National Institute for Health and Care Excellence

Draft

Thyroid cancer

[P] Evidence review for stimulated or highly sensitive thyroglobulin assays

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.6 to 1.5.9 in the NICE guideline

June 2022

Draft for Consultation

These evidence reviews were developed by National Guideline Centre

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Disclaimer

The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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1 Measuring thyroglobulin

1.1 Review question

1.1.1 For people who have had treatment for differentiated thyroid cancer and who have undetectable thyroglobulin on standard assays, what is the clinical and cost effectiveness of using stimulated thyroglobulin or highly sensitive thyroglobulin assays, to re-assess risk of recurrence after initial treatment and to tailor their follow-up regimen?

Introduction

In contrast to some other malignancies, differentiated thyroid cancer can be monitored using a tumour marker called thyroglobulin (Tg). This protein is produced by thyroid cells, and as such is present in the blood of all people with thyroid tissue. However, it is also produced by thyroid cancer cells and therefore levels can be monitored during follow up after treatment for thyroid cancer.

Traditionally, patients underwent total thyroidectomy with thyroid hormone replacement therapy. Thyroid hormone treatment could then be withdrawn to result in an increase in thyroid stimulating hormone (TSH), which in turn would lead to a rise in blood levels of thyroglobulin. An alternative to this would be artificial stimulation of TSH with recombinant TSH (rTSH). These approaches allowed Tg levels to increase which improved the ability to detect its presence in the blood.

However, over recent years improvements in the ability to detect extremely low levels of Tg (super sensitive Tg assays) has improved. This has called in to question the need to drive up TSH levels either by leaving patients hypothyroid (hormone withdrawal) or stimulating with rTSH.

These improvements in biochemical assays, in addition to an improved understanding of the low risk of recurrence and death from disease in many patients with differentiated thyroid cancer have led to the question of which approach is most appropriate in the routine monitoring of patients following treatment. This review seeks to determine the effectiveness of stimulated thyroglobulin and/or highly sensitive thyroglobulin assays to re-assess risk of recurrence after initial treatment and to tailor their follow-up regimen.

1.1.2 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: People aged 16 or over who have had treatment (total thyroidectomy and radioactive iodine) for differentiated thyroid cancer. Patients who have an undetectable thyroglobulin on a standard assay (<1). Patients are at 6-18 months post ablation Exclusion: Children under 16 <6 or >18 months post ablation
Intervention	• Stimulated thyroglobulin

	• Highly sensitive thyroglobulin assays (<0.2microg/L)
Comparison	• Usual care (including no thyroglobulin assay or standard thyroglobulin assay, but not stimulated or highly sensitive thyroglobulin assay) • Each other
Outcomes	• Mortality • Quality of life • Local cancer progression • Incidence of distant metastases • Cancer recurrence
Study design	• Systematic reviews of RCTs • RCTs Non-randomised studies will be excluded.

1.1.3 Methods and process

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

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

1.1.4 Effectiveness evidence

1.1.4.1 Included studies

No relevant randomised trials comparing different methods of measuring thyroglobulin versus each other or usual care / ultrasound were identified.

See also the study selection flow chart in Appendix C, study evidence tables in 0, forest plots in Appendix E and GRADE tables in Appendix F.

1.1.4.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.5 Economic evidence

1.1.5.1 Included studies

No health economic studies were included.

1.1.5.2 Excluded studies

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

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

1.1.6 Summary of included economic evidence

None.

1.1.7 Economic model

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

1.1.8 Economic evidence statements

No relevant economic evaluations were identified.

1.1.9 The committee's discussion and interpretation of the evidence

1.1.9.1 The outcomes that matter most

The outcomes considered for this review were mortality, health related quality of life, local cancer progression, incidence of distant metastases and cancer recurrence. For purposes of decision-making all outcomes were equally regarded as being of critical importance. No evidence was identified for any of these outcomes as no relevant articles were included in the review.

1.1.9.2 The quality of the evidence

No evidence was included in the review.

1.1.9.3 Benefits and harms

The committee agreed to form recommendations by consensus as no evidence was available from the literature. It was discussed that if thyroglobulin is not detected on a standard assay this should not be taken as a sign that no recurrence has occurred. This was based on the knowledge that thyroglobulin evidence of recurrence can be covert and quiescent and that often a highly sensitive thyroglobulin assay, or a stimulated measurement, is needed for detection of recurrence that otherwise might be missed. The committee did not express a preference for either option – stimulated thyroglobulin or a highly sensitive assay – believing both to have equal merits. The committee suggested strategies for using each method.

When using stimulated thyroglobulin, there were three levels of response suggested. A reading of below 2 µg/L was considered low risk and led to the recommendation that follow up and TSH suppression could be relaxed. A reading of between 2 and 10 µg/L was considered an indeterminate response and led to the recommendation to consider continuation of TSH suppression. A reading of 10 µg/L or more led to recommendations to consider further investigations and treatment. This gradation of actions, from a relaxation of vigilance, to a strengthening of it, was based on the changing perception of recurrence risk associated with the stimulated thyroglobulin measurements.

When using a highly sensitive assay, which can detect thyroglobulin levels lower than 0.2 µg/L, there were two levels of response suggested. A reading of below 0.2 µg/L was considered low risk and led to the recommendation that follow up and TSH suppression could be relaxed. A reading of between 0.2 and 0.1 µg/L led to the recommendation to consider stimulated thyroglobulin which can be helpful in separating patients into lower and higher risk categories. If medium risk on stimulated thyroglobulin this would suggest continuing with the same strategy and not relaxing TSH suppression, but if high risk, this would indicate the consideration of further investigations and treatment.

The committee stressed that the presence of anti-thyroglobulin antibodies can distort thyroglobulin measurements, both stimulated and highly sensitive, and that therefore caution should be used when interpreting results in this situation.

Finally, the committee discussed how thyroglobulin measurement is designed to recurrence that may not yet be evident structurally. Therefore, if structural recurrence is detected in people who have been treated with total thyroidectomy and RAI, further thyroglobulin measurement is unnecessary, and such patients should be immediately discussed with a surgeon.

1.1.9.4 Cost effectiveness and resource use

No health economics evidence was included for this question.

The committee made a consensus recommendation drawing from their experience and in line with current practice. The committee did not recommend stimulated thyroglobulin over highly sensitive assay or vice versa as they recognized that both have their utility and are widely used in practice. Hence, the recommendation is unlikely to change current practice and require additional resource.

However, clear indications were provided for further monitoring strategy based on the level of stimulated thyroglobulin detected which should harmonize current practice in the NHS and ultimately improves its efficiency.

1.1.9.5 Other factors the committee took into account

One equality issue was also considered. Stimulated thyroglobulin may involve TSH stimulation by withdrawal of thyroid hormonal supplementation. This may be harmful to those people who have significant physical and mental co-morbidities and disabilities and should be considered during the management of the patient.

1.1.10 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.6 to 1.5.9.

References

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Appendices

Appendix A – Review protocols

A.1 Review protocol for stimulated or highly sensitive thyroglobulin assays

Field	Content
PROSPERO registration number	Not registered
Review title	The clinical and cost effectiveness of using stimulated thyroglobulin or highly sensitive thyroglobulin assays, to re-assess risk of recurrence after initial treatment and to tailor their follow-up regimen, for people who have undetectable thyroglobulin on standard assays and who have had treatment for differentiated thyroid cancer.
Review question	For people who have had treatment for differentiated thyroid cancer and who have undetectable thyroglobulin on standard assays, what is the clinical and cost effectiveness of using stimulated thyroglobulin or highly sensitive thyroglobulin assays, to re-assess risk of recurrence after initial treatment and to tailor their follow-up regimen?
Objective	To determine the effectiveness of stimulated thyroglobulin and/or highly sensitive thyroglobulin assays to re-assess risk of recurrence after initial treatment and to tailor their follow-up regimen
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches:

Field	Content
	• Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final submission of the review and further studies retrieved for inclusion if relevant. The full search strategies for MEDLINE database will be published in the final review.
Condition or domain being studied	Thyroid cancer
Population	Inclusion: People aged 16 or over who have had treatment (total thyroidectomy and radioactive iodine) for differentiated thyroid cancer. Patients who have an undetectable thyroglobulin on a standard assay (<1). Patients are at 6-18 months post ablation Exclusion: Children under 16 <6 or >18 months post ablation
Intervention/Exposure/Test	• stimulated thyroglobulin • highly sensitive thyroglobulin assays (<0.2microg/L)
Comparator/Reference standard/Confounding factors	• Usual care (including no thyroglobulin assay or standard thyroglobulin assay, but not stimulated or highly sensitive thyroglobulin assay) • Each other
Types of study to be included	• Systematic reviews • RCTs Non-randomised studies will be excluded.
Other exclusion criteria	Non-English language studies. Abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	N/A

Field	Content
Primary outcomes (critical outcomes)	• mortality • quality of life • local cancer progression • incidence of distant metastases • cancer recurrence
Secondary outcomes (important outcomes)	N/A
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. Titles and/or abstracts of studies retrieved using the search strategy and those from additional sources will be screened for inclusion. The full text of potentially eligible studies will be retrieved and will be assessed for eligibility in line with the criteria outlined above. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. An in-house developed database; EviBase, will be used for data extraction. A standardised form is followed to extract data from studies (see Developing NICE guidelines: the manual section 6.4) and for undertaking assessment of study quality. Summary evidence tables will be produced including information on: study setting; study population and participant demographics and baseline characteristics; details of the intervention and control interventions; study methodology' recruitment and missing data rates; outcomes and times of measurement; critical appraisal ratings. A second reviewer will quality assure the extracted data. Discrepancies will be identified and resolved through discussion (with a third reviewer where necessary).
Risk of bias (quality) assessment	Risk of bias will be assessed using the appropriate checklist as described in Developing NICE guidelines: the manual. For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS)

Field	Content
	• Randomised Controlled Trial: Cochrane RoB (2.0) Disagreements between the review authors over the risk of bias in particular studies will be resolved by discussion, with involvement of a third review author where necessary.
Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome. If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
Analysis of sub-groups	<u>Stratification</u> Staging <u>Sub-grouping</u>

Field	Content
	If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: None
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
Language	English
Country	England
Named contact	**Named contact** National Guideline Centre **Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Mark Perry, Senior systematic reviewer Alfredo Mariani, Health economist Lina Gulhane, Head of Information specialists

Field	Content
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.
Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: https://www.nice.org.uk/guidance/indevelopment/gid-ng10150/documents
Other registration details	N/A
Reference/URL for published protocol	N/A
Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
Keywords	Thyroid cancer
Details of existing review of same topic by same authors	N/A
Additional information	N/A
Details of final publication	www.nice.org.uk

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A.2 Review protocol health economic evidence

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 0 below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, 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).[7] **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 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as ‘Not applicable’.
- Studies published before 2005 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.

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Appendix B - Literature search strategies

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, 2014 (updated 2020) https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission.

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

Clinical literature search strategy

This literature search strategy was used for the following review:

- For people who have had treatment for differentiated thyroid cancer, what is the clinical and cost effectiveness of using stimulated thyroglobulin or highly sensitive thyroglobulin assays, to re-assess risk of recurrence after initial treatment and to tailor their follow-up regimen?

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 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1946 – 13 January 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 13 January 2022	Randomised controlled trials Systematic review studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, December 2021 Cochrane Central Register of Controlled Trials to Issue 12 of 12, December 2021	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filters and limits applied
Epistemonikos (The Epistemonikos Foundation)	Inception – 13 January 2022	Systematic review Exclusions (Cochrane reviews) English language

1 **Medline (Ovid) search terms**

1.	exp Thyroid Neoplasms/
2.	(thyroid adj3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to english language
26.	(exp child/ or exp pediatrics/ or exp infant/) not (exp adolescent/ or exp adult/ or exp middle age/ or exp aged/)
27.	25 not 26
28.	Thyroglobulin/
29.	(thyroglob* or thyreoglob* or thyrotrop* or thyreotrop* or thyractin).ti,ab.
30.	(thyroid stimulat* adj2 hormone*).ti,ab.
31.	(tsh or rhTSH).ti,ab.
32.	(thyroid adj2 (globulin* or globlin*)).ti,ab.
33.	or/28-32
34.	27 and 33

35.	randomized controlled trial.pt.
36.	controlled clinical trial.pt.
37.	randomi#ed.ab.
38.	placebo.ab.
39.	randomly.ab.
40.	clinical trials as topic.sh.
41.	trial.ti.
42.	or/35-41
43.	Meta-Analysis/
44.	Meta-Analysis as Topic/
45.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
46.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
47.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
48.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
49.	(search* adj4 literature).ab.
50.	(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.
51.	cochrane.jw.
52.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
53.	or/43-52
54.	34 and (42 or 53)

1 **Embase (Ovid) search terms**

1.	exp Thyroid Cancer/
2.	(thyroid adj3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)).ti,ab.
5.	or/1-4
6.	letter.pt. or letter/
7.	note.pt.
8.	editorial.pt.
9.	case report/ or case study/
10.	(letter or comment*).ti.
11.	(conference abstract or conference paper).pt.
12.	or/6-11
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 or rodent*).ti.
22.	or/14-21
23.	5 not 22
24.	limit 23 to english language
25.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
26.	24 not 25
27.	thyroglobulin/ or thyroglobulin antibody/ or thyroglobulin blood level/
28.	(thyroglob* or thyreoglob* or thyrotrop* or thyreotrop* or thyractin).ti,ab.
29.	(thyroid stimulat* adj2 hormone*).ti,ab.
30.	(tsh or rhTSH).ti,ab.
31.	(thyroid adj2 (globulin* or globlin*)).ti,ab.
32.	or/27-31
33.	26 and 32
34.	random*.ti,ab.
35.	factorial*.ti,ab.
36.	(crossover* or cross over*).ti,ab.
37.	((doubl* or singl*) adj blind*).ti,ab.
38.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
39.	crossover procedure/
40.	single blind procedure/
41.	randomized controlled trial/
42.	double blind procedure/
43.	or/34-42
44.	systematic review/
45.	Meta-Analysis/
46.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
47.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
48.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
49.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
50.	(search* adj4 literature).ab.
51.	(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.
52.	cochrane.jw.
53.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
54.	or/44-53
55.	33 and (43 or 54)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2.	(thyroid near/3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)):ti,ab
#3.	DTC:ti,ab

#4.	((papillar* or anaplastic) near/2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)):ti,ab
#5.	#1 or #2 or #3 or #4
#6.	conference:pt or (clinicaltrials or trialsearch):so
#7.	#5 not #6
#8.	MeSH descriptor: [Thyroglobulin] explode all trees
#9.	(thyroglob* or thyreoglob* or thyrotrop* or thyreotrop* or thyractin):ti,ab
#10.	(thyroid stimulat* near/2 hormone*):ti,ab
#11.	(tsh or rhTSH):ti,ab
#12.	(thyroid near/2 (globulin* or globlin*)):ti,ab
#13.	(or #8-#12)
#14.	#7 and #13

Epistemonikos search terms

1.	(title:((title:(thyroid) OR abstract:(thyroid)) AND (title:(cancer* OR neoplasm* OR nodule* OR carcinoma*) OR abstract:(cancer* OR neoplasm* OR nodule* OR carcinoma*)) AND (title:(thyroglob* OR thyreoglob* OR thyrotrop* OR thyreotrop* OR thyractin OR globulin* OR globlin* OR thyrid stimult* OR tsh OR rhTSH) OR abstract:(thyroglob* OR thyreoglob* OR thyrotrop* OR thyreotrop* OR thyractin OR globulin* OR globlin* OR thyrid stimult* OR tsh OR rhTSH))) OR abstract:((title:(thyroid) OR abstract:(thyroid)) AND (title:(cancer* OR neoplasm* OR nodule* OR carcinoma*) OR abstract:(cancer* OR neoplasm* OR nodule* OR carcinoma*)) AND (title:(thyroglob* OR thyreoglob* OR thyrotrop* OR thyreotrop* OR thyractin OR globulin* OR globlin* OR thyrid stimult* OR tsh OR rhTSH) OR abstract:(thyroglob* OR thyreoglob* OR thyrotrop* OR thyreotrop* OR thyractin OR globulin* OR globlin* OR thyrid stimult* OR tsh OR rhTSH))))

Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Thyroid Cancer population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies
	Quality of Life 1946 – 16 December 2021	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies

Database	Dates searched	Search filters and limits applied
	Quality of Life 1974 – 16 December 2021	Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA) (Centre for Research and Dissemination – CRD)	Inception – 31st March 2018	
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2021	English language

1 **Medline (Ovid) search terms**

1.	exp Thyroid Neoplasms/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21

23.	4 not 22
24.	limit 23 to english language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.
36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/52-70
63.	24 and 62

1 **Embase (Ovid) search terms**

1.	exp Thyroid Cancer/

2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/
15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to english language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36
38.	quality-adjusted life years/
39.	"quality of life index"/
40.	short form 12/ or short form 20/ or short form 36/ or short form 8/
41.	sickness impact profile/
42.	(quality adj2 (wellbeing or well being)).ti,ab.
43.	sickness impact profile.ti,ab.

44.	disability adjusted life.ti,ab.
45.	(qal* or qtime* or qwb* or daly*).ti,ab.
46.	(euroqol* or eq5d* or eq 5*).ti,ab.
47.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
48.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
49.	(hui or hui1 or hui2 or hui3).ti,ab.
50.	(health* year* equivalent* or hye or hyes).ti,ab.
51.	discrete choice*.ti,ab.
52.	rosser.ti,ab.
53.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
54.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
55.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
56.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
57.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
58.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
59.	or/37-58
60.	22 and 59

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic) NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)))
#4.	#1 OR #2 OR #3

2 **INHATA search terms**

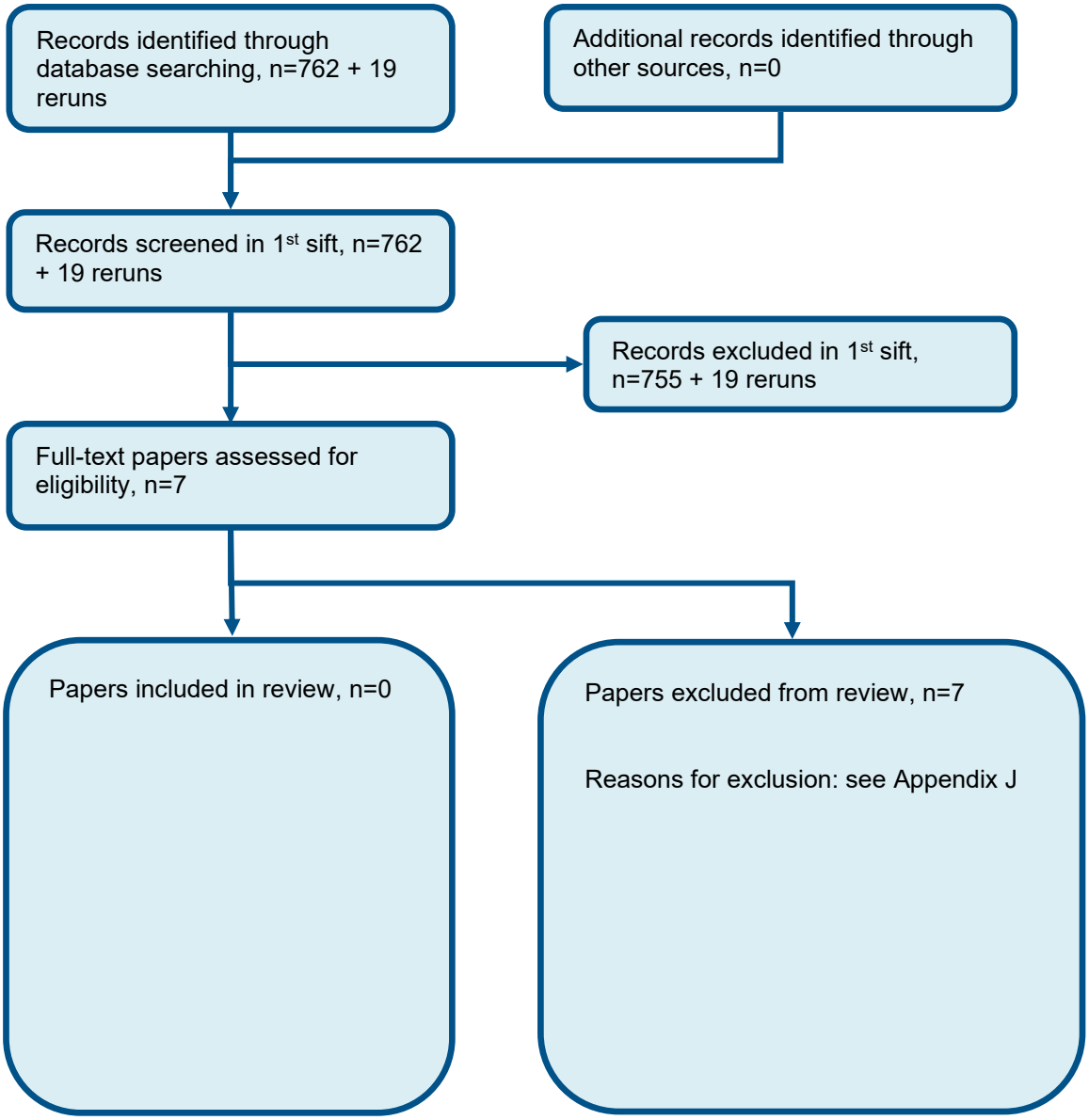
1.	(Thyroid Neoplasms)[mh] OR (thyroid neoplasms) AND (thyroid cancers)

3

4

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of stimulated or highly sensitive thyroglobulin assays



Appendix D – Effectiveness evidence

No evidence found

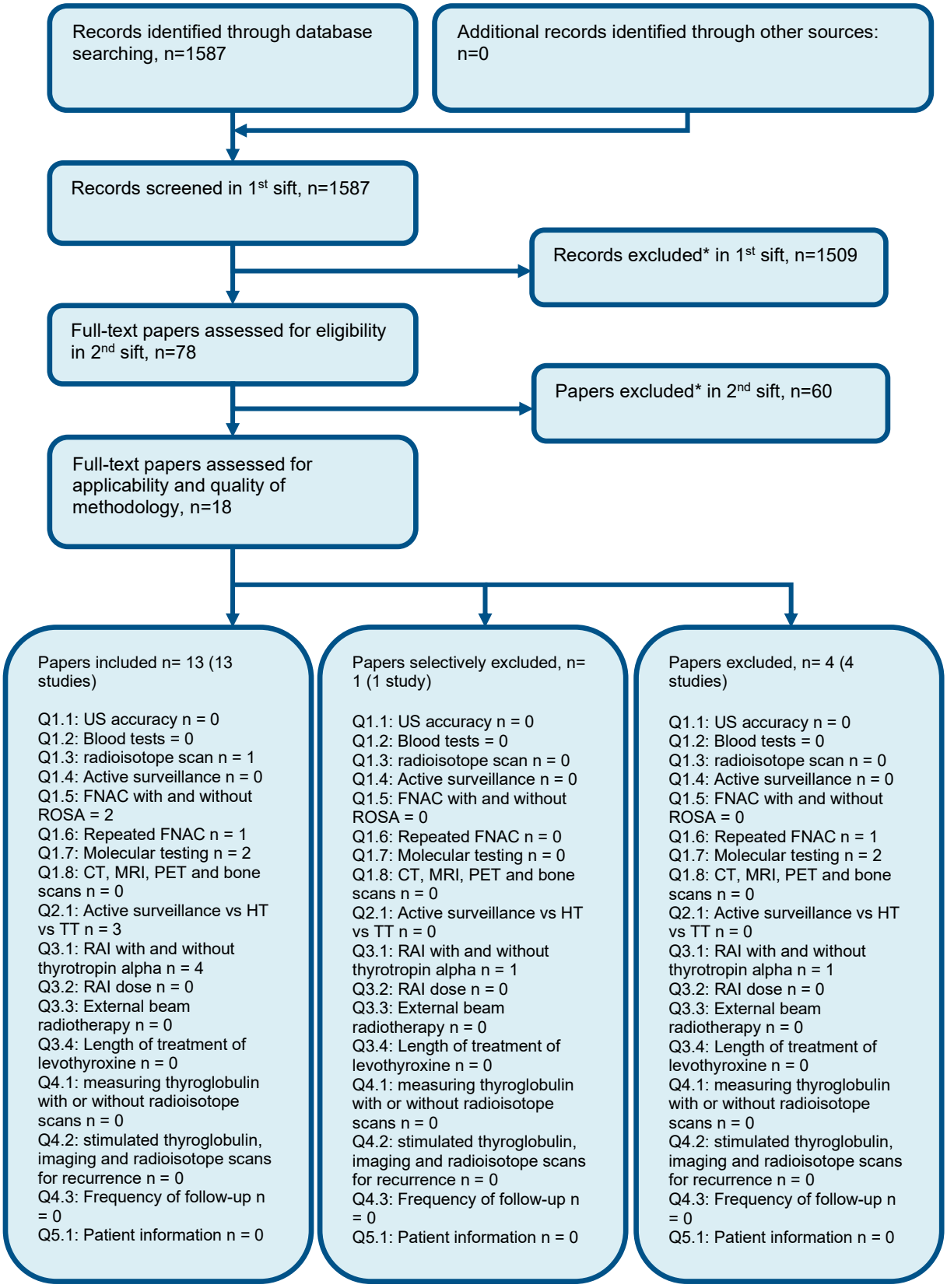
Appendix E – Forest plots

No evidence found

Appendix F – GRADE and/or GRADE-CERQual tables

No evidence found

Appendix G – Economic evidence study selection



* Non-relevant population, intervention, comparison, design or setting; non-English language

Appendix H – Economic evidence tables

None.

Appendix I – Excluded studies

I.1 Clinical studies

Table 3: Studies excluded from the clinical review

Reference	Reason for exclusion
Dai, 1996[1]	Did not evaluate patients with undetectable thyroglobulin – instead sera from three groups of patients were used; no relevant outcomes measured
Ferrari, 2004[2]	Non-randomised study; Did not evaluate protocol outcomes
Giovanella, 2019[3]	Systematic review - references checked. No randomised studies.
Giovanella, 2014[4]	Systematic review - references checked. No randomised studies.
Jammah, 2020[5]	Non-randomised study
Lee, 2020[6]	Systematic review - references checked. No randomised studies.
Webb, 2012[8]	Systematic review - references checked. No randomised studies.

I.2 Health Economic studies

Published health economic studies that met the inclusion criteria (relevant population, comparators, economic study design, published 2005 or later and not from non-OECD country or USA) but that were excluded following appraisal of applicability and methodological quality are listed below. See the health economic protocol for more details.

None.