National Institute for Health and Care Excellence

FINAL

Thyroid disease: assessment and management

[K] Management of thyrotoxicosis: surgical options

NICE guideline NG145

Intervention evidence review underpinning recommendations 1.6.13, 1.6.14, 1.6.16, 1.6.17, 1.6.19, 1.6.20 in the guideline. See also evidence reviews I, J, L and D

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1.1 Review question: When surgery is indicated, what is the most clinically and cost-effective way of using surgery to treat thyrotoxicosis (for example total vs subtotal thyroidectomy)?

1.2 Introduction

Surgery has long been considered a valid treatment option for the management of thyrotoxicosis. It sits alongside antithyroid drugs and radioactive iodine in the armamentarium of the multidisciplinary team for the definitive treatment of this condition. The committee acknowledge that these modalities have their advantages and disadvantages and may be more or less applicable depending on the clinical presentation of the patient and local expertise. The definition of surgery encompasses procedures from total to subtotal thyroidectomy.

The committee considered the role of surgery in its various forms (total, subtotal and hemi-thyroidectomy) in the definitive management of thyrotoxicosis in comparison to the other options (anti-thyroid drugs and radioactive iodine) for treatment. The efficacy and safety profile as well as the cost effectiveness of surgery was considered in the present review, while surgery was compared to the aforementioned treatment options in Evidence review I.

1.3 PICO table

For full details see the review protocol in Appendix A:.

Table 1: PICO characteristics of review question

Population	People requiring/opting for surgery for thyrotoxicosis
Interventions	Total thyroidectomy Subtotal thyroidectomy Unilateral thyroidectomy
Comparisons	Any of the above with any other
Outcomes	**Critical** Mortality (dichotomous, ≥1 year) Quality of life (continuous) **Important** Thyroid ophthalmopathy (dichotomous) Euthyroidism (dichotomous) Hypothyroidism (dichotomous) Relapse of hyperthyroidism (dichotomous) Cardiovascular morbidity (ischaemic heart disease, dichotomous) Arrhythmia (dichotomous) Osteoporosis (dichotomous) Cognitive impairment (dichotomous)

	Pain (continuous) Symptom scores (continuous) Patient/family/carer experience (continuous) Healthcare contacts (rates/dichotomous) Recurrent laryngeal nerve (RLN) damage (dichotomous) Hypocalcaemia (dichotomous) Hypoparathyroidism (dichotomous) Bleeding (dichotomous) Infection (dichotomous)
Study design	RCTs only, NRS to be considered if no RCTs available and key confounders (see protocol) adjusted for

1.4 Clinical evidence

1.4.1 Included studies

Three studies were included in the review;[9, 40, 91] these are summarised in table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

All three studies were RCTs in adults with Graves' disease, comparing subtotal thyroidectomy with total thyroidectomy. Two RCTs included only people with ophthalmopathy and the remaining RCT had a population in which the majority had ophthalmopathy.

The majority of the population in all three RCTs had been treated with antithyroid drugs prior to their surgery.

One Cochrane review was identified that was relevant to this review[49], its references were checked and included or excluded as per the protocol for this review.

See also the study selection flow chart in Appendix C:, study evidence tables in Appendix D:, forest plots in Appendix E: and GRADE tables in Appendix F:.

1.4.2 Excluded studies

See the excluded studies list in Appendix J:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Barczynski 2012[9]	Total thyroidectomy, n = 100 Subtotal thyroidectomy, n = 100 Bilateral subtotal with 2g of normal tissue left intact on each side	Adults (mean age 46) Graves' disease with mild ophthalmopathy Treated with ATDs to achieve euthyroidism pre-operatively 33% of patients had recurrence of hyperthyroidism after ATD treatment Poland	Mortality Improvement in ophthalmopathy Recurrent hyperthyroidism 5 years follow-up	
Jarhult 2005[40]	Total thyroidectomy, n = 22 Macroscopic inspection Subtotal thyroidectomy, n = 22 Either bilateral subtotal or hemithyroidectomy with unilateral subtotal with no more than 4g remnant	Adults (mean age 43, range 21-69) Graves' disease with moderate-severe ophthalmopathy Previously treated with ATDs for at least 3 months to euthyroidism 14% of patients had recurrence of hyperthyroidism after	Hypoparathyroidism Recurrent laryngeal nerve damage 3 years follow-up	All given post-surgical levothyroxine substitution

Study	Intervention and comparison	Population	Outcomes	Comments
		previous treatment Sweden		
Witte 2000[91]	Total thyroidectomy, n = 50 Subtotal thyroidectomy, n = 100 Combination of bilateral subtotal and unilateral total with contralateral subtotal arms	Adults (mean age 30.2, range 12-73) Graves' disease, 66% with ophthalmopathy 98% previously treated with ATDs for mean of 3 years prior to surgery 37% of patients had recurrence of hyperthyroidism after ATD treatment Germany	Improvement in ophthalmopathy Hypoparathyroidism Recurrent laryngeal nerve damage Minimum 6 months follow-up	Some switching between arms permitted based on surgical decisions during operation (n = 4)

See Appendix D: for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Subtotal vs total thyroidectomy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Total thyroidectomy	Risk difference with Subtotal thyroidectomy (95% CI)
Mortality	191 (1 study)	⨁⊖⊖⊖ VERY LOW1,2	Peto OR 0.14	10 per 1000	9 fewer per 1000 (from 10 fewer to 55 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Total thyroidectomy	Risk difference with Subtotal thyroidectomy (95% CI)
	5 years	due to risk of bias, imprecision	(0 to 6.89)		
Improvement in ophthalmopathy	278 (2 studies) 0.5-5 years	⊕⊕⊕⊕ HIGH	RR 0.98 (0.88 to 1.09)	798 per 1000	16 fewer per 1000 (from 96 fewer to 72 more)
Relapse of hyperthyroidism	191 (1 study) 5 years	⊕⊕⊕⊕ HIGH	Peto OR 8.16 (2.15 to 31)	0 per 1000	90 more per 1000 (from 30 more to 160 more)3
Hypoparathyroidism	384 (3 studies) 0.5-5 years	⊕⊕⊖⊖ LOW1,4 due to risk of bias, imprecision	Peto OR 0.21 (0.06 to 0.73)	91 per 1000	70 fewer per 1000 (from 23 fewer to 85 fewer)
RLN damage/vocal cord palsy	384 (3 studies) 0.5-5 years	⊕⊕⊖⊖ LOW2 due to imprecision	RR 0.7 (0.19 to 2.56)	20 per 1000	6 fewer per 1000 (from 16 fewer to 31 more)
Wound infection	150 (1 study) 6 months	⊕⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	RR 0.75 (0.13 to 4.34)	40 per 1000	10 fewer per 1000 (from 35 fewer to 134 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
3 Zero events in control arm
4 Zero events in both arms

See Appendix F: for full GRADE tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

No health economic studies that were relevant to this question were excluded due to assessment of limited applicability or methodological limitations.

See also the health economic study selection flow chart in Appendix G:.

1.5.3 Health economic modelling

This area was not prioritised for new cost-effectiveness analysis.

1.5.4 Resource costs

Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 4: UK costs of thyroid surgery

Intervention	*Unit cost*	Average length of stay- Days
Surgery (Thyroid Procedures with CC Score 0-4+)(a)	£3,689	1.6

Source: NHS reference costs 2016-17, total HRG schedule [26].

(a) Weighted average of all 3 combined thyroid procedures with CC scores 0-1, 2-3, 4+(KA09C, KA09D, KA09E) including excess bed days

1.6 Evidence statements

1.6.1 Clinical evidence statements

Subtotal thyroidectomy vs total thyroidectomy

No clinically important difference was found for mortality (1 study, very low quality), improvement in ophthalmopathy (2 studies, high quality), relapse of hyperthyroidism (1 study, high quality), hypoparathyroidism (3 studies, high quality), RLN damage (3 studies, low quality), wound infection (1 study, very low quality).

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Mortality and quality of life were the critical outcomes for this review. Ophthalmopathy, euthyroidism, hypothyroidism, relapse of hyperthyroidism, cardiovascular morbidity, arrhythmia, osteoporosis, cognitive impairment, pain, symptom scores, experience of care,

healthcare contacts, recurrent laryngeal nerve damage, hypocalcaemia, hypoparathyroidism, bleeding and infection were the important outcomes for this review.

1.7.1.2 The quality of the evidence

The quality of the evidence ranged from high to very low quality. Evidence was generally downgraded for risk of bias and imprecision. There was no evidence identified on quality of life.

The committee noted that the length of follow-up was relatively short (maximum 5 years), they agreed that longer follow-up would probably have found a higher relapse of hyperthyroidism in both groups but particularly in the subtotal thyroidectomy arm. Adverse events like hypoparathyroidism and RLN palsy on the other hand were likely to be picked up relatively early.

1.7.1.3 Benefits and harms

There were no differences for any outcomes between treatments that breached the standard minimally important differences of 100 events per 1000 people treated. However, the committee noted that the evidence was tending towards total thyroidectomy having more risk of hypoparathyroidism and less relapse of hyperthyroidism. The direction of these findings was consistent with the committee's experience and consensus.

In the experience of the committee, relapse rates post subtotal or hemithyroidectomy for Graves' disease are high. These high relapse rates are particularly relevant in children and younger people who have longer to live in remission. People who choose surgery are opting for a definitive treatment of their condition and repeat surgery after relapse is very difficult technically.

There was no evidence on hypothyroidism as an outcome after surgery, the committee noted that there is a theoretical benefit of less aggressive surgery in terms of hypothyroidism. This benefit would be of most impact for people where there was the least risk of relapse (for example those with a single toxic nodule) making a hemithyroidectomy an appropriate option.

Length of stay following surgery was not an outcome in the protocol for this review. The committee noted that in their experience, subtotal thyroidectomy can, in some centres, be done as a day case (although a significant proportion of cases still require overnight admission) whereas total thyroidectomy typically requires at least an overnight stay in hospital. The studies in the review did not report any difference between surgeries in terms of length of stay.

The committee noted that for older people and those with high risk features, less aggressive surgery may be appropriate.

The committee noted that in their experience, almost all surgery done for children in this area involves total thyroidectomy.

1.7.2 Cost effectiveness and resource use

There was no health economic evidence identified for this question. The committee considered potential resource use differences between options alongside the clinical evidence to inform their considerations about cost effectiveness.

Total and subtotal thyroidectomy are both grouped into the same HRG in the NHS reference costs and so this could not be used to compare the differences in costs. The committee agreed that surgery time would be similar for both procedures but that total thyroidectomy would usually require a longer length of hospital stay. On this basis, they agreed that total

thyroidectomy was likely to be higher cost than subtotal thyroidectomy in terms of initial costs.

However, the committee highlighted that patients that have undergone a subtotal thyroidectomy tend to relapse and therefore require further treatment i.e. RAI, re-operation or drugs. Second round interventions have costs and complications associated with them, for example, one of the risks of reoperation is the possibility of nerve damage. Furthermore, reoperations are also considered to reduce patients' quality of life. Having considered this information, total thyroidectomy is likely to be cost saving as these would offset initial differences in cost when compared to subtotal thyroidectomy. This is mainly due to the high reoperation rates with subtotal thyroidectomy where patients relapse and require second surgeries. However, the committee noted that not all patients that relapse have a second operation. In fact, some may opt for different interventions, i.e. RAI, or drugs as definitive treatment.

There was no economic or clinical evidence for the management of thyrotoxicosis in people with toxic nodular goitre. Hence, the committee used their experience to make a recommendation to offer RAI as first line definitive treatment unless it is unsuitable, to offer total thyroidectomy (current practice) for Graves' disease and toxic multinodular goitre, whereas hemithyroidectomy should be offered for unilateral toxic nodules.

The committee agreed that these recommendations largely reflect current practice and are not expected to result in a substantial resource impact to the NHS in England.

1.7.3 Other factors the committee took into account

The committee agreed that total thyroidectomy is current practice for Graves' disease and toxic multinodular goitre, whereas hemithyroidectomy is employed for unilateral toxic nodules.

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Appendices

Appendix A: Review protocols

Table 5:

ID	Field	Content
I	Review question	What is the clinical and cost effectiveness of using radioactive iodine vs antithyroid drugs (ATD) vs surgery to treat thyrotoxicosis secondary to Graves' disease? What is the clinical and cost effectiveness of using radioactive iodine vs surgery to treat thyrotoxicosis secondary to toxic nodular goitre? When antithyroid drugs are used, what is the most clinically and cost-effective way of using these drugs to treat thyrotoxicosis (for example choice of drugs, different treatment regimens)? When radioactive iodine is used, what is the most clinically and cost-effective way of using this treatment to treat thyrotoxicosis (for example different dosing strategies)? When surgery is indicated, what is the most clinically and cost-effective way of using surgery to treat thyrotoxicosis (for example total vs subtotal thyroidectomy)?
II	Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	Provide clinically and cost effective recommendations on how to manage thyrotoxicosis
IV	Eligibility criteria – population / disease / condition / issue / domain	People diagnosed with thyrotoxicosis (TSH below normal reference ranges, free T3/T4 above normal reference range)

V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Radioactive iodine
		  ○ Fixed administered activity strategy vs calculated absorbed radiation dose strategy
		  ○ Pre-/post- treatment with ATD vs no pre-/post- treatment
		• Antithyroid drugs
		  ○ Carbimazole/methimazole vs propylthiouracil
		  ○ Block and replace (including levothyroxine) vs titration regimen
		  ○ Duration of treatment: 6-<12 months vs 12-18 months vs >18 months
		• Surgery
		  ○ Total thyroidectomy vs subtotal thyroidectomy vs near total (Dunhill) thyroidectomy vs one sided only (hemithyroidectomy/lobectomy/isthmectomy)

VI	Eligibility criteria – comparator(s) / control or	• Comparisons between modalities • Comparisons between submodalities

	reference (gold) standard	
VII	Outcomes and prioritisation	**Critical** • Mortality (dichotomous, ≥1 year) • Quality of life (continuous) **Important (general)** • Thyroid ophthalmopathy (dichotomous) • Euthyroidism (dichotomous) • Hypothyroidism (dichotomous) • Relapse of hyperthyroidism (dichotomous) • Cardiovascular morbidity (ischaemic heart disease, dichotomous) • Arrhythmia (dichotomous) • Osteoporosis (dichotomous) • Cognitive impairment (dichotomous) • Pain (continuous) • Symptom scores (continuous) • Patient/family/carer experience (continuous) • Healthcare contacts (rates/dichotomous) **Important (surgical)** • Recurrent laryngeal nerve damage (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Bleeding (dichotomous) • Infection (dichotomous) **Important (pharmacological)** • Agranulocytosis (dichotomous) • Liver failure (dichotomous) • Minor drug related adverse effects (dichotomous) • Teratogenesis (dichotomous) **Important (radioiodine)** • Infertility (dichotomous) • Malignancy (dichotomous) • Thyrotoxic storm (dichotomous) • Growth abnormalities (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Teratogenesis (dichotomous) Minimum duration as for the minimum duration for inclusion of studies unless specified.
VIII	Eligibility criteria – study design	• Minimum follow-up of 3 months • RCTs • Non-randomised cohort studies to be considered if adjusted for key confounders (age, co-existing conditions, baseline T4, size of goitre) and insufficient RCTs evidence found, on an intervention by intervention basis
IX	Other inclusion / exclusion criteria	• Excluding studies in pregnancy • Excluding studies aimed specifically at treating thyroid eye disease • Excluding studies in context of thyroid malignancy
X	Proposed	**Stratifications**

	sensitivity / subgroup analysis, or meta-regression	• Age – young children (0-4), children and young people (4-18), adults (>18-65), older adults (>65) • For antithyroid drugs vs radioactive iodine vs surgery - Cause of thyrotoxicosis (Graves' disease, toxic nodular goitre, thyroiditis) • Treatment stage – naïve/general (non-naïve, downgraded for indirectness), second line (remain symptomatic despite previous treatment, as defined by studies) **Subgroup analyses** • Gender (male only vs female only) • Age subdivisions (4-12, 12-18, 18-50, 50-65, 65-85, >85) • Comparison not under investigation (for example for block and replace vs titration, if some studies use methimazole and others use propylthiouracil)
XI	Selection process – duplicate screening / selection / analysis	• A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline.
XII	Data management (software)	• EndNote was used for reference management, sifting, citations and bibliographies. • EviBASE was used for data extraction and quality assessment for clinical studies. • Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome.
XIII	Information sources – databases and dates	• Medline, Embase and the Cochrane Library
XIV	Identify if an update	Not an update
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10074
XVI	Highlight if amendment to previous protocol	Not an amendment
XVII	Search strategy – for one database	For details please see Appendix B:
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used and published as an appendix of the evidence report.
XIX	Data items – define all variables to be collected	For details please see evidence tables in Appendix D: (clinical evidence tables) or Appendix H: (health economic evidence tables).
XX	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/
XXI	Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 6: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[63] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

	• Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations. *Health economic study type:* • Cost–utility analysis (most applicable). • Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis). • Comparative cost analysis. • Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations. *Year of analysis:* • The more recent the study, the more applicable it will be. • Studies published in 2003 or later but that depend on unit costs and resource data entirely or predominantly from before 2003 will be rated as 'Not applicable'. • Studies published before 2003 will be excluded before being assessed for applicability and methodological limitations. *Quality and relevance of effectiveness data used in the health economic analysis:* • The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B: Literature search strategies

The literature searches for this review are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual 2014, updated 2018 https://www.nice.org.uk/guidance/pmg20/resources/developing-nice-guidelines-the-manual-pdf-72286708700869

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

Searches were constructed using a PICO framework where population (P) terms were combined with Intervention (I) and in some cases Comparison (C) terms. Outcomes (O) are rarely used in search strategies for interventions as these concepts may not be well described in title, abstract or indexes and therefore difficult to retrieve. Search filters were applied to the search where appropriate.

Table 7: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 07 January 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 07 January 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 1 or 12 CENTRAL to 2019 Issue 1 or 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Medline (Ovid) search terms

1.	exp goiter/
2.	exp Hyperthyroidism/
3.	(hyperthyroid* or thyrotoxicosis).ti,ab.
4.	(toxic adj4 (node* or nodul* or multi?nodul* or goitre or goiter)).ti,ab.
5.	(graves' disease or plummer's disease).ti,ab.
6.	5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.

15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	randomized controlled trial.pt.
26.	controlled clinical trial.pt.
27.	randomi#ed.ti,ab.
28.	placebo.ab.
29.	randomly.ti,ab.
30.	Clinical Trials as topic.sh.
31.	trial.ti.
32.	or/25-31
33.	Meta-Analysis/
34.	exp Meta-Analysis as Topic/
35.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
36.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
37.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
38.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
39.	(search* adj4 literature).ab.
40.	(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.
41.	cochrane.jw.
42.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
43.	or/33-42
44.	Epidemiologic studies/
45.	Observational study/
46.	exp Cohort studies/
47.	(cohort adj (study or studies or analys* or data)).ti,ab.
48.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
49.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
50.	Controlled Before-After Studies/
51.	Historically Controlled Study/
52.	Interrupted Time Series Analysis/
53.	(before adj2 after adj2 (study or studies or data)).ti,ab.
54.	or/4-53
55.	exp case control study/
56.	case control*.ti,ab.

57.	or/55-56
58.	54 or 57
59.	Cross-sectional studies/
60.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
61.	or/59-60
62.	54 or 61
63.	54 or 57 or 61
64.	6 not 24
65.	limit 64 to English language
66.	65 and (32 or 43 or 64)

Embase (Ovid) search terms

1.	goiter/
2.	hyperthyroidism/ or graves disease/ or thyrotoxicosis/ or toxic goiter/
3.	(hyperthyroid* or thyrotoxicosis).ti,ab.
4.	(toxic adj4 (node* of nodul* or multi?nodul* or goitre or goiter)).ti,ab.
5.	(graves' disease or plummer's disease).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	random*.ti,ab.
25.	factorial*.ti,ab.
26.	(crossover* or cross over*).ti,ab.
27.	((doubl* or singl*) adj blind*).ti,ab.
28.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
29.	crossover procedure/
30.	single blind procedure/
31.	randomized controlled trial/
32.	double blind procedure/
33.	or/24-32
34.	systematic review/

35.	meta-analysis/
36.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
37.	((systematic* or evidence*) adj3 (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.
42.	cochrane.jw.
43.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
44.	or/34-43
45.	Clinical study/
46.	Observational study/
47.	family study/
48.	longitudinal study/
49.	retrospective study/
50.	prospective study/
51.	cohort analysis/
52.	follow-up/
53.	cohort*.ti,ab.
54.	52 and 53
55.	(cohort adj (study or studies or analys* or data)).ti,ab.
56.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
57.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	(before adj2 after adj2 (study or studies or data)).ti,ab.
59.	or/45-51,54-58
60.	exp case control study/
61.	case control*.ti,ab.
62.	or/60-61
63.	59 or 62
64.	cross-sectional study/
65.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
66.	or/64-65
67.	59 or 66
68.	59 or 62 or 66
69.	23 and (33 or 44 or 68)
70.	limit 69 to English language

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Goiter] explode all trees
#2.	MeSH descriptor: [Hyperthyroidism] explode all trees
#3.	(hyperthyroid* or thyrotoxicosis):ti,ab
#4.	(toxic near/4 (node* or nodul* or multinodul* or multi-nodul* or goitre or goiter)):ti,ab

#5.	MeSH descriptor: [Graves Disease] explode all trees
#6.	(grave* near/4 (thyrotoxicos* or hyperthyr*)):ti,ab
#7.	graves' disease:ti,ab
#8.	(or #1-#7)

B.2 Health Economics literature search strategy

Health economic evidence was identified by conducting a broad search relating to a thyroid disease population in NHS Economic Evaluation Database (NHS EED – this ceased to be updated after March 2015) and the Health Technology Assessment database (HTA) with no date restrictions. NHS EED and HTA databases are hosted by the Centre for Research and Dissemination (CRD). Additional searches were run on Medline and Embase for health economics, economic modelling and quality of life studies.

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline	2014 – 07 January 2019	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Embase	2014 – 07 January 2019	Exclusions Health economics studies Health economics modelling studies Quality of life studies
Centre for Research and Dissemination (CRD)	HTA - Inception – 07 January 2019 NHSEED - Inception to March 2015	None

Medline (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.

17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	quality-adjusted life years/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.

61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/54-72
74.	26 and (43 or 53 or 73)

Embase (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis*.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/

27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	statistical model/
40.	exp economic aspect/
41.	39 and 40
42.	*theoretical model/
43.	*nonbiological model/
44.	stochastic model/
45.	decision theory/
46.	decision tree/
47.	monte carlo method/
48.	(markov* or monte carlo).ti,ab.
49.	econom* model*.ti,ab.
50.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
51.	or/41-50
52.	quality adjusted life year/
53.	"quality of life index"/
54.	short form 12/ or short form 20/ or short form 36/ or short form 8/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.
61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.

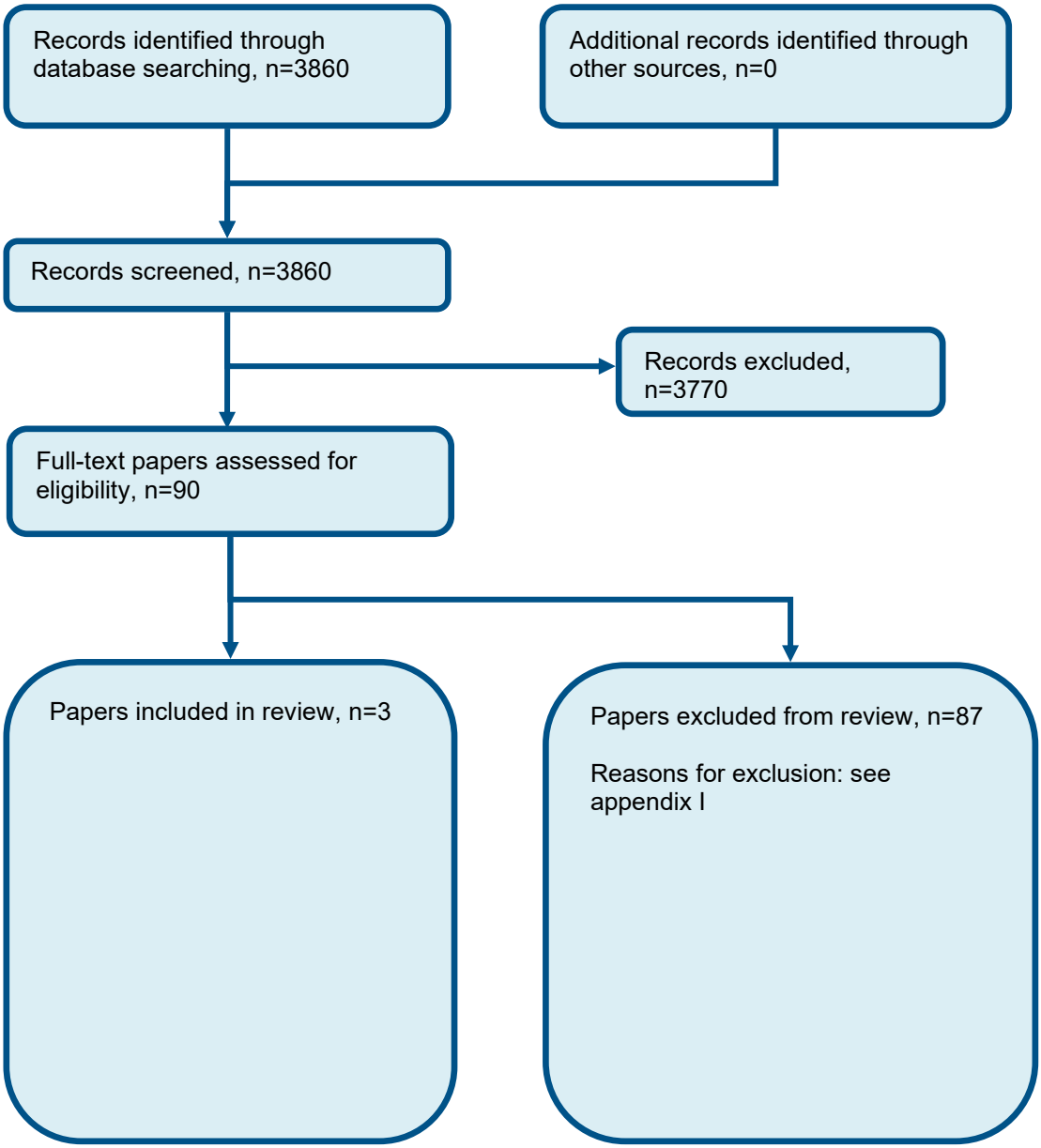
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/52-72
74.	24 and (38 or 51 or 73)

NHS EED and HTA (CRD) search terms

#1.	MeSH DESCRIPTOR Thyroid Diseases EXPLODE ALL TREES
#2.	hyperthyroid*
#3.	hypothyroid*
#4.	thyrotoxicosis*
#5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*))
#6.	#1 OR #2 OR #3 OR #4 or #5

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of surgical management of thyrotoxicosis



Appendix D: Clinical evidence tables

Study	Barczynski 2012[9]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=200)
Countries and setting	Conducted in Poland
Line of therapy	1st line
Duration of study	Intervention + follow up: 5 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Planned surgery for GD, mild active ophthalmopathy
Exclusion criteria	Previous thyroid/parathyroid surgery, recurrent hyperthyroidism after RAI, history of GD of more than 24 months, nodules within posterior aspect of lobe, suspicion of cancer, pre-op RLN palsy, pregnancy, lactation, age <18 years, ASA grade IV or inability to comply with follow-up
Recruitment/selection of patients	Those referred to surgical centre
Age, gender and ethnicity	Age - Other: Mean 46. Gender (M:F): 11:89. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	33% presenting with relapse post-treatment with ATDs
Indirectness of population	No indirectness
Interventions	(n=100) Intervention 1: Total. Thyroid removed completely. Duration 5 years follow-up. Concurrent medication/care: RLNs were exposed, branches of superior and inferior thyroid arteries were divided close to the capsule. No intraoperative nerve monitoring. Effort made to identify all 4 PTH glands, any inadvertently removed were auto transplanted into SCM muscle. 1, 3, 6, 9, 12 monthly follow-ups. Post op levothyroxine for all, aimed at TSH of 0.4-4.2 munits/L. Indirectness: No indirectness

	(n=100) Intervention 2: Subtotal. Bilateral subtotal with 2g of normal tissue left on each side. Efforts made to remove entire pyramidal thyroid lobe. Duration 5 years. Concurrent medication/care: As for total. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SUBTOTAL versus TOTAL

Protocol outcome 1: Mortality
- Actual outcome: Death (not specified when during follow-up) at 5 year follow-up; Group 1: 0/95, Group 2: 1/97
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 for economic reasons, 2 personal problems; Group 2 Number missing: 3, Reason: 3 for economic reasons, 1 death

Protocol outcome 2: Thyroid ophthalmopathy
- Actual outcome: Improvement in ophthalmopathy at 5 year follow-up;
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 for economic reasons, 2 personal problems; Group 2 Number missing: 4, Reason: 3 for economic reasons, 1 death

Protocol outcome 3: Relapse of hyperthyroidism
- Actual outcome: Recurrent hyperthyroidism (persistently lowered TSH and elevated T3/T4 despite at least 4 weeks off levothyroxine) at 5 year follow-up; Group 1: 9/95, Group 2: 0/96
Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 for economic reasons, 2 personal problems; Group 2 Number missing: 4, Reason: 3 for economic reasons, 1 death

Protocol outcome 4: Recurrent laryngeal nerve damage
- Actual outcome: Permanent RLN palsy at 5 year follow-up; Group 1: 2/95, Group 2: 1/96
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 for economic reasons, 2 personal problems; Group 2 Number missing: 3, Reason: 3 for economic reasons, 1 death

Protocol outcome 5: Hypoparathyroidism
- Actual outcome: Permanent hypoparathyroidism at 5 year follow-up; Group 1: 0/95, Group 2: 1/96
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;
Indirectness of outcome: No indirectness ; Group 1 Number missing: 5, Reason: 3 for economic reasons, 2 personal problems; Group 2 Number missing: 3, Reason: 3 for

economic reasons, 1 death	
Protocol outcomes not reported by the study	Quality of life; Euthyroidism; Hypothyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Hypocalcaemia; Bleeding; Infection

Study	**Järhult 2005[40]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=44)
Countries and setting	Conducted in Sweden; Setting: Not stated
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves', pre-treatment with ATD for at least 3 months, ophthalmopathy of at least moderate degree
Exclusion criteria	Previous thyroid or parathyroid surgery, treatment with RAI, TSH >200% above normal during ATD treatment,
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 43 (21-69). Gender (M:F): 9:91. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	Median ATD treatment 9 months, 6 patients had previously had Graves' and this was a relapse
Indirectness of population	No indirectness
Interventions	(n=22) Intervention 1: Total. Macroscopic removal of gland. Duration 3-years . Concurrent medication/care: Thyroxine substitution after surgery, followed at 4 weeks, 6 weeks, 3 months, 6 months, 1, 1.5, 2, 3 years. Indirectness: No indirectness (n=22) Intervention 2: Subtotal. ST bilateral resection or hemithyroidectomy plus unilateral subtotal resection, no more than 4g total of remnant tissue based on visual inspection and weighing of comparable surgical specimen. Duration 3 years. Concurrent medication/care: As for total. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SUBTOTAL versus TOTAL Protocol outcome 1: Recurrent laryngeal nerve damage	

- Actual outcome: Permanent (>9 months) vocal cord palsy at 3 years; Group 1: 1/21, Group 2: 3/22 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Refused to commit to follow-up; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Euthyroidism; Hypothyroidism; Relapse of hyperthyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care ; Healthcare contacts; Hypocalcaemia; Hypoparathyroidism Bleeding; Infection

Study	Witte 2000[91]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=150)
Countries and setting	Conducted in Germany; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention + follow up: Up to 36 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease
Exclusion criteria	None specified
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (range): 30.2 (12-73). Gender (M:F): 25: 125 Ethnicity: Not stated.
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	90% previously treated conservatively prior to surgery
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: Total. Total aimed to have less than 1ml remaining. Duration 6-36 months follow-up. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=100) Intervention 2: Subtotal. 50 randomised to unilateral total and contralateral subtotal, 50 randomised to bilateral subtotal. Duration 6-36 months follow-up. Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: SUBTOTAL versus TOTAL

Protocol outcome 1: Thyroid ophthalmopathy
- Actual outcome: Improvement in opthalmopathy for those with baseline GO (66%) at 6-36 months: Group 1: 41/56, Group 2: 22/31

Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 switching, Reason: Some switching between the two subtotal arms; Group 2 Number missing: 3 switching, Reason: 3 in total arm did not receive total Protocol outcome 2: Recurrent laryngeal nerve damage - Actual outcome: Permanent RLN palsy at 6-36 months; Group 1: 1/100, Group 2: 1/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 switching, Reason: Some switching between the two subtotal arms; Group 2 Number missing: 3 switching, Reason: 3 in total arm did not receive total Protocol outcome 3: Hypoparathyroidism - Actual outcome: Permanent hypoparathyroidism at 6-36 months; Group 1: 3/100, Group 2: 5/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 switching, Reason: Some switching between the two subtotal arms; Group 2 Number missing: 3 switching, Reason: 3 in total arm did not receive total Protocol outcome 4: Infection - Actual outcome: Wound infection at 6-36 months; Group 1: 3/100, Group 2: 2/50 Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 5 switching, Reason: Some switching between the two subtotal arms; Group 2 Number missing: 3 switching, Reason: 3 in total arm did not receive total	
Protocol outcomes not reported by the study	Quality of life; Mortality; Euthyroidism; Hypothyroidism; Relapse of hyperthyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Hypocalcaemia; Bleeding

Appendix E: Forest plots

E.1 Subtotal vs total thyroidectomy

Figure 2: Mortality

Study or Subgroup	Subtotal Events	Subtotal Total	Total Events	Total Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Barczynski 2012	0	95	1	96	100.0%	0.14 [0.00, 6.89]
Total (95% CI)		**95**		**96**	**100.0%**	**0.14 [0.00, 6.89]**
Total events	0		1			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.99 (P = 0.32)

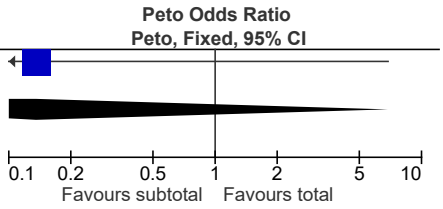


Figure 3: Improvement in ophthalmopathy

Study or Subgroup	Subtotal Events	Subtotal Total	Total Events	Total Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barczynski 2012	81	95	85	96	74.9%	0.96 [0.86, 1.08]
Witte 2000	41	56	22	31	25.1%	1.03 [0.78, 1.36]
Total (95% CI)		**151**		**127**	**100.0%**	**0.98 [0.88, 1.09]**
Total events	122		107			

Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 0.36 (P = 0.72)

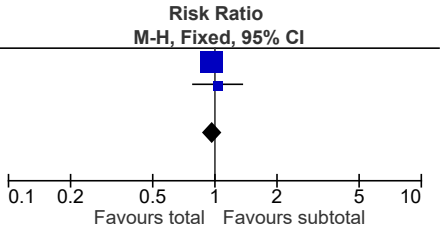


Figure 4: Relapse of hyperthyroidism

Study or Subgroup	Subtotal Events	Subtotal Total	Total Events	Total Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Barczynski 2012	9	95	0	96	100.0%	8.16 [2.15, 31.00]
Total (95% CI)		**95**		**96**	**100.0%**	**8.16 [2.15, 31.00]**
Total events	9		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.08 (P = 0.002)

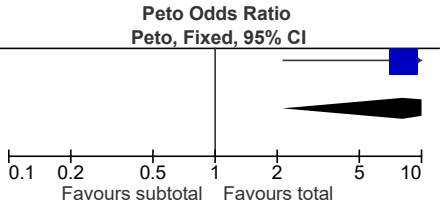


Figure 5: Permanent hypoparathyroidism

Study or Subgroup	Subtotal Events	Subtotal Total	Total Events	Total Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Barczynski 2012	0	95	1	96	10.3%	0.14 [0.00, 6.89]
Jarhult 2005	0	21	2	22	20.1%	0.14 [0.01, 2.23]
Witte 2000	3	100	5	50	69.7%	0.25 [0.06, 1.14]
Total (95% CI)		**216**		**168**	**100.0%**	**0.21 [0.06, 0.73]**
Total events	3		8			

Heterogeneity: Chi² = 0.20, df = 2 (P = 0.91); I² = 0%
Test for overall effect: Z = 2.44 (P = 0.01)

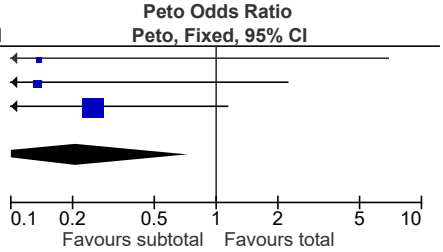


Figure 6: Permanent recurrent laryngeal nerve palsy

Study or Subgroup	Subtotal Events	Subtotal Total	Total Events	Total Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Barczynski 2012	2	95	1	96	18.9%	2.02 [0.19, 21.92]
Jarhult 2005	1	21	3	22	55.7%	0.35 [0.04, 3.10]
Witte 2000	1	100	1	50	25.4%	0.50 [0.03, 7.83]
Total (95% CI)		**216**		**168**	**100.0%**	**0.70 [0.19, 2.56]**
Total events	4		5			

Heterogeneity: Chi² = 1.21, df = 2 (P = 0.55); I² = 0%
Test for overall effect: Z = 0.53 (P = 0.59)

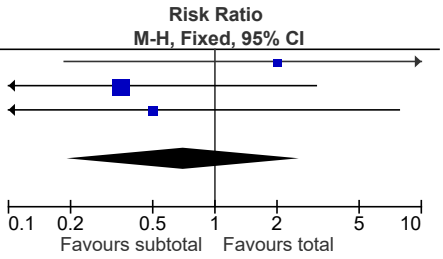
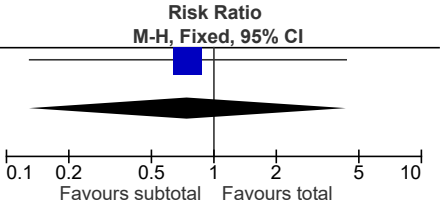


Figure 7: Wound infection

Study or Subgroup	Subtotal Events	Subtotal Total	Total Events	Total Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Witte 2000	3	100	2	50	100.0%	0.75 [0.13, 4.34]
Total (95% CI)		**100**		**50**	**100.0%**	**0.75 [0.13, 4.34]**
Total events	3		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



Appendix F: GRADE tables

Table 9: Clinical evidence profile: subtotal vs total thyroidectomy

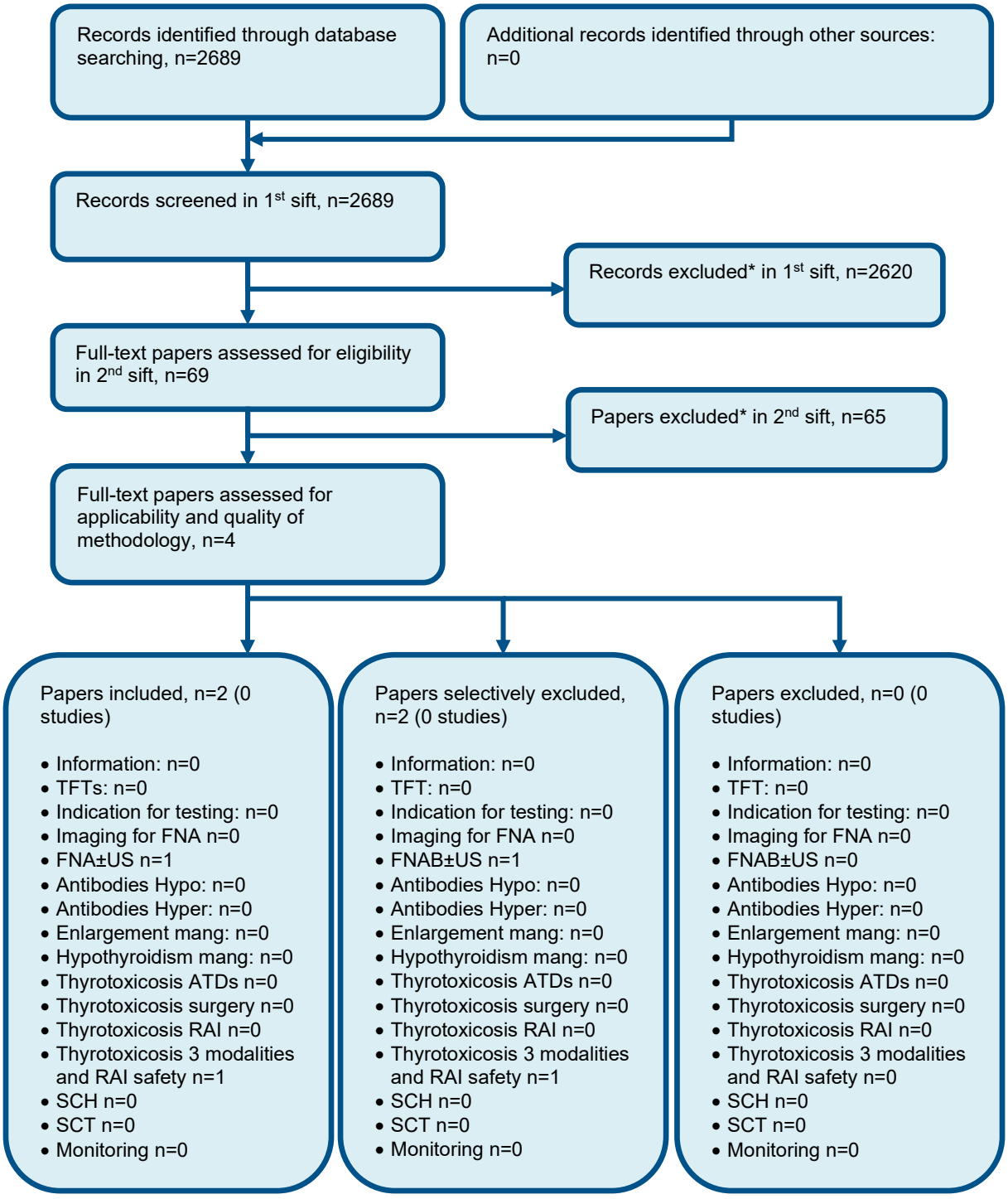
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Subtotal thyroidectomy	Total thyroidectomy	Relative (95% CI)	Absolute		
Mortality (follow-up 5 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/95 (0%)	1%	Peto OR 0.14 (0 to 6.89)	9 fewer per 1000 (from 10 fewer to 55 more)	⊕OOO VERY LOW	CRITICAL
Improvement in ophthalmopathy (follow-up 0.5-5 years)												
2	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	122/151 (80.8%)	79.8%	RR 0.98 (0.88 to 1.09)	16 fewer per 1000 (from 96 fewer to 72 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Relapse of hyperthyroidism (follow-up 5 years)												
1	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	9/95 (9.5%)	0%	Peto OR 8.16 (2.15 to 31)	90 more per 1000 (from 30 more to 160 more)[3]	⊕⊕⊕⊕ HIGH	IMPORTANT
Hypoparathyroidism (follow-up 0.5-5 years)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	none	3/216 (1.4%)	9.1%	Peto OR 0.21 (0.06 to 0.73)	70 fewer per 1000 (from 23 fewer to 85 fewer)	⊕⊕OO LOW	IMPORTANT
RLN damage/vocal cord palsy (follow-up 0.5-5 years)												
3	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[2]	none	4/216 (1.9%)	2%	RR 0.7 (0.19 to 2.56)	6 fewer per 1000 (from 16 fewer to 31 more)	⊕⊕OO LOW	IMPORTANT

Wound infection (follow-up 6 months)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	3/100 (3%)	4%	RR 0.75 (0.13 to 4.34)	10 fewer per 1000 (from 35 fewer to 134 more)	⊕OOO VERY LOW	IMPORTANT

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs
[3] Zero events in control arm
[4] Zero events in multiple arms

Appendix G: Health economic evidence selection

Figure 8: Flow chart of health economic study selection for the guideline



* Non-relevant population, intervention, comparison, design or setting; non-English language
TFT; thyroid function test, FNA; fine-needle aspiration, US; ultrasound, RAI; radioactive iodine, ATDs; antithyroid drugs, Mang; management, SCH; Subclinical hypothyroidism, SCT; Subclinical thyrotoxicosis.

Appendix H: Health economic evidence tables

None

Appendix I: Health economic analysis

None

Appendix J: Excluded studies

J.1 Excluded clinical studies

Table 10: Studies excluded from the clinical review

Study	Exclusion reason
Abraham 2010[2]	Systematic review is not relevant to review question or unclear PICO
Abraham-nordling 2007[1]	No usable outcomes
Allannic 1990[3]	Incorrect interventions
Andrade 1999[4]	Less than minimum duration
Andrade 2001[5]	Incorrect interventions
Andrade 2004[6]	Incorrect interventions
Azizi 2012[8]	Wrong study design
Azizi 2018 [7]	NRS where RCTs are available
Barczynski 2010[10]	Abstract only
Barczynski 2018[11]	Incorrect population
Benker 1995[13]	Incorrect interventions
Benker 1998[12]	Incorrect interventions
Bonnema 2003[14]	Incorrect interventions
Bonnema 2004[15]	Incorrect interventions
Bonnema 2011[16]	Inappropriate comparison
Braga 2002[17]	Less than minimum duration
Burch 2001[18]	No usable outcomes
Buscemi 2007[19]	Not guideline condition
Canto 2016[20]	Incorrect interventions
Chen 2011[21]	Inappropriate comparison
Chen 2014[22]	No additional outcomes to those reported elsewhere
Chi 2005[23]	Inappropriate comparison
Connell 1987[24]	No usable outcomes
De Luca 2018[25]	SR, checked for references
Edmonds 1994[27]	Incorrect interventions
Esfahani 2005[28]	Inappropriate comparison
García-mayor 1992[29]	Incorrect interventions
Glinoer 2001[30]	Incorrect interventions
Goni iriarte 1995[31]	Not in English
Grebe 1998[32]	Incorrect interventions
Hamide 2014[33]	NRS where RCTs are available
Hashizume 1991[34]	NRS without adequate adjustment

Study	Exclusion reason
He 2004[35]	Incorrect interventions
Hoermann 2002[36]	Incorrect interventions
Homsanit 2001[37]	Incorrect interventions
Howarth 2001[38]	Incorrect interventions
Jaiswal 2014[39]	Incorrect interventions
Jorde 1995[41]	Incorrect interventions
Kallner 1996[42]	Incorrect interventions
Kung 1995[43]	Incorrect interventions
Leclere 1994[44]	Not in English
Leslie 2003[45]	Incorrect interventions
Leung 2017 [46]	SR, checked for references
Li 2016[47]	SR, checked for references
Liu 2017[48]	Incorrect interventions
Ljunggren 1998[50]	No usable outcomes
Lucas 1997[51]	Incorrect interventions
Ma 2008[52]	SR, checked for references
Ma 2016[53]	SR checked for references
Marcocci 1989[54]	Incorrect interventions
Mashio 1997[55]	Inappropriate comparison
Mastorakos 2003[56]	Incorrect interventions
Maugendre 1999[57]	Incorrect interventions
Mciver 1996[58]	Incorrect interventions
Menconi 2007[59]	No usable outcomes
Miranda-padua 2014[60]	Incorrect interventions
Müller 2001[61]	Inappropriate comparison
Nakamura 2007[62]	Incorrect interventions
Nedrebo 2002[64]	Incorrect interventions
Noh 2015[65]	Incorrect interventions
Orsini 2012[66]	Inappropriate comparison
Peixoto 2006[67]	Incorrect interventions
Peters 1995[68]	Incorrect interventions
Peters 1996[69]	No usable outcomes
Peters 1997[70]	Incorrect interventions
Pfeilschifter 1997[71]	Inappropriate comparison
Pirnat 2011[72]	Incorrect interventions
Pusuwan 2011[73]	Inappropriate comparison
Raber 2000[74]	Incorrect interventions
Reinwein 1993[75]	Inappropriate comparison
Rittmaster 1998[76]	Incorrect interventions
Rokni 2014[77]	SR checked for references
Romaldini 1983[78]	Incorrect interventions
Santos 2004[79]	NRS without adequate adjustment
Santos 2012[80]	Inappropriate comparison
Sapienza 2015[81]	Inappropriate comparison
Schneider 2005[82]	Inappropriate comparison

Study	Exclusion reason
Singhal 2014[83]	Withdrawn Cochrane review
Taïeb 2016[84]	Incorrect interventions
Thientunyakit 2010[85]	Inappropriate comparison
Tian 2001[86]	Not in English
Unalp 2009[87]	No usable outcomes
Walter 2006[88]	NRS without adequate adjustment
Wang 2016[89]	SR, checked for references
Weetman 1994[90]	Incorrect interventions
Yousefi 2011[92]	Not in English
Yuan 2017[93]	SR, checked for references

J.2 Excluded health economic studies

None