratio

[1] *Hansdorfer-Korzon 2016 - Unclear randomisation, blinding, and attrition and high risk of selective reporting*
[2] *95%CI crossed null effect and one boundary of default MID; <300 events*

Table 13: Clinical evidence profile: Comparison 5: Yoga plus exercise versus exercise alone

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga plus exercise versus Exercise alone	Control	Relative (95% CI)	Absolute	Quality	Importance
Change in arm function - 10 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Serious[4]	None	39	39	-	MD 0.6 higher (0.61 lower to 1.81 higher)	VERY LOW	CRITICAL
Change in arm function - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 1.9 higher (0.66 to 3.14 higher)	VERY LOW	CRITICAL
Change in quickdash - 10 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 2.4 lower (7.75 lower to 2.95 higher)	VERY LOW	CRITICAL
Change in quickdash - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 3.5 lower (8.69 lower to 1.69 higher)	VERY LOW	CRITICAL
Change in level of pain - 10 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 0.5 lower (1.14 lower to	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Yoga plus exercise versus Exercise alone	Control	Relative (95% CI)	Absolute		
										0.14 higher)		
Change in level of pain - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 1.4 lower (2.09 to 0.71 lower)	VERY LOW	CRITICAL
Change in oxford shoulder score - 10 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 0.4 higher (1.98 lower to 2.78 higher)	VERY LOW	CRITICAL
Change in oxford shoulder score - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 1.4 lower (3.79 lower to 0.99 higher)	VERY LOW	CRITICAL
Change in FACT-B score - 10 weeks (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 1.3 lower (6.53 lower to 3.93 higher)	VERY LOW	CRITICAL
Change in FACT-B score - 6 months (Better indicated by lower values)												
1	Randomised trials	Serious[1]	No serious inconsistency	Serious[2]	Very serious[3]	None	39	39	-	MD 1.3 higher (3.61 lower to 6.21 higher)	VERY LOW	CRITICAL

CI: confidence interval; DASH: disability of shoulder, arm and hand questionnaire; FACT-B: functional assessment of cancer therapy for breast cancer; RR: risk ratio
[1] Harder 2015 - unblinded participants
[2] Harder 2015 - participants in both arms received exercises
[3] 95%CI crossed null effect and one boundary of default MID; N<400
[4] N<400

Table 14: Clinical evidence profile: [Comparison 6: Education versus no education

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With or without education	Control	Relative (95% CI)	Absolute	Quality	Importance
Lymphoedema - Any stage												
1	Observational studies	Serious[1]	Serious[2]	No serious indirectness	Very serious[3]	None	101/202 (50%)	77/154 (50%)	RR 0.98 (0.66 to 1.47)	10 fewer per 1000 (from 170 fewer to 235 more)	VERY LOW	CRITICAL
Lymphoedema - Stage 1												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	65/101 (64.4%)	42/77 (54.5%)	RR 1.18 (0.92 to 1.52)	98 more per 1000 (from 44 fewer to 284 more)	VERY LOW	CRITICAL
Lymphoedema - Stage 2 or 3												
1	Observational studies	Serious[1]	No serious inconsistency	No serious indirectness	Very serious[4]	None	36/101 (35.6%)	35/77 (45.5%)	RR 0.78 (0.55 to 1.12)	100 fewer per 1000 (from 205 fewer to 55 more)	VERY LOW	CRITICAL
Reported frequencies of lymphoedema-related symptoms (Better indicated by lower values)												
1	Observational studies	Serious[5]	No serious inconsistency	No serious indirectness	Very serious[4]	None	77	59	-	MD 1.68 lower (2.61 to 0.75 lower)	VERY LOW	CRITICAL
DASH Disability scores (higher score, greater disability) - 3 months (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	39	30	-	MD 0.1 higher (3.88 lower to 4.08 higher)	VERY LOW	CRITICAL
Change in upper arm girth at 3 months (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	With or without education	Control	Relative (95% CI)	Absolute		
1	Observational studies	Serious[6]	Serious[7]	No serious indirectness	Very serious[4]	None	90	59	-	MD 0.31 higher (0.48 lower to 1.09 higher)	VERY LOW	CRITICAL
Change in upper arm girth at 3 months - ALND (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	39	30	-	MD 0.7 higher (0.2 to 1.2 higher)	VERY LOW	CRITICAL
Change in upper arm girth at 3 months - SLNB (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Serious[9]	None	51	29	-	MD 0.1 lower (0.63 lower to 0.43 higher)	VERY LOW	CRITICAL
Change in flexion shoulder at 3 months (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	90	59	-	MD 2.8 higher (0.81 lower to 6.41 higher)	VERY LOW	CRITICAL
Change in flexion shoulder at 3 months - ALND (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	39	30	-	MD 3.5 higher (1.21 lower to 8.21 higher)	VERY LOW	CRITICAL
Change in flexion shoulder at 3 months - SLNB (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	51	29	-	MD 1.8 higher (3.83 lower to 7.43 higher)	VERY LOW	CRITICAL
Change in abduction shoulder at 3 months (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Serious[9]	None	90	59	-	MD 1.42 higher (2.24 lower to 5.09 higher)	VERY LOW	CRITICAL
Change in abduction shoulder at 3 months - ALND (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	With or without education	Control	Relative (95% CI)	Absolute		
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	39	30	-	MD 0.6 higher (4.37 lower to 5.57 higher)	VERY LOW	CRITICAL
Change in abduction shoulder at 3 months - SLNB (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	51	29	-	MD 2.4 higher (3.02 lower to 7.82 higher)	VERY LOW	CRITICAL
Change in horizontal extension shoulder at 3 months (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	90	59	-	MD 0.16 lower (1.9 lower to 1.58 higher)	VERY LOW	CRITICAL
Change in horizontal extension shoulder at 3 months - ALND (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	39	30	-	MD 0.1 lower (2.86 lower to 2.66 higher)	VERY LOW	CRITICAL
Change in horizontal extension shoulder at 3 months - SLNB (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Serious[9]	None	51	29	-	MD 0.2 lower (2.43 lower to 2.03 higher)	VERY LOW	CRITICAL
Change in grip strength at 3 months (Better indicated by lower values)												
1	Observational studies	Serious[6]	Serious[8]	No serious indirectness	Very serious[4]	None	90	59	-	MD 0.92 lower (2.89 lower to 1.03 higher)	VERY LOW	CRITICAL
Change in grip strength at 3 months - ALND (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	Very serious[4]	None	39	30	-	MD 2 lower (3.8 to 0.2 lower)	VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	With or without education	Control	Relative (95% CI)	Absolute		
Change in grip strength at 3 months - SLNB (Better indicated by lower values)												
1	Observational studies	Serious[6]	No serious inconsistency	No serious indirectness	No serious imprecision	None	51	29	-	MD 0 higher (1.43 lower to 1.43 higher)	VERY LOW	CRITICAL

ALND: axillary lymph node dissection; CI: confidence interval; DASH: disability of shoulder, arm and hand questionnaire; RR: risk ratio; SLNB: sentinel lymph node biopsy
[1] Lu 2015 - allocation to treatment by the surgeon and no attempt to control confounders
[2] I2=71%
[3] 95%CI crossed null effect and two boundaries of default MID; <300 events
[4] 95%CI crossed null effect and one boundary of default MID; N<400
[5] Fu 2010 - Retrospective study and group was formed by recalled memory of women regarding receipt of lymphoedema education from healthcare providers;
[6] Sato 2014 - group was formed by patients' preference; short follow-up period
[7] I2=78%
[8] I2=66%
[9] N<400

Appendix G – Economic evidence study selection

Economic evidence study selection for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

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

Economic evidence study selection for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

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

Appendix H – Economic evidence tables

Economic evidence tables for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

No economic evidence was identified for this review question.

Economic evidence tables for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

No economic evidence was identified for this review question.

Appendix I – Health economic evidence profiles

Health economic evidence profiles for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

No economic evidence was identified for this review question.

Health economic evidence profiles for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

No economic evidence was identified for this review question.

Appendix J – Health economic analysis

Health economic analysis for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

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

Health economic analysis for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

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

Appendix K – Excluded studies

Excluded studies for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

Clinical studies

Excluded studies –2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?	
Study	**Reason for exclusion**
Bing, A. U., Kerr, G. R., Jack, W., Chetty, U., Williams, L. J., Rodger, A., Dixon, J. M., Pooled long-term outcomes from two randomized trials of axillary node sampling with axillary radiotherapy versus axillary node clearance in patients with operable node-positive breast cancer, The British journal of surgery, 103, 81-7, 2016	Compares ALND with axillary sampling plus RT
Bing, A., Kerr, G., Jack, W., Williams, L., Roger, A., Chetty, U., Dixon, M., Pooled long term outcomes from two randomised trials of axillary node sampling with axillary radiotherapy if node positive versus axillary node clearance in patients with operable breast cancer, European Journal of Surgical Oncology, 41, S21, 2015	Abstract only - see Bing 2016 for full publication
Bonneau, C., Hequet, D., Estevez, J. P., Pouget, N., Rouzier, R., Impact of axillary dissection in women with invasive breast cancer who do not fit the Z0011 ACOSOG trial because of three or more metastatic sentinel lymph nodes, European journal of surgical oncology, 41, 998-1004, 2015	Non-randomised (SEER database) study
Bromham, Nathan, Schmidt-Hansen, Mia, Astin, Margaret, Hasler, Elise, Reed, Malcolm W, Axillary treatment for operable primary breast cancer, Cochrane Database of Systematic Reviews, 2017	Clinically negative axillary node population
Budach, W., Bolke, E., Kammers, K., Gerber, P. A., Nestle-Kramling, C., Matuschek, C., Adjuvant radiation therapy of regional lymph nodes in breast cancer - a meta-analysis of randomized trials- an update, Radiation OncologyRadiat, 10, 258, 2015	Abstract only - not all LN
Chen, K., Ouyang, Q., Zhu, L., Su, F., Song, E., The association between axillary surgery and survival in T1-2 breast cancer patients with 1-2 positive lymph nodes varies by age and hormone receptor status, International Journal of Gynecological CancerInt J Gynecol Cancer, 1), 126, 2015	Not an RCT
Cipolla, C., Graceffa, G., La Mendola, R., Fricano, S., Fricano, M., Vieni, S., The prognostic value of sentinel lymph node micrometastases in patients with invasive breast carcinoma, Annali Italiani di ChirurgiaAnn Ital Chir, 86, 497-502, 2015	Not an RCT
de Boniface, J., Frisell, J., Andersson, Y., Bergkvist, L., Ahlgren, J., Ryden, L., Olofsson Bagge, R., Sund, M., Johansson, H., Lundstedt, D., Senomac Trialists' Group, Survival and axillary recurrence following sentinel node-positive breast cancer without completion axillary lymph node dissection: the randomized controlled SENOMAC trial, BMC Cancer, 17, 379, 2017	Trial protocol only
Donker, M., van Tienhoven, G., Straver, M. E., Meijnen, P., van de Velde, C. J., Mansel, R. E., Cataliotti, L., Westenberg, A. H., Klinkenbijl, J. H., Orzalesi, L., Bouma, W. H., van der Mijle, H. C., Nieuwenhuijzen, G. A., Veltkamp, S. C., Slaets, L., Duez, N. J., de Graaf, P. W., van Dalen, T., Marinelli, A., Rijna, H., Snoj, M., Bundred, N. J., Merkus, J. W., Belkacemi, Y.,	AMAROS trial - already included in Schmidt-Hansen 2016 meta-analysis

Excluded studies –2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?	
Study	**Reason for exclusion**
Petignat, P., Schinagl, D. A., Coens, C., Messina, C. G., Bogaerts, J., Rutgers, E. J., Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer (EORTC 10981-22023 AMAROS): a randomised, multicentre, open-label, phase 3 non-inferiority trial, Lancet OncologyLancet Oncol, 15, 1303-10, 2014	
Dorchin, M., Soleiman, S. S., Moha Manashi, M., Zahere Fahad, F., Sentinel-node biopsy comparison with routine axillary dissection in breast cancer in al-bairounihospital in Damascus City, International Journal of Gynecological CancerInt J Gynecol Cancer, 1), 704, 2015	Potentially relevant RCT - but abstract only and insufficient detail to include
El Hage Chehade, H., Headon, H., El Tokhy, O., Heeney, J., Kasem, A., Mokbel, K., Is sentinel lymph node biopsy a viable alternative to complete axillary dissection following neoadjuvant chemotherapy in women with node-positive breast cancer at diagnosis? An updated meta-analysis involving 3,398 patients, American journal of surgery, 212, 969-981, 2016	Diagnostic accuracy of SLNB after neoadjuvant chemotherapy
El Hage Chehade, H., Headon, H., El Tokhy, O., Wazir, U., Heeney, J., Kasem, A., Mokbel, K., In the era of conservative surgery, can patients presenting with node positive breast cancer be spared axillary node dissection post neoadjuvant chemotherapy? A meta-analysis and review of literature, European journal of surgical oncology, 42 (11), S245, 2016	No RCTs included
Fowble, B., Jairam, A., Lazar, A., Wang, F., Peled, A., Esserman, L., Park, C., Indications for post-mastectomy radiation (PMRT) following neoadjuvant chemotherapy (NAC) in ypN0 and ypN1-3 axillary node positive women, Journal of Investigative Medicine, 64 (1), 176, 2016	Not an RCT - abstract only
Giuliano, A. E., McCall, L. M., Beitsch, P. D., Whitworth, P. W., Morrow, M., Blumencranz, P. W., Leitch, A. M., Saha, S., Hunt, K., Ballman, K. V., ACOSOG Z0011: A randomized trial of axillary node dissection in women with clinical T1-2 N0 M0 breast cancer who have a positive sentinel node, Journal of Clinical Oncology, 28, no pagination, 2010	ACOSOG-Z0011 trial - already included in Schmidt-Hansen 2016 meta-analysis
Goyal, A., POSNOC-Positive sentinel node: Adjuvant therapy alone versus adjuvant therapy plus clearance or axillary radiotherapy. A randomised trial looking at axillary treatment in early breast cancer (POSNOC Trialists Group), European Journal of Cancer, 51, S309, 2015	Relevant ongoing trial
Ho, A. Y., Cody, H. S., Which patients with sentinel node-positive breast cancer can avoid axillary dissection?, American Society of Clinical Oncology Educational BookAm, 61-5, 2013	Expert review
Holmberg, S. B., Crivellari, D., Zahrieh, D., Forbes, J. F., Rey, P., Dent, D. M., Schaefer, P., Bernhard, J., Campbell, I., Rudenstam, C. M., A randomized trial comparing axillary clearance versus no axillary clearance in older patients (> 60 years) with breast cancer: First results of International Breast Cancer Study Group Trial 10-93, Journal of clinical oncology, 22, 505, 2004	Not LN
Houvenaeghel, G., Boher, J. M., Reyal, F., Cohen, M., Garbay, J. R., Classe, J. M., Rouzier, R., Giard, S., Faure, C., Charitansky, H., Tunon de Lara, C., Darai, E., Hudry, D., Azuar, P., Gimbergues, P., Villet, R., Sfumato, P., Lambaudie, E., Impact of completion axillary lymph node dissection in patients with breast cancer and isolated tumour cells or micrometastases in sentinel nodes, European journal of cancer, 67, 106-118, 2016	Non-randomised study

Excluded studies –2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?	
Study	**Reason for exclusion**
Huang, T. W., Kuo, K. N., Chen, K. H., Chen, C., Hou, W. H., Lee, W. H., Chao, T. Y., Tsai, J. T., Su, C. M., Huang, M. T., Tam, K. W., Recommendation for axillary lymph node dissection in women with early breast cancer and sentinel node metastasis: A systematic review and meta-analysis of randomized controlled trials using the GRADE system, International Journal Of SurgeryInt J Surg, 34, 73-80, 2016	Systematic review, includes ACOSOG-Z001; IBCSG 23-01 and AATRM 048/13/2000
Jagsi, R., Contemporary role of radiotherapy in axillary management, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Expert review, abstract only
Joyce, D. P., Manning, A., Carter, M., Hill, A. D., Kell, M. R., Barry, M., Meta-analysis to determine the clinical impact of axillary lymph node dissection in the treatment of invasive breast cancer, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 153, 235-40, 2015	Systematic review - includes trials already included in the current evidence review
Joyce, D., Manning, A., Hill, A., Kell, M., Barry, M., Meta-analysis to determine the clinical impact of axillary lymph node dissection in the treatment of invasive breast cancer, Irish journal of medical science, 1), S402, 2015	Not sentinel node positive
Julian, T. B., Anderson, S. J., Mamounas, E. P., Krag, D. N., Weaver, D., Ashikaga, T., Harlow, S. P., Wolmark, N., Effect of axillary dissection for occult detected sentinel nodes metastases on survival: NSABP B-32, Journal of clinical oncology, 29, 80, 2011	Not randomised when LN (occult metastases)
Juraskova, I., Butow, P., Fisher, A., Bonner, C., Anderson, C., Bu, S., Scarlet, J., Stockler, M. R., Wetzig, N., Ung, O., Campbell, I., Development and piloting of a decision aid for women considering participation in the Sentinel Node Biopsy versus Axillary Clearance 2 breast cancer trial, Clinical TrialsClin, 12, 409-17, 2015	Not LN disease
Li, C. Z., Zhang, P., Li, R. W., Wu, C. T., Zhang, X. P., Zhu, H. C., Axillary lymph node dissection versus sentinel lymph node biopsy alone for early breast cancer with sentinel node metastasis: A meta-analysis, European journal of surgical oncology, 41, 958-66, 2015	Systematic review - includes trials already included in the current evidence review
Li, J. W., Mo, M., Yu, K. D., Chen, C. M., Hu, Z., Hou, Y. F., Di, G. H., Wu, J., Shen, Z. Z., Shao, Z. M., Liu, G. Y., ER-poor and HER2-positive: a potential subtype of breast cancer to avoid axillary dissection in node positive patients after neoadjuvant chemo-trastuzumab therapy, 9, e114646, 2014	Not a randomised study
Li, S., Liu, F., Chen, K., Rao, N., Xie, Y., Su, F., Zhu, L., The Extent of Axillary Surgery Is Associated with Breast Cancer-specific Survival in T1-2 Breast Cancer Patients with 1 or 2 Positive Lymph Nodes, Medicine (United States), 95 (14) (no pagination), 2016	Not an RCT
Liang, S., Hallet, J., Simpson, J. S., Tricco, A. C., Scheer, A. S., Omission of axillary staging in elderly patients with early stage breast cancer impacts regional control but not survival: A systematic review and meta-analysis, Journal of Geriatric OncologyJ Geriatr Oncol, 13, 13, 2016	Not node-positive disease
Liu, X. H., Zhang, L., Chen, B., A meta-analysis of the prognosis in patients with breast cancer with ipsilateral supraclavicular lymph node metastasis versus patients with stage IIIb/c or IV breast cancer, Chronic Diseases and Translational Medicine, 1, 236-242, 2015	Not an RCT

Excluded studies –2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?	
Study	**Reason for exclusion**
Lyman, G. H., Somerfield, M. R., Bosserman, L. D., Perkins, C. L., Weaver, D. L., Giuliano, A. E., Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update, Journal of clinical oncology, JCO2016710947, 2016	Guideline
Mamounas, E. P., Optimal management of the axilla: A look at the evidence, Cancer Research. Conference: 38th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 76, 2016	Expert review, abstract only
Mamounas, E. P., Bandos, H., White, J. R., Julian, T. B., Khan, A. J., Shaitelman, S. F., Torres, M. A., McCloskey, S. A., Vicini, F. A., Ganz, P. A., Paik, S., Gupta, N., Costantino, J. P., Curran Jr, W. J., Wolmark, N., Will chest wall and regional nodal radiotherapy post mastectomy or the addition of regional nodal radiotherapy to breast radiotherapy post lumpectomy reduce the rate of invasive cancer events in patients with positive axillary nodes who convert to ypN0 af, Cancer Research, 75, no pagination, 2015	Trial protocol only
Mamounas, E. P., Bandos, H., White, J. R., Julian, T. B., Khan, A. J., Shaitelman, S. F., Torres, M. A., McCloskey, S. A., Vicini, F. A., Ganz, P. A., Paik, S., Gupta, N., Costantino, J. P., Curran, W. J., Wolmark, N., NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) will reduce invasive cancer events in patients (pts) with positive axillary (Ax) nodes who are ypN0 after neoadjuvant chemotherapy (NC), Journal of Clinical Oncology, 33, no pagination, 2015	Trial protocol only
Mamounas, E. P., Bandos, H., White, J. R., Julian, T. B., Khan, A. J., Shaitelman, S. F., Torres, M. A., Vicini, F. A., Ganz, P. A., McCloskey, S. A., Paik, S., Gupta, N., Li, X. A., DiCostanzo, D. J., Costantino, J. P., Curran Jr, W. J., Wolmark, N., NRG Oncology/NSABP B-51/RTOG 1304: A phase III clinical trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) will reduce invasive cancer events in patients (pts) with positive axillary (Ax) nodes who are ypN0 after neoadjuvant chemotherapy (NC), Cancer Research, 76, no pagination, 2016	Trial protocol only
Mamounas, E. P., Bandos, H., White, J. R., Julian, T. B., Khan, A. J., Shaitelman, S. F., Torres, M. A., Vicini, F., Ganz, P. A., McCloskey, S. A., Paik, S., Gupta, N., Li, X. A., Di Costanzo, D. J., Costantino, J. P., Curran, W. J., Wolmark, N., NRG Oncology/NSABP B-51/RTOG 1304: Phase III trial to determine if chest wall and regional nodal radiotherapy (CWRNRT) post mastectomy (Mx) or the addition of RNRT to breast RT post breast-conserving surgery (BCS) reduces invasive breast cancer recurrence free interval (IBCRFI) in patients (pts) with positive axillary (PAx) nodes who are ypN0 after neoadjuvant chemotherapy (NC), Journal of Clinical Oncology, 34, no pagination, 2016	Trial protocol only
Manterola, A., Asin, G., Arias, F., Errasti, M., Barrado, M., Campo, M., Visus, I., Dominguez, M., Management of the axilla after neoadjuvant systemic therapy in breast cancer: A systematic revision, Radiotherapy and Oncology, 119, S566-S567, 2016	Population not in PICO
Marshall, D. A., Deal, K., Bombard, Y., Leighl, N., Macdonald, K. V., Trudeau, M., How do women trade-off benefits and risks in chemotherapy treatment decisions based on gene expression profiling for early-stage breast cancer? A discrete choice experiment, BMJ OpenBMJ Open, 6 (6) (no pagination), 2016	Not a randomised trial

Excluded studies –2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?	
Study	**Reason for exclusion**
Martin, M., Ruiz Simon, A., Ruiz Borrego, M., Ribelles, N., Rodriguez-Lescure, A., Munoz-Mateu, M., Gonzalez, S., Margeli Vila, M., Barnadas, A., Ramos, M., Del Barco Berron, S., Jara, C., Calvo, L., Martinez-Janez, N., Mendiola Fernandez, C., Rodriguez, C. A., Martinez de Duenas, E., Andres, R., Plazaola, A., de la Haba-Rodriguez, J., Lopez-Vega, J. M., Adrover, E., Ballesteros, A. I., Santaballa, A., Sanchez-Rovira, P., Baena-Canada, J. M., Casas, M., del Carmen Camara, M., Carrasco, E. M., Lluch, A., Epirubicin Plus Cyclophosphamide Followed by Docetaxel Versus Epirubicin Plus Docetaxel Followed by Capecitabine As Adjuvant Therapy for Node-Positive Early Breast Cancer: Results From the GEICAM/2003-10 Study, Journal of clinical oncology, 33, 3788-95, 2015	Intervention not in PICO
Mohamed, O. O., Neary, P. M., Fiuza-Castineira, C., O'Donoghue, G. T., Questioning the role of axillary node dissection in sentinel node positive early stage breast cancer in the South Eastern Cancer Centre, Irish journal of medical science, 184, 189-94, 2015	Not an RCT
Nottegar, A., Veronese, N., Senthil, M., Roumen, R. M., Stubbs, B., Choi, A. H., Verheuvel, N. C., Solmi, M., Pea, A., Capelli, P., Fassan, M., Sergi, G., Manzato, E., Maruzzo, M., Bagante, F., Koc, M., Eryilmaz, M. A., Bria, E., Carbognin, L., Bonetti, F., Barbareschi, M., Luchini, C., Extra-nodal extension of sentinel lymph node metastasis is a marker of poor prognosis in breast cancer patients: A systematic review and an exploratory meta-analysis, European journal of surgical oncology, 42, 919-25, 2016	Intervention not in PICO
Oba, M. S., Imoto, S., Toh, U., Wada, N., Kawada, M., Kitada, M., Masuda, N., Taguchi, T., Minami, S., Jinno, H., Sakamoto, J., Morita, S., Japanese Society for Sentinel Node Navigation, Surgery, Observational study of axilla treatment for breast cancer patients with 1-3 positive micrometastases or macrometastases in sentinel lymph nodes, Japanese Journal of Clinical OncologyJpn J Clin Oncol, 44, 876-9, 2014	Non-randomised study
Offersen, B. V., Elective LN irradiation in early breast cancer with pN1 disease, Radiotherapy and Oncology, 111, S45, 2014	Expert review
Reimer, T., Von Minckwitz, G., Loibl, S., Hildebrandt, G., Denkert, C., Nekljudova, V., Kundt, G., Becker, D., Gerber, B., Comparison of axillary sentinel lymph node biopsy versus no axillary surgery in patients with early-stage invasive breast cancer and breast-conserving surgery: A randomized prospective surgical trial. The intergroup-sentinel-mamma (INSEMA)-trial, Cancer Research, 76, no pagination, 2016	Not LN, trial protocol for RCT
Savolt, A., Matrai, Z., Polgar, C. S., Udvarhelyi, N., Rubovszky, G., Kovacs, E., Musonda, P., Peley, G., Optimal treatment of the axilla after positive sentinel lymph node biopsy in primary invasive breast cancer patients (surgery versus radiotherapy)eOTOASOR trial: 5 years follow-up of a randomized clinical trial, European journal of surgical oncology, 40 (11), S37-S38, 2014	OTOASOR trial - already included in Schmidt-Hansen 2016 meta-analysis
Savolt, A., Matrai, Z., Polgar, C., Udvarhelyi, N., Sinkovics, I., Kovacs, E., Peley, G., Optimal treatment of the axilla after positive sentinel lymph node biopsy in primary invasive breast cancer patients (surgery versus radiotherapy). Final results of the OTOASOR trial. 10 years follow-up of a randomized clinical trial, European journal of cancer, 57, S15, 2016	OTOASOR trial - already included in Schmidt-Hansen 2016 meta-analysis
Schem, C., Jonat, W., Ostertag, H., German, Kiss study group, Observation or standard axillary dissection after sentinel-node biopsy in breast cancer: Final results from the German KISS study, Journal of clinical oncology, 29, 1012, 2011	Not LN

Excluded studies –2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?	
Study	**Reason for exclusion**
Syed, A, Nabi, W, Eleti, Sr, Lawrence, J, Gray, E, ZOO11 trial: Does it influence our clinical practice in the UK?, European Journal of Surgical Oncology. Conference: Association of Breast Surgery Conference and AGM, ABS 2015 Bournemouth United Kingdom. Conference Start: 20150615 Conference End: 20150616. Conference Publication: (var.pagings), 41, S33-s34, 2015	Not a randomised trial
Tinterri, C., Canavese, G., Bruzzi, P., Dozin, B., SINODAR ONE, an ongoing randomized clinical trial to assess the role of axillary surgery in breast cancer patients with one or two macrometastatic sentinel nodes, BreastBreast, 30, 197-200, 2016	Trial protocol only
Tinterri, C., Marrazzo, E., Sagona, A., Gatzemeier, W., Barbieri, E., Testori, A., Errico, V., Rossetti, C., Eboli, M., Rubino, A., Canavese, G., Multicentric randomized Italian trial: Axillary dissection or not in sentinel node macrometastasis of breast cancer, Annals of Surgical OncologyAnn Surg Oncol, 24 (2 Supplement 1), 189-191, 2017	Trial protocol only
van den Hoven, I., Voogd, A. C., Roumen, R. M., A Paradigm Shift in Axillary Breast Cancer Treatment; From "Treat All-Except," Toward "Treat None-Unless", Clinical breast cancer, 15, 399-402, 2015	Expert review
van Roozendaal, L. M., de Wilt, J. H., van Dalen, T., van der Hage, J. A., Strobbe, L. J., Boersma, L. J., Linn, S. C., Lobbes, M. B., Poortmans, P. M., Tjan-Heijnen, V. C., Van de Vijver, K. K., de Vries, J., Westenberg, A. H., Kessels, A. G., Smidt, M. L., The value of completion axillary treatment in sentinel node positive breast cancer patients undergoing a mastectomy: a Dutch randomized controlled multicentre trial (BOOG 2013-07), BMC cancer, 15, 610, 2015	Relevant ongoing trial
Vrieling, C., Moser, L., Collette, L., Bogaerts, J., Collette, S., Litiere, S., Slaets, L., Poortmans, P., Rutgers, E., Struikmans, H., Van Tienhoven, G., Bartelink, H., Fourquet, A., EORTC breast cancer survivorship project: First analysis of 3 large early breast cancer radiotherapy trials, European Journal of Cancer, 57, S47-S48, 2016	Abstract only - includes data from AMAROS but insufficient detail
Zhang, J., Wang, C., Axillary radiotherapy: an alternative treatment option for adjuvant axillary management of breast cancer, Scientific ReportsSci, 6, 26304, 2016	Systematic review - includes trials already included in the current evidence review
Zhao, M., Liu, W. G., Zhang, L., Jin, Z. N., Li, Z., Liu, C., Li, D. B., Ma, Y., Zhang, J. W., Jin, F., Chen, B., Can axillary radiotherapy replace axillary dissection for patients with positive sentinel nodes? A systematic review and meta-analysis, Chronic Diseases and Translational Medicine, 3, 41-50, 2017	Systematic review - includes trials already included in the current review

ACOSOG-Z011, American College of Surgeons Oncology Group-Z0011; ALND, axillary lymph node dissection; AMAROS, After mapping of the axilla: radiotherapy or surgery; IBCSG-23-01, International Breast Cancer Study Group-23-01; LN, lymph node; OTOASOR, The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy; PICO, population, intervention, comparison, outcome; RCT, randomised controlled trial; RT, radiotherapy; SLNB, sentinel lymph node biopsy

Economic studies

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

Excluded studies for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

Clinical studies

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Touch therapy decreases lymphedema following breast- cancer surgery, Massage Magazine, 86-86, 2010	Article unavailable; Likely conference abstract publication only
Breast cancer programme reduces lymphoedema risk, Wounds International, 3, 8-8, 2012	Article unavailable; Likely conference abstract publication only
Exercise May Prevent Lymphedema after Breast Cancer, American Institute for Cancer Research Newsletter, 10-10, 2011	Article unavailable; Likely conference abstract publication only
The efficacy of complex decongestive physiotherapy and predictive factors of lymphedema severity and response to CDP in breast cancer-related lymphedema, Journal of Rehabilitation Medicine (Stiftelsen Rehabiliteringsinformation), 37-37, 2012	Conference abstract publication only
Early physiotherapy may help prevent lymphedema after breast cancer surgery, Dissector, 37, 8-9, 2010	Commentary
Ah, Lee S, Kang, Jy, Duck, Kim Y, An, Ar, Kim, Sy, Kim, Ys, Lim, Jy, Effects of a scapula-oriented shoulder exercise programme on upper limb dysfunction in breast cancer survivors: a randomized controlled pilot trial, Clinical rehabilitation, 24, 600-13., 2010	Non-randomised study for exercise vs control comparison
Alamri, Y., Does measuring blood pressure post-breast cancer surgical intervention increase the risk of developing ipsilateral arm lymphoedema?, Journal of Lymphoedema, 11, 15-19, 2016	Systematic review and included studies being checked for relevancy
Aldridge Jr, R. L., Young, M., Lymphedema 101: A journey in education, Rehabilitation Oncology, 26, 18-21, 2008	Study does not have a comparison group
Anonymous,, Upper-body weight lifting does not increase women's risk of breast cancer-related lymphedema, Journal of the National Medical Association, 103, 460-461, 2011	Abstract publication only
Asdourian, M. S., Skolny, M. N., Brunelle, C., Seward, C. E., Salama, L., Taghian, A. G., Precautions for breast cancer-related lymphoedema: risk from air travel, ipsilateral arm blood pressure measurements, skin puncture, extreme temperatures, and cellulitis, The Lancet Oncology, 17, e392-e405, 2016	Systematic review and included studies being checked for relevancy
Bates, S., Sedgwick, R., Decreasing the risk of iatrogenic lymphoedema after axillary surgery: a threefold intervention, BMJ Quality Improvement ReportsBMJ qual, 2, 2013	Intervention was not relevant-involved interventions to alert practitioners to patients at risk for LE

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Beurskens, C., Hidding, J. T., Nijhuis-Van Der Sanden, M. W. G., Evidence based statement physiotherapy and breast cancer, Physiotherapy (United Kingdom), 97, eS1435-eS1436, 2011	Abstract publication only
Bloomquist, K., Karlsmark, T., Bang Christensen, K., Adamsen, L., Prevalence of breast cancer-related lymphedema after participation in a mulitmodal exercise intervention including heavy resistance training, Asia-Pacific Journal of Clinical Oncology, 12, 162, 2016	Abstract publication only
Boccardo, F. M., Ansaldi, F., Bellini, C., Accogli, S., Taddei, G., Murdaca, G., Campisi, C. C., Villa, G., Icardi, G., Durando, P., Puppo, F., Campisi, C., Prospective evaluation of a prevention protocol for lymphedema following surgery for breast cancer (Lymphology (2009) 42, (1-9)), Lymphology, 42, 149, 2009	Intervention not relevant, included surgical interventions
Brown, J. C., Schmitz, K. H., Weight lifting and physical function among survivors of breast cancer: A post hoc analysis of a randomized controlled trial, Journal of clinical oncology, 33, 2184-2189, 2015	Lymphoedema was present before starting intervention
Campbell, A., Mutrie, N., Tovey, S., Barry, S., McLoed, J., Five year follow up of an exercise intervention during breast cancer treatment, Journal of science and medicine in sport, 15, S334, 2012	Abstract publication only
Campbell, K. L., Singh, C. A., The effect of prospective monitoring and early physiotherapy intervention on the incidence of arm morbidity, Archives of physical medicine and rehabilitation, 93 (10), E54, 2012	Abstract publication only
Cemal, Y., Pusic, A., Mehrara, B. J., Preventative measures for lymphedema: Separating fact from fiction, Journal of the American College of Surgeons, 213, 543-551, 2011	Systematic review and included studies being checked for relevancy
Chan, D. N. S., Lui, L. Y., So, W. K., Effectiveness of exercise programmes on shoulder mobility and lymphoedema after axillary lymph node dissection for breast cancer: systematic review, Journal of Advanced Nursing, 66, 1902-1914, 2010	Systematic review and included studies being checked for relevancy
Chandrakaladharan, B. S., Paul, M. J., Nair, A., Randomized control trial to evaluate the influence of class II compression stockings in preventing the development of lymphoedema in breast carcinoma patients, Annals of Oncology, 20, ii69, 2009	Abstract publication only
Cheema, B. S., Kilbreath, S. L., Fahey, P. P., Delaney, G. P., Atlantis, E., Safety and efficacy of progressive resistance training in breast cancer: a systematic review and meta-analysis, Breast Cancer Research and Treatment, 148, 249-268, 2014	Systematic review and relevant studies being checked for relevancy
Cheng, C. T., Deitch, J. M., Haines, I. E., Porter, D. J., Kilbreath, S. L., Do medical procedures in the arm increase the risk of lymphoedema after axillary surgery? A review, ANZ journal of surgery, 84, 510-4, 2014	Systematic review and included studies being checked for relevancy
Cho, H. S. M., Davis, G. C., Paek, J. E., Rao, R., Zhao, H., Xie, X. J., Yousef, M. G., Fedric, T., Euhus, D. H., Leitch, M., A randomised trial of nursing interventions supporting recovery of the postmastectomy patient, Journal of clinical nursing, 22, 919-929, 2013	No outcomes of interest

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Chung, C., Lee, S., Hwang, S., Park, E., Systematic review of exercise effects on health outcomes in women with breast cancer, Asian Nursing Research, 7, 149-159, 2013	Systematic review and included studies being checked for relevancy
Dawson, R., Piller, N., Diet and BCRL: Facts and fallacies on the web, Journal of Lymphoedema, 6, 36-42, 2011	Study was not a systematic review and also examined grey literature
De Groef, A., Van Kampen, M., Dieltjens, E., Christiaens, M. R., Neven, P., Geraerts, I., Devoogdt, N., Effectiveness of postoperative physical therapy for upper-limb impairments after breast cancer treatment: A systematic review, Archives of physical medicine and rehabilitation, 96, 1140-1153, 2015	Systematic review and included studies being checked for relevancy
De Groef, A., Van Kampen, M., Vervloesem, N., De Geyter, S., Christiaens, M. R., Neven, P., Geraerts, I., Devoogdt, N., Effectiveness of myofascial techniques in addition to a standard physical therapy program as postoperative intervention for upper limb pain in breast cancer patients: A randomized controlled trial, Cancer Research. Conference: 39th Annual CTRC AACR San Antonio Breast Cancer Symposium. United States, 77, 2017	Abstract publication only
de Oliveira, M. M., de Rezende, L. F., do Amaral, M. T., Pinto e Silva, M. P., Morais, S. S., Gurgel, M. S., Manual lymphatic drainage versus exercise in the early postoperative period for breast cancer, Physiotherapy Theory & PracticePhysiother, 30, 384-9, 2014	Manual lymphatic drainage for treatment of lymphoedema
Devoogdt, N, Christiaens, Mr, Geraerts, I, Truijen, S, Smeets, A, Leunen, K, Abstract S5-3: Is Manual Lymph Drainage Applied after Axillary Lymph Node Dissection for Breast Cancer Effective To Prevent Arm Lymphoedema? A Randomised Controlled Trial, 70, 2010	Abstract publication only
Devoogdt, N., Van Kampen, M., Geraerts, I., Coremans, T., Christiaens, M. R., Different physical treatment modalities for lymphoedema developing after axillary lymph node dissection for breast cancer: A review, European Journal of Obstetrics Gynecology and Reproductive Biology, 149, 3-9, 2010	Interventions for treatment of lymphoedema
Di Blasio, A., Morano, T., Bucci, I., Di Santo, S., D'Arielli, A., Castro, C. G., Cugusi, L., Cianchetti, E., Napolitano, G., Physical exercises for breast cancer survivors: effects of 10 weeks of training on upper limb circumferences, Journal of Physical Therapy ScienceJ Phys Ther Sci, 28, 2778-2784, 2016	Mixed population with women with lymphoedema and no subgroup analysis
Dos Santos, S., Hill, N., Morgan, A., Smith, J., Thai, C., Cheifetz, O., Acupuncture for treating common side effects associated with breast cancer treatment: A systematic review, Medical Acupuncture, 22, 81-97, 2010	Systematic review and references being checked for relevancy
Ecclestone, Christine, Bedard, Gillian, Popovic, Marko, Thavarajah, Nemica, Lam, Henry, Verma, Sunil, Leahey, Angela, McDonald, Rachel, Wong, Erin, Chow, Edward, Prevention of lymphedema following complete decongestive physiotherapy in breast cancer patients: A literature review, 115-122, 2015	Systematic review and included studies being checked for relevancy
El Haj, Ahmad, The effect of providing information to prevent lymphedema among treated breast cancer women, Middle East Journal of Nursing, 5, 16-18, 2011	Article unavailable; Likely narrative review

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Ezzo, Jeanette, Manheimer, Eric, McNeely, Margaret L, Howell, Doris M, Weiss, Robert, Johansson, Karin I, Bao, Ting, Bily, Linda, Tuppo, Catherine M, Williams, Anne F, Karadibak, Didem, Manual lymphatic drainage for lymphedema following breast cancer treatment, Cochrane Database of Systematic Reviews, 2015	Manual lymphatic drainage for treatment of lymphoedema
Falcon, Ashley, Use of a dvd-based strength training program by breast cancer survivors in the home setting, Dissertation Abstracts International: Section B: The Sciences and Engineering, 76, No Pagination Specified, 2016	Study was an RCT and some participants already had LE at baseline
Ferguson, C. M., Miller, C. L., Horick, N., Skolny, M. N., Swaroop, M. N., Jammallo, L. S., O'Toole, J. A., Specht, M. C., Taghian, A. G., Blood draws, injections, blood pressure readings in the at-risk arm, and flying might not be associated with increases in arm volume: A prospective study, Cancer Research. Conference: 37th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Start, 75, 2015	Conference abstract
Ferguson, C. M., Swaroop, M. N., Horick, N., Skolny, M. N., Miller, C. L., Jammallo, L. S., Brunelle, C., O'Toole, J. A., Salama, L., Specht, M. C., Taghian, A. G., Impact of ipsilateral blood draws, injections, blood pressure measurements, and air travel on the risk of lymphedema for patients treated for breast cancer, Journal of Clinical Oncology, 34, 691-698, 2016	Study does not have a comparison group
Fernandez-Lao, C., Cantarero-Villanueva, I., Ariza-Garcia, A., Courtney, C., Fernandez-De-Las-Penas, C., Arroyo-Morales, M., Water versus land-based multimodal exercise program effects on body composition in breast cancer survivors: A controlled clinical trial, Supportive Care in Cancer, 21, 521-530, 2013	Non-randomised study
Fu, M. R., Axelrod, D., Guth, A. A., Cartwright, F., Qiu, Z., Goldberg, J. D., Kim, J., Scagliola, J., Kleinman, R., Haber, J., Proactive Approach to Lymphedema Risk Reduction: A Prospective Study, Annals of Surgical Oncology, 21, 3481-3489, 2014	Study does not have a comparison group
Fu, M., Haber, J., Axelrod, D., Lymphedema education and risk reduction in breast cancer survivors, Oncology nursing forum, 35, 546-546, 2008	Abstract publication only
Furmaniak, Anna C, Menig, Matthias, Markes, Martina H, Exercise for women receiving adjuvant therapy for breast cancer, Cochrane Database of Systematic Reviews, 2016	Systematic review and included studies being checked for relevancy
Godoy, M. D. F. G., De Godoy, A. C. P., De Godoy, J. M. P., Effect of exercise while utilizing a device with an arm compression sleeve to reduce lymphedema, Clinical and Experimental Obstetrics and Gynecology, 44, 17-19, 2017	RCT data for the same interventions was already found
Goyal, A., Newcombe, R. G., Chhabra, A., Mansel, R. E., Morbidity in breast cancer patients with sentinel node metastases undergoing delayed axillary lymph node dissection (ALND) compared with immediate ALND, Annals of surgical oncology, 15, 262-267, 2008	lymph node dissection was not part of intervention of interest to prevent lymphoedema
Hamaji, Mariana Pereira, Sousa, Fernando Henrique, de Oliveira Júnior, Vicente Alves, de Sousa, Carla Aparecida Pinto, Oliveira, Fernando Rocha, Valenti, Vitor Engrácia, CARE TO MASTECTOMY WITH AXILLARY LYMPHADENECTOMY,	Systematic review and included studies being checked for relevancy

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
LYMPHEDEMA PREVENTION: AN INTEGRATIVE REVIEW, Journal of Nursing UFPE / Revista de Enfermagem UFPE, 8, 1064-1071, 2014	
Hanssens, S., Fontaine, C., Decoster, L., Schallier, D. C. C., Luyten, R., Watthy, C., Van Hemelrijck, R., De Greve, J., The effect of a varied exercise program (VEP) on shoulder function and lymphedema (LE) in breast cancer survivors (BCs): A pilot study, Journal of Clinical Oncology. Conference, 30, 2012	Abstract publication only
Hayes, S., Battistutta, D., Eakin, E., Evaluating telephone versus face-to-face modes of exercise intervention delivery to women during and following treatment for breast cancer, Asia-Pacific Journal of Clinical Oncology, 8, 117-118, 2012	Abstract publication only
Hidding, J. T., Beurskens, C. H., van der Wees, P. J., van Laarhoven, H. W., Nijhuis-van der Sanden, M. W., Treatment related impairments in arm and shoulder in patients with breast cancer: a systematic review, PLoS ONE [Electronic Resource]PLoS ONE, 9, e96748, 2014	Different types of treatment for breast cancers were not interventions of interest to prevent lymphoedema
Hsiao, P. C., Hong, R. B., Ho, C. H., Yuan, K. S., Chou, W., The role of patient education in lymphedema control following breast cancer surgery, Archives of Physical Medicine and Rehabilitation, 95 (10), e45, 2014	Conference abstract
Huang, T. W., Tseng, S. H., Lin, C. C., Bai, C. H., Chen, C. S., Hung, C. S., Wu, C. H., Tam, K. W., Effects of manual lymphatic drainage on breast cancer-related lymphedema: a systematic review and meta-analysis of randomized controlled trials, World Journal of Surgical Oncology, 11, 15, 2013	Systematic review and included studies being checked for relevancy
Hughes, D. C., Darby, N., Gonzalez, K., Boggess, T., Morris, R. M., Ramirez, A. G., Effect of a six-month yoga exercise intervention on fitness outcomes for breast cancer survivors, Physiother Theory PractPhysiotherapy theory and practice, 31, 451-60, 2015	No relevant population - 20% of participants already had lymphedema at baseline
Jakes, A. D., Twelves, C., Breast cancer-related lymphoedema and venepuncture: a review and evidence-based recommendations, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 154, 455-61, 2015	Systematic review and included studies being checked for relevancy
Jammallo, L. S., Miller, C. L., Singer, M., Horick, N. K., Skolny, M. N., Specht, M. C., O'Toole, J., Taghian, A. G., Impact of body mass index and weight fluctuation on lymphedema risk in patients treated for breast cancer, Breast Cancer Research and Treatment, 142, 59-67, 2013	No intervention of interest, study was a risk factor analysis
Jeffs, E., Purushotham, A., The prevalence of lymphoedema in women who attended an information and exercise class to reduce the risk of breast cancer-related upper limb lymphoedema, SpringerplusSpringerplus, 5, 21, 2016	< 100 participants in the cohort study
Kawada, K., Taira, N., Hatono, M., Takahashi,, Miyoshi,, Nogami, T., Iwamoto, T., Motoki, T., Sien, T., Matsuoka, J., Doihara, H., Ikeda, M., Ogasawara, Y., Takabatake, D., Yoshitomi, S., Kiyoto, S., Yamamoto, S., Mizota, Y., Oka, K., Influence of exercise or educational programs on long-term physical activity by patients after surgery for primary breast cancer: A randomized trial, Cancer Research. Conference: 39th Annual CTRC AACR San Antonio Breast Cancer Symposium. United States, 77, 2017	Abstract publication only
Keilani, M., Hasenoehrl, T., Neubauer, M., Crevenna, R., Resistance exercise and secondary lymphedema in breast cancer survivors-a systematic review, Supportive Care in Cancer, 24, 1907-1916, 2016	Women had lymphoedema before resistance exercise

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Kilbreath, S, Refshauge, K, Beith, J, Simpson, J, Ward, L, Lee, M, Is a Weekly Supervised Upper Limb Exercise Program of Value for Women with Early Breast Cancer?, 69, 2010	Abstract publication only
Kilbreath, S. L., Refshauge, K. M., Beith, J. M., Ward, L. C., Simpson, J. M., Lee, M., Does a weekly-supervised, 8-week exercise program improve health-related quality of life for women treated for breast cancer?, Asia-Pacific Journal of Clinical Oncology, 5, A157, 2009	Abstract publication only
Kilbreath, S. L., Ward, L. C., Lane, K., McNeely, M., Dylke, E. S., Refshauge, K. M., McKenzie, D., Lee, M. J., Peddle, C., Battersby, K. J., Effect of air travel on lymphedema risk in women with history of breast cancer, Breast Cancer Research and Treatment, 120, 649-654, 2010	Some participants had lymphoedema at baseline
Kilgour, R. D., Jones, D. H., Keyserlingk, J. R., Effectiveness of a self-administered, home-based exercise rehabilitation program for women following a modified radical mastectomy and axillary node dissection: a preliminary study, Breast Cancer Research & TreatmentBreast Cancer Res Treat, 109, 285-95, 2008	Outcomes were not relevant
Kuznecova, G., Kuznecovs, S., Kuznecovs, I., Jegina, K., Knowledge about lymphedema, risk perception and primary prevention in breast cancer patients, Supportive Care in Cancer, 1), S351, 2011	Conference abstract
L, J. H., Huang, T. W., Effects of manual lymphatic drainage on breast cancer-related lymphedema: A systematic review and meta-analysis of randomized controlled trials, Supportive Care in Cancer, 21, S83-S84, 2013	Abstract publication only
Leibbrand, B., Kahnert, H., Exner, A., Rehabilitation moves. Role of nordic walking, walking, physical activity for functional capability and sustained success of rehabilitation in breast cancer, Onkologie, 35, 243, 2012	Abstract publication only
Lund, E., Turner, J., Retrospective audit of a prevention clinic for BCRL, Journal of Lymphoedema, 6, 17-21, 2011	Non-comparative study
Maher, J., Refshauge, K., Ward, L., Paterson, R., Kilbreath, S., Change in extracellular fluid and arm volumes as a consequence of a single session of lymphatic massage followed by rest with or without compression, Supportive Care in Cancer, 20, 3079-3086, 2012	Lymphoedema was present before starting intervention
Malicka, I., Niklewicz, A., The effects of Kinesiotaping on the extent of lymphedema in women after axillary lymphadenectomy due to breast cancer, Acta Angiologica, 22 (2), 65-66, 2016	Conference abstract
McDowell, M., Dice, K., Lymphedema: identifying nursing strategies for prevention and management in breast cancer patients, Oncology nursing forum, 35, 536-536, 2008	Abstract publication only
McLaughlin, S. A., Koonce, S., Gibson, T., Diehl, N., Crook, J., Bagaria, S., Nguyen, J., Patterns of lymphedema risk reducing behaviors in clinical practice after axillary lymph node surgery, Annals of Surgical Oncology, 1), S41, 2013	Conference abstract
McNeely, Margaret L, Campbell, Kristin, Ospina, Maria, Rowe, Brian H, Dabbs, Kelly, Klassen, Terry P, Mackey, John, Courneya, Kerry, Exercise interventions for upper-limb dysfunction due to breast cancer treatment, Cochrane Database of Systematic Reviews, 2010	Systematic review and included studies being checked for relevancy
Mirabeau-Beale, K. L., Ferguson, C., Swaroop, M., Skolny, M., Horick, N., Miller, C., O'Toole, J., Taghian, A., Quality of life (QOL) in women with breast cancer enrolled on a prospective lymphedema screening protocol, International Journal of Radiation Oncology Biology Physics, 1), S250-S251, 2014	Conference abstract

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Mulero Portela, A. L., Colon Santaella, C. L., Cruz Gomez, C., Burch, A., Feasibility of an exercise program for Puerto Rican women who are breast cancer survivors, Rehabilitation oncology, 26, 20-31, 2008	Not clear whether these women had lymphoedema at the start of study
Nelson, N. L., Breast Cancer-Related Lymphedema and Resistance Exercise: A Systematic Review, Journal of Strength & Conditioning ResearchJ Strength Cond Res, 30, 2656-65, 2016	Systematic review and included studies being checked for relevancy
Ochalek, K., Partsch, H., Gradalski, T., Compression in the prevention of lymphedema in women after breast cancer. Preliminary report, Acta Angiologica, 22 (2), 66, 2016	Abstract publication only
O'Toole, J., Russell, T. A., Taghian, A. G., Effectiveness of early physiotherapy to prevent lymphoedema after surgery for breast cancer: Randomised, single blinded, clinical trial, Breast Diseases, 21, 220-221, 2010	Study is a commentary on a previously published trial
Ozesenli, I. G., Alper, S., Kosehasanotullari, M., Additional effects of the pneumatic compression treatment associated with the complete decongestive therapy in breast cancer treatment related lymphedema. [Turkish, English], Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi, 57, 147, 2011	Article unavailable; Likely conference abstract publication only
Pan, Y. Q., Yang, K. H., Wang, Y. L., Zhang, L. P., Liang, H. Q., Massage interventions and treatment-related side effects of breast cancer: a systematic review and meta-analysis, International Journal of Clinical Oncology, 19, 829-841, 2014	Systematic review and included studies being checked for relevancy
Park, J. H., Lee, W. H., Chung, H. S., Incidence and risk factors of breast cancer lymphoedema, Journal of Clinical Nursing, 17, 1450-1459, 2008	Study does not have a comparison group
Pillai, P. R., Sharma, S., Ahmed, S. Z., Vijaykumar, D. K., Study of incidence of lymphedema in Indian patients undergoing axillary dissection for breast cancer, Indian Journal of Surgical Oncology, 1, 263-9, 2010	Outcomes were not relevant
Pulenzas, N., Ecclestone, C., Bedard, G., Popovic, M., Thavarajah, N., Lam, H., Verma, S., Leahey, A., McDonald, R., Wong, E., Lao, N., Chow, E., Prevention of lymphedema following complete decongestive physiotherapy in breast cancer patients: A literature review, Supportive Care in Cancer, 1), S103, 2015	Abstract publication only
Pylkkanen, L., Uluturk, A., Saz Parkinson, Z., Deandrea, S., Bramesfeld, A., Neamtiu, L., Ambrosio, M., Lerda, D., A systematic review on the effects of manual lymphatic drainage in operated breast cancer patients with lymphoedema, Annals of Oncology. Conference: 41st European Society for Medical Oncology Congress, ESMO, 27, 2016	Abstract publication only
Ramadan, M. M., Incidence and risk factors of arm edema following surgical treatment of breast cancer, Journal of Medical Sciences, 8, 498-502, 2008	Outcomes were not relevant
Ranallo, L., Lymphedema prevention education: nurse practitioner clinic to provide pre-surgical education for patients undergoing axillary sampling for breast cancer, Oncology nursing forum, 35, 983-983, 2008	Abstract publication only
Rebegea, L., Firescu, D., Dumitru, M., Anghel, R., The incidence and risk factors for occurrence of arm lymphedema after treatment of breast cancer, Chirurgia (Bucharest, Romania : 1990), 110, 33-37, 2015	Outcomes were not relevant

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Reeves, M. M., Spark, L., Winkler, E. A. H., Lawler, S. P., McCarthy, N., Demark-Wahnefried, W., Eakin, E. G., Living well after breast cancer: Feasibility, acceptability and efficacy of a weight loss intervention for women following breast cancer treatment, Asia-Pacific Journal of Clinical Oncology, 10, 114, 2014	Abstract publication only
Reul-Hirche, H., Manual lymph drainage when added to advice and exercise may not be effective in preventing lymphoedema after surgery for breast cancer, Journal of PhysiotherapyJ Physiother, 57, 258, 2011	Commentary
Ridner, S. H., Fu, M. R., Wanchai, A., Stewart, B. R., Armer, J. M., Cormier, J. N., Self-management of lymphedema: A systematic review of the literature from 2004 to 2011, Nursing research, 61, 291-299, 2012	Majority of articles included were interventions for lymphoedema management
Ridner, S., Shah, C., Dietrich, M., Vicini, F., A randomized trial evaluating bioimpedance spectroscopy vs. Tape measurement in the prevention of lymphedema following breast cancer treatment, Cancer Research. Conference: 39th Annual CTRC AACR San Antonio Breast Cancer Symposium. United States, 77, 2017	Abstract publication only
Romesberg, M., Rodzewich, A., Tucker, A., Kuzminski, K., Tremback-Ball, A., Effects of Resistance Exercises on Secondary Lymphedema Due to Treatment of Breast Cancer: A Systematic Review, Journal of Women's Health Physical Therapy, 41, 55-56, 2017	Abstract publication only
Sadoon, Malak, Al-Atiyyat, Nijmeh, The efficacy of manual lymph drainage for breast cancer-related lymphoedema, British Journal of Community Nursing, 18, S18-22, 2013	Unavailable
Sagen, A., Karesen, R., Risberg, M., Influence of physical activity on the development of arm lymphedema after breast cancer surgery. A prospective, randomized controlled trial with a 2-year follow-up, Journal of clinical oncology, 26, 9542, 2008	Abstract publication only
Sander, A. P., A safe and effective upper extremity resistive exercise program for women post breast cancer treatment, Rehabilitation Oncology, 26, 3-10, 2008	Non-RCT and <100 participants
Sarri, A. J., Sonia, M. M., RogeRio, D., Stela, V. P., da Silva, E. T., Katia, H. K., Matthes, A. G. Z., Santos, M. J. D., Rocha, E. T., Raphael, L. H., Physiotherapeutic stimulation: Early prevention of lymphedema following axillary lymph node dissection for breast cancer treatment, Experimental and Therapeutic Medicine, 1, 147-152, 2010	No relevant outcomes
Saul, M., Battistella, L. R., Bazan, M., Brito, C. M. M., Imamura, M., Lourencao, M. I. P., Otsubo, P. S., Guidelines on therapeutic exercises for patients with breast cancer, PM and R, 1), S212, 2012	Abstract publication only
Schmidt, T., Berner, J., Jonat, W., Van Mackelenbergh, M., Weisser, B., Rocken, C., Mundhenke, C., Influence of arm crank ergometry on development of lymphedema in breast cancer patients after axillary dissektion, Oncology Research and Treatment, 39, 143, 2016	Article unavailable; Likely conference abstract publication only
Schmidt, T., Berner, J., Jonat, W., Weisser, B., Rocken, C., van Mackelenbergh, M., Mundhenke, C., Influence of arm crank ergometry on development of lymphedema in breast cancer patients after axillary dissection: A randomized controlled trail, Journal of rehabilitation medicine, 49, 78-83, 2017	According to study aim, there is mixed population of lymphoedema and no subgroup analysis.

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Sharma, M., Lingam, V., Nahar, V., Yoga as an integrative therapy for breast cancer, Journal of Alternative and Complementary Medicine, 22 (6), A92, 2016	Systematic review and included studies being checked for relevancy
Sherman, K. A., Koelmeyer, L., The role of information sources and objective risk status on lymphedema risk-minimization behaviors in women recently diagnosed with breast cancer, Oncology nursing forum, 38, E27-E36, 2011	Outcomes were not relevant
Singh, C., De Vera, M., Campbell, K. L., The effect of prospective monitoring and early physiotherapy intervention on arm morbidity following surgery for breast cancer: a pilot study, Physiotherapy CanadaPhysiother Can, 65, 183-91, 2013	Non-RCT and n<100 participants
Soran, A., Menekse, E., Girgis, M., DeGore, L., Johnson, R., Breast cancer-related lymphedema after axillary lymph node dissection: does early postoperative prediction model work?, Supportive Care in Cancer, 24, 1413-1419, 2016	Outcomes were not relevant
Soyder, A., Tastaban, E., Ozbas, S., Boylu, S., Ozgun, H., Frequency of early-stage lymphedema and risk factors in postoperative patients with breast cancer, Meme Sagligi Dergisi / Journal of Breast Health, 10, 92-97, 2014	Outcomes were not relevant
Speck, R. M., Gross, C. R., Hormes, J. M., Ahmed, R. L., Lytle, L. A., Hwang, W. T., Schmitz, K. H., Changes in the body image and relationship scale following a one-year strength training trial for breast cancer survivors with or at risk for lymphedema, Breast Cancer Research and Treatment, 121, 421-430, 2010	No outcomes of interest; did not include lymphoedema as an outcome
Stuiver, Martijn M, ten, Tusscher Marieke R, Agasi-Idenburg, Carla S, Lucas, Cees, Aaronson, Neil K, Bossuyt, Patrick Mm, Conservative interventions for preventing clinically detectable upper-limb lymphoedema in patients who are at risk of developing lymphoedema after breast cancer therapy, Cochrane Database of Systematic Reviews, 2015	Systematic review and included studies being checked for relevancy
Taghian, A. G., Ferguson, C., Swaroop, M., Horick, N., Skolny, M., Miller, C., Brunelle, C., Jammallo, L., O'Toole, J., Specht, M., Impact of ipsilateral blood pressure measurements, blood draws, infusions, and air travel on the risk of lymphedema for patients treated for breast cancer: A prospective study, International Journal of Radiation Oncology Biology Physics, 1), S106, 2015	Abstract publication only
Taghian, A. G., Skolny, M. N., O'Toole, J., Miller, C. L., Jammallo, L. S., Horick, N., Elliott, K., Specht, M. C., The PREDICT study (prospective, randomized early detection and intervention after breast cancer-Treatment, for women at risk of lymphedema), Cancer Research. Conference: 36th Annual CTRC AACR San Antonio Breast Cancer Symposium. San Antonio, TX United States. Conference Publication:, 73, 2013	Abstract publication only
Thakur, Revati, Bhat, Anjali, Kaur, Amrit, Effectiveness of Early Physiotherapy to Prevent Lymphedema after Breast Cancer Related Surgery, Indian Journal of Physiotherapy & Occupational Therapy, 10, 96-101, 2016	Unavailable
Togawa, K., Sullivan-Halley, J., Lu, Y., Smith, A. W., Alfano, C., Imayama, I., McTiernan, A., Neuhouser, M. L., Ma, H., Ballard-Barbash, R., Bernstein, L., Risk factors for self-reported arm lymphedema among female breast cancer survivors in Health, Eating, Activity, and Lifestyle (HEAL) Study, Cancer Prevention Research. Conference: 11th Annual AACR International Conference on Frontiers in Cancer Prevention Research. Anaheim, CA United States. Conference Publication:, 5, 2012	Outcomes were not relevant
Torralba-Puebla, T., Ortiz-Fernandez, L., Zamarripa-Cuesta, M., Patient education program: School of lymphedema prevention, European Journal of Lymphology and Related Problems, 27, 25-27, 2015	Non-comparative study

Excluded studies –2.2 What are the best strategies to prevent lymphoedema following axillary intervention?	
Study	**Reason for exclusion**
Toyserkani, N. M., Jorgensen, M. G., Haugaard, K., Sorensen, J. A., Seroma indicates increased risk of lymphedema following breast cancer treatment: A retrospective cohort study, Breast, 32, 102-104, 2017	Outcomes were not relevant
Ugur, S., Arici, C., Yaprak, M., Mesci, A., Arici, G. A., Dolay, K., Ozmen, V., Risk factors of breast cancer-related lymphedema, Lymphatic Research and Biology, 11, 72-75, 2013	Outcomes were not relevant
Vieira, R. A., da Costa, A. M., de Souza, J. L., Coelho, R. R., de Oliveira, C. Z., Sarri, A. J., Junior, R. J., Zucca-Matthes, G., Risk Factors for Arm Lymphedema in a Cohort of Breast Cancer Patients Followed up for 10 Years, Breast CareBreast Care (Basel), 11, 45-50, 2016	Outcomes were not relevant
Wagner, J. L., Hunt, K. K., Effect of active resistive exercise on breast cancer-related lymphedema: A randomized controlled trial, Breast Diseases, 22, 255-256, 2011	The intervention was for treatment of lymphedema
Wang, L., Li, H. P., Liu, A. N., Wang, D. B., Yang, Y. J., Duan, Y. Q., Zhang, Q. N., A Scoring System to Predict Arm Lymphedema Risk for Individual Chinese Breast Cancer Patients, Breast Care, 11, 52-6, 2016	Outcomes were not relevant
Winge, C., Mattiasson, A. C., Schultz, I., After axillary surgery for breast cancer--is it safe to take blood samples or give intravenous infusions?, Journal of Clinical Nursing, 19, 1270-1274, 2010	Study does not have a comparison group
Winters-Stone,K.M., Dobek,J., Bennett,J.A., Nail,L.M., Leo,M.C., Schwartz,A., The effect of resistance training on muscle strength and physical function in older, postmenopausal breast cancer survivors: A randomized controlled trial, Journal of Cancer Survivorship, 6, 189-199, 2012	No relevant population - some participants already had lymphoedema at the start of the trial No outcome of interest
Yanagita, Y., Miyamoto, T., Fujisawa, T., Matsumoto, H., Saitoh, T., Arisawa, F., Matsushima, R., Katayama, K., Hirakata, T., Ichikawa, K., In post-operative adjuvant chemotherapy, does using the arm on the operated side after axillary lymph node dissection following breast cancer surgery induce lymphoedema?, European Journal of Cancer, 50, S89-S90, 2014	Abstract publication only
Yuste Sanchez, M. J., Lacomba, M. T., Sanchez, B. S., Merino, D. P., da Costa, S. P., Tellez, E. C., Zapico Goni, T., Health related quality of life improvement in breast cancer patients: Secondary outcome from a simple blinded, randomised clinical trial, Breast, 24, 75-81, 2015	No outcomes of interest - did not include lymphoedema as an outcome
Zhang, X., He, X., Tang, B., Yang, H., Ding, X., Yu, Y., Chen, D., Mo, W., Xia, X., Ni, J., Zhang, Y., Jiang, C., Shi, J., Zou, D., Risk factors of lymphedema on affected side of upper limb after breast cancer surgery - report from a single center of China, International Journal of Clinical and Experimental Medicine, 10, 1592-1601, 2017	Outcomes were not relevant

Economic studies

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

Appendix L – Research recommendations

Research recommendations for 2.1 Is there a subgroup of people who do not need axillary treatment when the axilla has been found to contain metastatic disease?

No research recommendations were made for this review question.

Research recommendations for 2.2 What are the best strategies to prevent lymphoedema following axillary intervention?

No research recommendations were made for this review question.