National Institute for Health and Care Excellence

Draft

Thyroid cancer

[O] Evidence review for measurement of thyroglobulin

NICE guideline <number>

Evidence reviews underpinning recommendations 1.5.1 to 1.5.5 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 thyroidectomy and radioactive iodine for differentiated thyroid cancer, what is the clinical and cost effectiveness of measuring thyroglobulin and thyroglobulin antibodies (with or without radioisotope scans) to assess residual or recurrent disease?

1.1.2 Introduction

Following treatment with total thyroidectomy (+/- neck dissection) and radioactive iodine for differentiated thyroid cancer, the aim is to leave the patient with no detectable thyroglobulin (Tg). During follow up, serial assessment of Tg and antibodies to Tg can be used to assess for residual or recurrent disease. A rising level of either or both measures is suggestive of disease recurrence, although the presence of structurally identifiable disease is generally the trigger for additional treatment.

This review seeks to determine the effectiveness of measuring thyroglobulin and thyroglobulin antibodies for detecting recurrent disease.

1.1.3 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 thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer. People will need to have had their first assessment with thyroglobulin between 3 and 6 months after ablation. If <3 months or 6months -1 year, downgrading for population indirectness will occur. Exclusion: Children under 16 First thyroglobulin assessment >1 year post-ablation
Intervention	• Measurement of thyroglobulin and thyroglobulin antibodies *with* radioisotope scans • Measurement of thyroglobulin and thyroglobulin antibodies *without* radioisotope scans • Measurement of thyroglobulin and thyroglobulin antibodies without clear (in terms of description in paper) indication of radioisotope scans
Comparison	Each other Usual care (except thyroglobulin) / Ultrasound
Outcomes	• mortality • quality of life • local cancer progression • incidence of distant metastases • detection of residual disease or detection of recurrent disease when no residual disease seen Time of follow up: longest available
Study design	• Systematic reviews of RCTs

- RCTs

Non-randomised studies will be excluded.

1.1.4 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.

1.1.5 Effectiveness evidence

1.1.5.1 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.

1.1.5.2 Excluded studies

The seven excluded studies included three systematic reviews that highlighted the lack of randomised trials in this area. The four primary studies were restricted to observational analyses as far as thyroglobulin measurement was concerned; two of these studies were randomised trials, but the groups were not randomised according to thyroglobulin measurement approaches. See the excluded studies list in Appendix I.

1.1.6 Economic evidence

1.1.6.1 Included studies

No health economic studies were included.

1.1.6.2 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.

1.1.7 Summary of included economic evidence

None.

1.1.8 Economic model

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

1.1.9 Economic evidence statements

No relevant economic evaluations were identified.

1.1.10 The committee's discussion and interpretation of the evidence

1.1.10.1 The outcomes that matter most

Protocol-specified outcomes of mortality, quality of life, local cancer progression, incidence of distant metastases, and detection of residual disease or detection of recurrent disease when no residual disease seen were all deemed critical and were therefore of equal importance in decision-making.

1.1.10.2 The quality of the evidence

No evidence was found for this question, and so recommendations were made on the basis of consensus.

1.1.10.3 Benefits and harms

In the absence of review evidence, the committee initially discussed how thyroglobulin measurement was part of current practice for evaluating recurrence of differentiated thyroid cancer after thyroidectomy and RAI. Harms of thyroglobulin measurement, such as over-investigation secondary to false positives, were not regarded as sufficient to negate the clinical benefits accrued from early detection of recurrence or progression of disease. The consensus was that since there was no feasible alternative method for measuring recurrence, thyroglobulin measurement should therefore be recommended. Frequency of thyroglobulin measurement was recommended in line with current practice: at 3-6 monthly intervals for the first 2 years, followed by 6-12 monthly intervals thereafter. These frequencies were agreed to be sufficiently high to permit detection of recurrences relatively early, with priority given to greater frequencies at the period where recurrences would be most expected.

The committee discussed the importance of measuring thyroglobulin antibodies alongside thyroglobulin. This was because the presence of thyroglobulin antibodies can have a significant impact upon thyroglobulin levels. In some assays the effect of antibodies is to reduce the thyroglobulin levels, increasing the risk of false negative results, though in other assays the reverse effect can occur, with an increased risk of false positive results. The committee agreed that this means that thyroglobulin antibodies should always be measured and is the reason why thyroglobulin antibody measurement is prescribed alongside thyroglobulin measurement in the first recommendation.

The committee agreed that if thyroglobulin antibodies are *not* detected, then thyroglobulin levels can be interpreted without complications. This forms the basis of the 'be aware' recommendation, which states that positive thyroglobulin tests in people with negative thyroglobulin antibodies indicate the presence of either residual thyroid tissue and/or residual or recurrent thyroid malignancy. The committee agreed that in such a case this initial evidence of recurrence should lead to further investigations to either confirm or refute whether recurrence has indeed occurred. In addition, they agreed that further investigation of recurrence should also occur in someone who has previously been cleared of having actual recurrence after a positive thyroglobulin test, but for whom thyroglobulin levels were now rising. This is because the current rise in thyroglobulin levels might denote a 'new' potential sign of recurrence, independent of the previous one, that needs re-investigation to confirm or refute the actual existence of recurrence.

The committee also considered what should happen if thyroglobulin antibodies are detected above the laboratory threshold. This was regarded as the more complex scenario. Initially the clinician would be expected to investigate how the assay might be affected by antibodies, and whether it might cause a shift upwards or downwards in measured thyroglobulin levels. This would influence how the thyroglobulin levels are interpreted, and, if there was sufficient uncertainty, moving to other investigations to confirm or refute actual recurrence, prompted

by a conservative suspicion of recurrence. It was also agreed that there should be further investigations if at a later point either the thyroglobulin levels or thyroglobulin antibodies start to rise. This was because each of these scenarios could, directly or indirectly, indicate recurrence.

Apart from addressing the value of measuring thyroglobulin and thyroglobulin antibodies, the review question also included consideration of the additional value of using radioisotope scans to facilitate the search for recurrence. However, the committee did not include a specific recommendation about radioisotope scans because the consensus was that such scans did not enhance the management strategy.

1.1.10.4 Cost effectiveness and resource use

No health economics or clinical evidence was included for this question. The committee made consensus recommendation drawing from their clinical experience and current practice.

The committee recommended to measure level of thyroglobulin and thyroglobulin antibodies at an interval of 3-6 months in the two years after ablation and then at 6-12 monthly intervals thereafter in line with current practice and thus not requiring additional NHS resources.

The additional recommendations reflect the importance of measuring antibodies together with thyroglobulin as this may change the interpretation of the results. Considering further testing depending on the results of both thyroglobulin and thyroglobulin antibodies represent best practice when monitoring patients who underwent surgery and ablation for thyroid cancer and should ensure that recurrences are promptly detected, thus improving the efficiency of the NHS and improving the quality of life of cancer survivors.

1.1.10.5 Other factors the committee took into account

A research recommendation for an RCT was not made because the consensus opinion was that it was unnecessary to provide experimental evidence that thyroglobulin testing was useful, given the lack of competing alternative strategies available, together with the overwhelming clinical opinion that thyroglobulin was a valid and useful measure of thyroid cancer recurrence. Furthermore, the implications of randomising people to not receive thyroglobulin testing in the above context were deemed unethical. An alternative randomised study comparing radioisotope scanning to no radioisotope scanning in two arms of patients who are both receiving thyroglobulin was considered but was agreed to be of relatively little interest to potential researchers, given the relative lack of clinical interest in the question around the use of radioisotope imaging alongside thyroglobulin measurement.

One inequality issue relevant to this review concerned pregnant women. Measurement of thyroglobulin with radioisotope scans may impose risks to the developing foetus and so this would need to be considered.

1.1.11 Recommendations supported by this evidence review

This evidence review supports recommendations 1.5.1 to 1.5.5.

References

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Appendices

Appendix A – Review protocols

A.1 Review protocol for measuring thyroglobulin and thyroglobulin antibodies

Field	Content
PROSPERO registration number	CRD42021282429
Review title	The clinical and cost effectiveness of measuring thyroglobulin and thyroglobulin antibodies (with or without radioisotope scans) to assess residual or recurrent disease, for people who have had thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer.
Review question	For people who have had thyroidectomy and radioactive iodine for differentiated thyroid cancer, what is the clinical and cost effectiveness of measuring thyroglobulin and thyroglobulin antibodies (with or without radioisotope scans) to assess residual or recurrent disease?
Objective	To determine the effectiveness of measuring thyroglobulin and thyroglobulin antibodies for detecting recurrent disease.
Searches	The following databases will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR)

Field	Content
	• Embase • MEDLINE Searches will be restricted by: • English language • Human studies • Letters and comments are excluded. Other searches: • 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:

Field	Content
	People aged 16 or over who have had thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer. People will need to have had their first assessment with thyroglobulin between 3 and 6 months after ablation. If <3 months or 6months -1 year, downgrading for population indirectness will occur. Exclusion: Children under 16 First thyroglobulin assessment >1 year post-ablation
Intervention/Exposure/Test	• Measurement of thyroglobulin and thyroglobulin antibodies WITH RADIOISOTOPE SCANS • Measurement of thyroglobulin and thyroglobulin antibodies WITHOUT RADIOISOTOPE SCANS • Measurement of thyroglobulin and thyroglobulin antibodies WITHOUT CLEAR (in terms of description in paper) INDICATION OF RADIOISOTOPE SCANS
Comparator/Reference standard/Confounding factors	Each other Usual care (except thyroglobulin) / Ultrasound

Field	Content
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	Thyroglobulin scans are now established tests for evaluating recurrence, but it is important to assess their efficacy before recommending their use. One important question around thyroglobulin testing is whether radioisotope scanning is a useful adjunct. This will be addressed as well by this question.
Primary outcomes (critical outcomes)	• mortality • quality of life • local cancer progression • incidence of distant metastases • detection of residual disease or detection of recurrent disease when no residual disease seen Time of follow up: longest available

Field	Content
Secondary outcomes (important outcomes)	None
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.

Field	Content
	For Intervention reviews the following checklist will be used according to study design being assessed: • Systematic reviews: Risk of Bias in Systematic Reviews (ROBIS) • 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.

Field	Content
	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 of disease <u>Sub-grouping</u> If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategies: 1. Different assays: highly sensitive and not specified 2. Length of follow up: 1 year or less; more than one year to 3 years; more than 3 years
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic ☐ Qualitative

Field	Content
	☐ 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
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.

Field	Content
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	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=282429
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

Field	Content
	• 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 Appendix B 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.

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 thyroidectomy and radioactive iodine for differentiated thyroid cancer, what is the clinical and cost effectiveness of measuring thyroglobulin and thyroglobulin antibodies (with or without radioisotope scans) to assess residual or recurrent disease?

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

Database	Dates searched	Search filters and limits applied
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)
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

Database	Dates searched	Search filters and limits applied
	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
	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

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

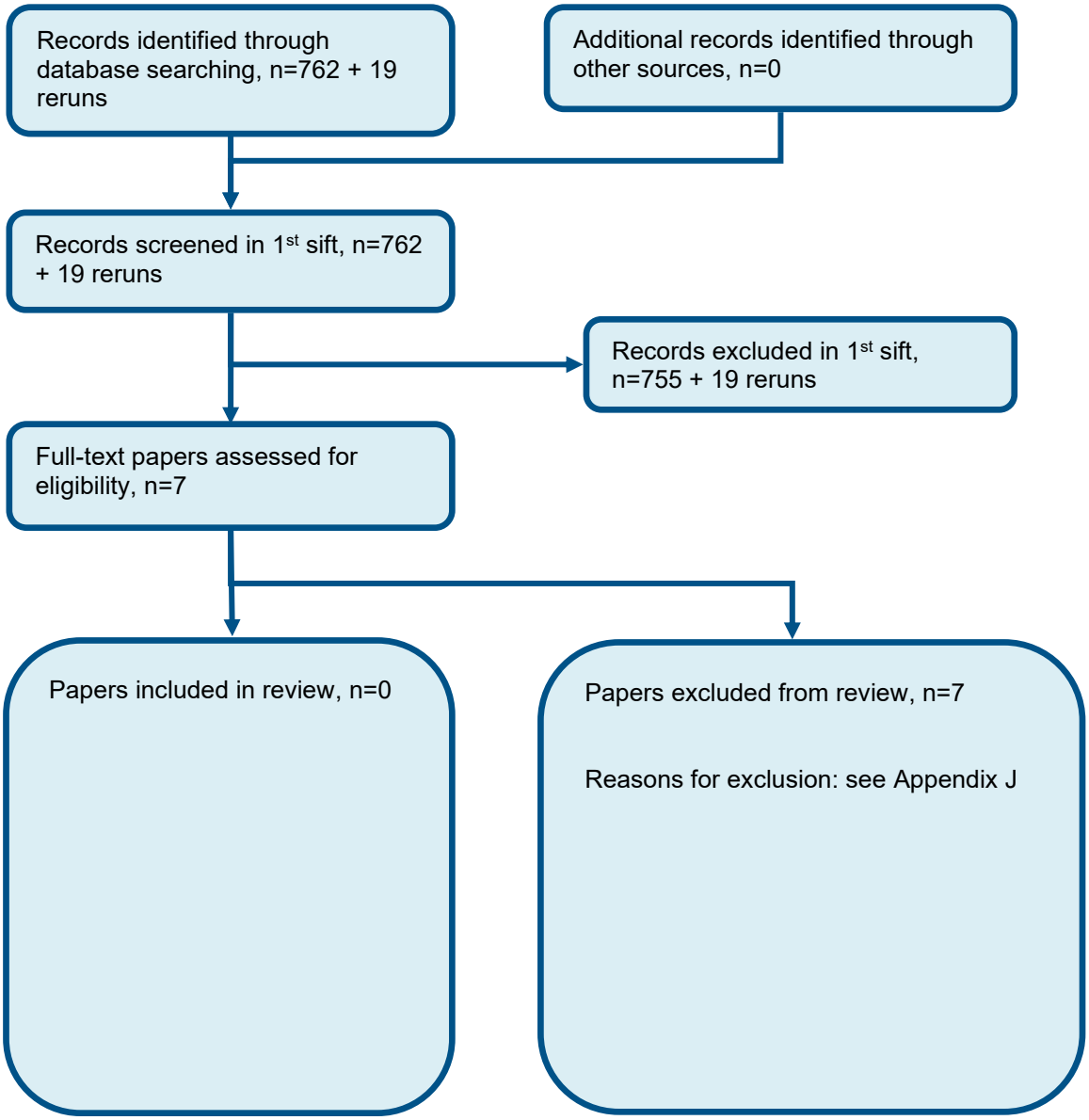
2 **INHATA search terms**

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

3

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of measuring thyroglobulin



Appendix D – Effectiveness evidence

No evidence was found

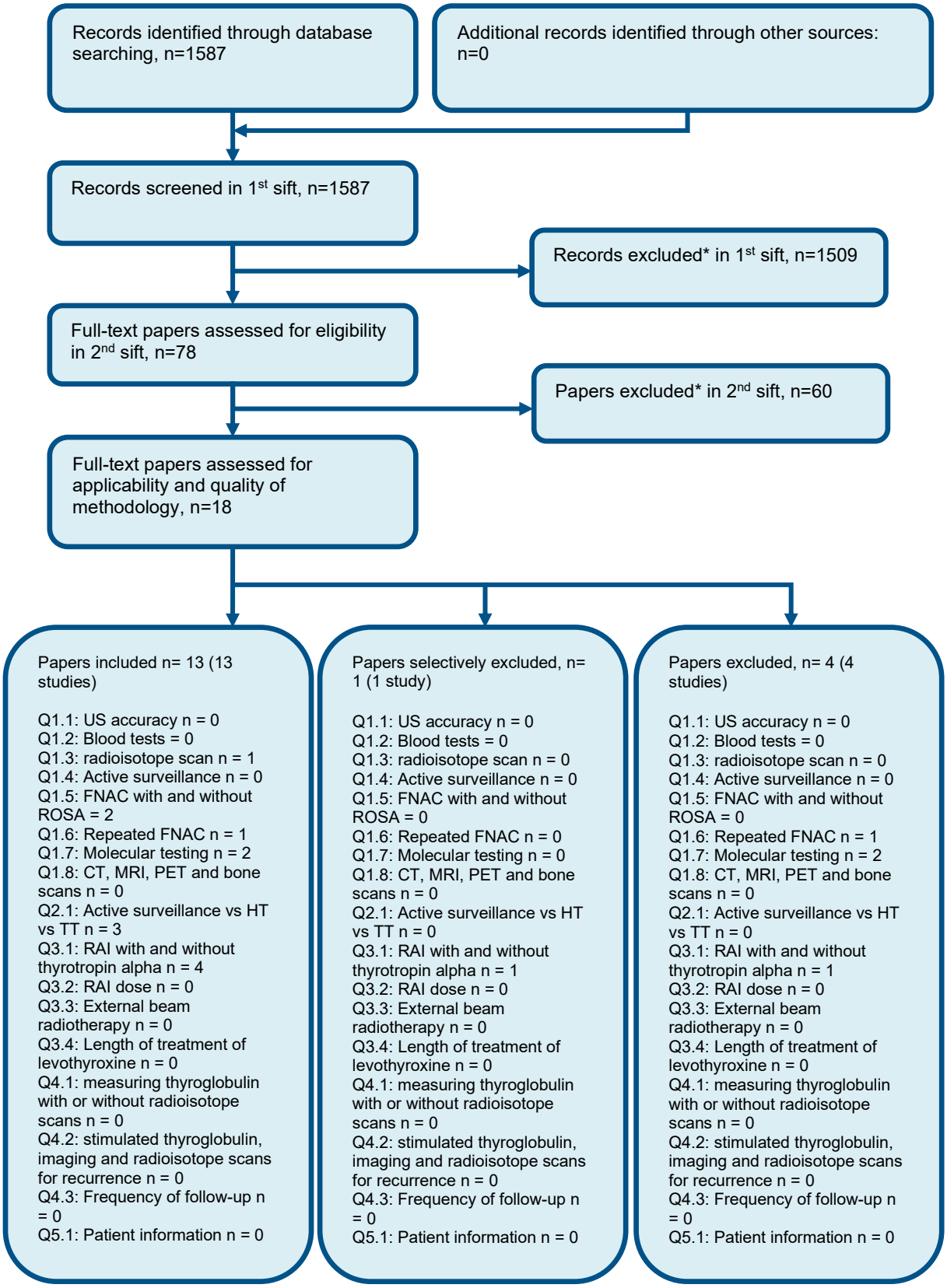
Appendix E – Forest plots

No evidence was found

Appendix F – GRADE and/or GRADE-CERQual tables

No evidence was 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
Brose, 2019[1]	Did not randomise to thyroid measurement or no thyroid measurement, or different types of thyroid measurement. Instead, this was a sub-analysis of an RCT comparing sorafenib to placebo, where associations of thyroglobulin levels with outcomes were evaluated for all patients.
Ferrari, 2004[2]	Non-randomised study; Did not evaluate protocol outcomes
Gray, 2018[3]	Systematic review - references checked
Jammah, 2020[4]	Non-randomised study
Ladenson, 2002[5]	Did not randomise to thyroid measurement or no thyroid measurement, or different types of thyroid measurement. Instead, this was an RCT comparing rTSH to T4 withdrawal in people having recurrence assessed with I131 and thyroglobulin measurement.
Lee, 2020[6]	Systematic review - references checked
Webb, 2012[8]	Systematic review - references checked

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.

References

1. Brose MS, Schlumbeger M, Jeffers M, Kappeler C, Meinhardt G, Pena CEA. Analysis of biomarkers and association with clinical outcomes in patients with differentiated thyroid cancer: Subanalysis of the sorafenib phase iii decision trial. Clinical Cancer Research. 2019; 25(24):7370-7380

2. Ferrari L, Seregni E, Aliberti G, Martinetti A, Pallotti F, Villano C et al. Comparative evaluation of two methods to assay thyroglobulin serum concentrations in patients with differentiated thyroid carcinomas. The Quarterly Journal of Nuclear Medicine & Molecular Imaging. 2004; 48(3):237-242

3. Gray JL, Singh G, Uttley L, Balasubramanian SP. Routine thyroglobulin, neck ultrasound and physical examination in the routine follow up of patients with differentiated thyroid cancer-Where is the evidence? Endocrine. 2018; 62(1):26-33

4. Jammah AA, Masood A, Akkielah LA, Alhaddad S, Alhaddad MA, Alharbi M et al. Utility of stimulated thyroglobulin in reclassifying low risk thyroid cancer patients' following thyroidectomy and radioactive iodine ablation: A 7-year prospective trial. Frontiers in Endocrinology. 2020; 11:603432

5. Ladenson PW. Recombinant thyrotropin for detection of recurrent thyroid cancer. Transactions of the American Clinical and Climatological Association. 2002; 113:21-30

6. Lee ZJO, Eslick GD, Edirimanne S. Investigating antithyroglobulin antibody as a prognostic marker for differentiated thyroid cancer: A meta-analysis and systematic review. Thyroid. 2020; 30(11):1601-1612

7. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

8. Webb RC, Howard RS, Stojadinovic A, Gaitonde DY, Wallace MK, Ahmed J et al. The utility of serum thyroglobulin measurement at the time of remnant ablation for predicting disease-free status in patients with differentiated thyroid cancer: a meta-analysis involving 3947 patients. Journal of Clinical Endocrinology and Metabolism. 2012; 97(8):2754-2763