National Institute for Health and Care Excellence

Draft

Thyroid Cancer

[N] Evidence review for duration of TSH suppression

NICE guideline <number>

Evidence reviews underpinning recommendations 1.4.5 and the research recommendation 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 Duration of TSH suppression

1.1 Review question

1.1.1 For people who have had thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer, what is the most clinically and cost-effective length of treatment with drugs (such as levothyroxine) to supress TSH to subnormal levels?

1.1.2 Introduction

Although TSH may be useful prior to radioactive iodine ablation to promote Iodine 131 uptake, it may also be a promotor of cancer growth and spread in the longer term. Hence levothyroxine (or similar) treatment is required in the post-iodine ablation phase of treatment to suppress TSH levels. It is currently uncertain how long such therapy should be continued. Levothyroxine supplementation is usually given to all patients after thyroid surgery to prevent hypothyroidism (when given in the dosages necessary to avoid hypothyroidism, the TSH levels should be fairly normal). However, this question concerns the length of time that additional amounts of levothyroxine would be given to ensure that TSH levels remain subnormal or extremely low.

Historically, lifelong TSH suppression has been advocated for all patients with differentiated thyroid cancer to reduce the risk of recurrent and progressive disease. This approach has been challenged in recent years with the increasing recognition of the adverse effects of long term TSH suppression therapy on the heart and on bone. Balancing the potential benefits of long term TSH suppression with risks is important considering the low risk for cancer-specific mortality and long term survival for many patients with differentiated thyroid cancer.

The optimal duration of TSH inhibition to maximise the benefits whilst minimising the risks is uncertain. Current practice varies with some clinicians stopping after five years and others continuing far longer. This review seeks to determine the most effective length of treatment with drugs such as levothyroxine to suppress TSH.

1.1.3 Summary of the protocol

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 Exclusion: Children under 16
Intervention(s)	• Treatment length of <5 years with T4 levothyroxine / other TSH lowering agents such as 'Armour thyroid' (levothyroxine and liothyronine) or liothyronine alone • Treatment length of 5-10 years with T4 levothyroxine / other TSH lowering agents such as 'Armour thyroid' (levothyroxine and liothyronine) or liothyronine alone • Treatment length of >10 years with T4 levothyroxine / other TSH lowering agents such as 'Armour thyroid' (levothyroxine and liothyronine) or liothyronine alone • Risk stratification approach – measure stimulated thyroglobulin at 1 year and adapt management accordingly
Comparison(s)	Each other.

	If two interventions within one time limit, include but downgrade for indirectness
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • thyroglobulin levels • mortality • quality of life (any validated scores) • local cancer progression • incidence of distant metastases • cancer recurrence • cardiovascular adverse effects • osteoporosis • second primary malignancy • time of follow up: open.
Study design	Published NMAs and IPDs will be considered for inclusion. • Systematic reviews • RCTs Non-randomised studies will be used if there are no RCT comparisons. These must adjust for plausible confounders but no specific confounders have been pre-specified.

For full details see the review protocol in Appendix A.

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 clinical studies assessing the length of treatment to suppress TSH levels were identified. The majority of studies did not compare different lengths of administration or were not from an appropriate population to be included within 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.

1.1.5.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.6 Summary of studies included in the effectiveness evidence

No studies were identified for this review

1.1.7 Summary of the effectiveness evidence

No studies were identified for this review

1.1.8 Economic evidence

1.1.8.1 Included studies

No health economic studies were included.

1.1.8.2 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.

1.1.9 Economic model

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

1.1.10 Economic evidence statements

No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

The outcomes considered were mortality, quality of life, thyroglobulin levels, local cancer progression, incidence of distant metastases, cancer recurrence, incidence of osteoporosis, cardiac complications and incidence of second primary malignancy. All outcomes were regarded as critical and of equal weight for decision-making. Reasons for this critical status are explained as follows. Mortality was critical because this is the key harm to consider in cancer treatment, and quality of life was critical because it encompasses global effects that are patient-centred. Thyroglobulin levels were critical because they provide a direct and highly specific measure of recurrence. Local cancer progression, incidence of distant metastases, second primary malignancy and cancer recurrence were all critical because they provide a patient-centred clinically relevant measure of long term effectiveness. Finally, osteoporosis and cardiac complications were critical because these are known to be key potential harms from TSH suppression, and therefore essential for adequate weighing up of benefits and harms.

1.1.11.2 The quality of the evidence

For the 'Duration of TSH suppression review' no relevant articles were included.

1.1.11.3 Benefits and harms

There was no evidence found for the optimal length of TSH suppression and the committee used consensus to make recommendations. Previously, patients would be kept on TSH suppression indefinitely. However, with regular monitoring and risk assessment, this pathway has changed recently, with patients tending to be removed from TSH suppression if indicated by the competing harms of comorbidities. The recommendations reflect that change in practice by highlighting the importance of factoring in each patient's comorbidities. The committee also emphasized that some patients may be reluctant to suddenly stop taking TSH suppression or to reduce it due to the psychological anxiety related with a change in their practice. Therefore, patients on TSH suppression for more than 10 years need a clinical review to assess their ongoing treatment, as well as the risks and benefits of TSH

suppression. Because of the lack of evidence about the actual duration of treatment, a research recommendation was also made for this question.

1.1.11.4 Cost effectiveness and resource use

No health economic evidence was found for this question.

There was no evidence regarding the length of the duration of TSH suppression. The committee recommended to review patients who had undergone TSH suppression therapy for a period greater than 10 years for an individualised assessment of risk and benefits of continuing the therapy. This reflects current practice where patients are followed up and reviewed during their TSH suppression and it is not expected to require additional NHS resources.

1.1.11.5 Other factors the committee took into account

Dynamic risk stratification is an established system used to assess the risk of recurrence of thyroid cancer by evaluating the patient's response to treatment. This re-evaluation of risk allows the follow-up strategy to be modified according to treatment response. The response to treatment is based on measurement of serum thyroglobulin Tg (and anti-thyroglobulin antibody TgAb) and on ultrasound imaging. An excellent response (undetectable Tg, undetectable TgAb, negative imaging) in a patient initially classified as low risk has a very low risk of recurrence. If the ultrasound shows persistent foci of tumour, the response is classified as structurally incomplete. A response termed indeterminate is when the Tg is measurable but low whilst a biochemically incomplete response consists of an elevated Tg.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendation 1.4.5 and the research recommendation on optimal length of TSH suppression for people with differentiated thyroid cancer who have had surgery and RAI.

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Appendices

Appendix A – Review protocols

A.1 Review protocol for duration of TSH suppression

Field	Content
PROSPERO registration number	CRD42021241580
Review title	The most clinically and cost-effective length of treatment with drugs* that suppress TSH to subnormal levels, for people who have had thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer. *for example, levothyroxine, or liothyronine
Review question	For people who have had thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer, what is the most clinically and cost-effective length of treatment with drugs (such as levothyroxine) to supress TSH to subnormal levels?
Objective	To determine the most effective length of treatment with drugs such as levothyroxine to suppress TSH. Although TSH may be useful prior to radioactive iodine ablation to promote Iodine 131 uptake, it may also be a promotor of cancer growth and spread in the longer term. Hence levothyroxine (or similar)

Field	Content
	treatment is required in the post-iodine ablation phase of treatment to suppress TSH levels. It is currently uncertain how long such therapy should be continued. Levothyroxine supplementation would always be given to all patients after thyroid surgery to prevent hypothyroidism (when given in the dosages necessary to avoid hypothyroidism, the TSH levels should be fairly normal). However, this question concerns the length of time that additional amounts of levothyroxine would be given to ensure that TSH levels remain subnormal or extremely low.
Searches	The following databases (from inception) 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.

Field	Content
	Other searches: • Inclusion lists of relevant systematic reviews will be checked by the reviewer. The searches may be re-run 6 weeks before final committee meeting and further studies retrieved for inclusion if relevant. The full search strategies will be published in the final review. Medline search strategy to be quality assured using the PRESS evidence-based checklist (see methods chapter for full details).
Condition or domain being studied	Thyroid cancer
Population	Inclusion: People aged 16 or over who have had thyroidectomy and radioactive iodine treatment for differentiated thyroid cancer Exclusion:

Field	Content
	Children under 16
Intervention/Exposure/Test	• Treatment length of <5 years with T4 levothyroxine / other TSH lowering agents such as 'Armour thyroid' (levothyroxine and liothyronine) or liothyronine alone • Treatment length of 5-10 years with T4 levothyroxine / other TSH lowering agents such as 'Armour thyroid' (levothyroxine and liothyronine) or liothyronine alone • Treatment length of >10 years with T4 levothyroxine / other TSH lowering agents such as 'Armour thyroid' (levothyroxine and liothyronine) or liothyronine alone • Risk stratification approach – measure stimulated thyroglobulin at 1 year and adapt management accordingly
Comparator/Reference standard/Confounding factors	Each other. If two interventions within one time limit, include but downgrade for indirectness
Types of study to be included	Published NMAs and IPDs will be considered for inclusion. • Systematic reviews • RCTs

Field	Content
	Non-randomised studies will be used if there are no RCT comparisons. These must adjust for plausible confounders but no specific confounders have been pre-specified.
Other exclusion criteria	Non-English language studies. Conference abstracts will be excluded as it is expected there will be sufficient full text published studies available.
Context	For people suitable for TSH suppression there is still uncertainty about the optimum length of treatment.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • Thyroglobulin levels • mortality • quality of life (any validated scores) • local cancer progression • incidence of distant metastases • cancer recurrence • cardiovascular adverse effects • osteoporosis

Field	Content
	• second primary malignancy Time of follow up: open.
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. 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. • 10% of all evidence reviews are quality assured by a senior research fellow. This includes checking: • papers were included /excluded appropriately • a sample of the data extractions • correct methods are used to synthesise data

Field	Content
	• a sample of the risk of bias assessments 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.
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) • Randomised Controlled Trial: Cochrane RoB (2.0) • Robins checklist for non-randomised trials
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.

Field	Content
	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> Degree of suppression of TSH: low normal vs below normal range vs undetectable <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:

Field	Content
	• Type of TSH lowering therapy used – T4 versus T4/liothyronine versus liothyronine • Achievement of intended suppression: Y/N
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**

Field	Content
	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 Vimal Bedia, Systematic reviewer Alfredo Mariani, Health economist Giulia Zuodar, Project manager 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.
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.

Field	Content
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=241580
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	None
Details of existing review of same topic by same authors	N/A

Field	Content
Additional information	N/A
Details of final publication	www.nice.org.uk

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).[11] **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:

- What is the clinical and cost effectiveness of TSH suppression versus no TSH suppression in different population groups, characterised by recurrence risk, ethnicity, gender and age?

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 Observational 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 Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children)

Database	Dates searched	Search filters and limits applied
		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)
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.	exp Thyrotropin/

29.	(thyrotropin* or thyreotropin* or thyrotrophin* or thyrotropic).ti,ab.
30.	(thyroid stimulating adj2 hormone*).ti,ab.
31.	TSH.ti,ab.
32.	((thyroid or hormon*) adj4 (suppress* or lower*)).ti,ab.
33.	Thyroxine/
34.	(thyroxine or thyroxin or tetraiodothyronine or levothyroxine or Lthyroxine or T4 or LT4).ti,ab.
35.	Eltroxin.ti,ab.
36.	Triiodothyronine/
37.	(triiodothyronine or tri-iodothyronine or liothyronine or Ltriiodothyronine or T3 or LT3).ti,ab.
38.	Tertroxin.ti,ab.
39.	"Thyroid (USP)"/
40.	((thryoid or hormone*) adj2 (natural or desiccated or extract* or preparation*)).ti,ab.
41.	((porcine or pig) adj thyroid).ti,ab.
42.	(NDT or DTE).ti,ab.
43.	Armour.ti,ab.
44.	or/28-43
45.	27 and 44
46.	randomized controlled trial.pt.
47.	controlled clinical trial.pt.
48.	randomi#ed.ab.
49.	placebo.ab.
50.	randomly.ab.
51.	clinical trials as topic.sh.
52.	trial.ti.
53.	or/46-52
54.	Meta-Analysis/
55.	Meta-Analysis as Topic/
56.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
57.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
58.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
59.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
60.	(search* adj4 literature).ab.
61.	(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.
62.	cochrane.jw.
63.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
64.	or/54-63
65.	Epidemiologic studies/
66.	Observational study/
67.	exp Cohort studies/
68.	(cohort adj (study or studies or analys* or data)).ti,ab.
69.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.

70.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
71.	Controlled Before-After Studies/
72.	Historically Controlled Study/
73.	Interrupted Time Series Analysis/
74.	(before adj2 after adj2 (study or studies or data)).ti,ab.
75.	exp case control study/
76.	case control*.ti,ab.
77.	Cross-sectional studies/
78.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	or/66-79
80.	45 and (53 or 64 or 79)

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.	exp Thyrotropin/
28.	(thyrotropin* or thyreotropin* or thyrotrophin* or thyrotropic).ti,ab.
29.	(thyroid stimulating adj2 hormone*).ti,ab.
30.	TSH.ti,ab.

31.	((thyroid or hormon*) adj4 (suppress* or lower*)).ti,ab.
32.	Thyroxine/
33.	(thyroxine or thyroxin or tetraiodothyronine or levothyroxine or Lthyroxine or T4 or LT4).ti,ab.
34.	Eltroxin.ti,ab.
35.	Liothyronine/
36.	(triiodothyronine or tri-iodothyronine or liothyronine or Ltriiodothyronine or T3 or LT3).ti,ab.
37.	Tertroxin.ti,ab.
38.	Thyroid Extract/
39.	((thryoid or hormone*) adj2 (natural or desiccated or extract* or preparation*)).ti,ab.
40.	((porcine or pig) adj thyroid).ti,ab.
41.	(NDT or DTE).ti,ab.
42.	Armour.ti,ab.
43.	or/27-42
44.	26 and 43
45.	random*.ti,ab.
46.	factorial*.ti,ab.
47.	(crossover* or cross over*).ti,ab.
48.	((doubl* or singl*) adj blind*).ti,ab.
49.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
50.	crossover procedure/
51.	single blind procedure/
52.	randomized controlled trial/
53.	double blind procedure/
54.	or/45-53
55.	Systematic Review/
56.	Meta-Analysis/
57.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
58.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
59.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
60.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
61.	(search* adj4 literature).ab.
62.	(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.
63.	cochrane.jw.
64.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
65.	or/55-64
66.	Clinical study/
67.	Observational study/
68.	Family study/
69.	Longitudinal study/
70.	Retrospective study/
71.	Prospective study/
72.	Cohort analysis/
73.	Follow-up/

74.	cohort*.ti,ab.
75.	74 and 75
76.	(cohort adj (study or studies or analys* or data)).ti,ab.
77.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
78.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
79.	(before adj2 after adj2 (study or studies or data)).ti,ab.
80.	exp case control study/
81.	case control*.ti,ab.
82.	cross-sectional study/
83.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
84.	or/67-73,76-84
85.	44 and (54 or 65 or 84)

1 **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.	MeSH descriptor: [Thyrotropin] explode all trees
#7.	(thyrotropin* or thyreotropin* or thyrotrophin* or thyrotropic):ti,ab
#8.	(thyroid stimulating near/2 hormone*):ti,ab
#9.	TSH:ti,ab
#10.	((thyroid or hormon*) near/4 (suppress* or lower*)):ti,ab
#11.	MeSH descriptor: [Thyroxine] this term only
#12.	(thyroxine or thyroxin or tetraiodothyronine or levothyroxine or Lthyroxine or T4 or LT4):ti,ab
#13.	Eltroxin:ti,ab
#14.	MeSH descriptor: [Triiodothyronine] this term only
#15.	(triiodothyronine or tri-iodothyronine or liothyronine or Ltriiodothyronine or T3 or LT3):ti,ab
#16.	Tertroxin:ti,ab
#17.	MeSH descriptor: [Thyroid (USP)] this term only
#18.	((thryoid or hormone*) near/2 (natural or desiccated or extract* or preparation*)):ti,ab
#19.	((porcine or pig) next thyroid):ti,ab
#20.	(NDT or DTE):ti,ab
#21.	Armour:ti,ab
#22.	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21
#23.	#5 and #22
#24.	conference:pt or (clinicaltrials or trialsearch):so
#25.	#23 not #24

2

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
	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

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

NHS EED and HTA (CRD) search terms

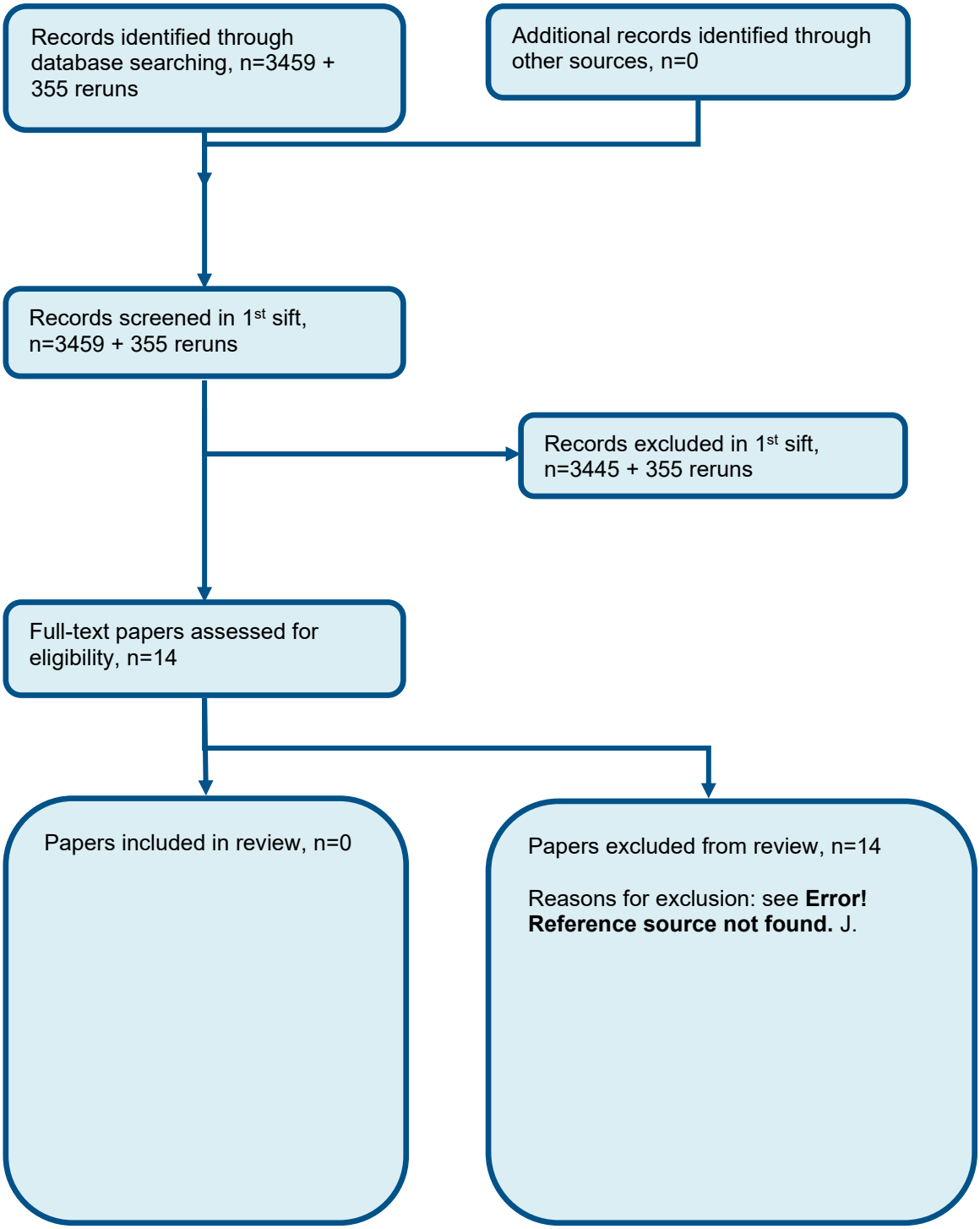
#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic)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

INHATA search terms

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

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of duration of TSH suppression



Appendix D – Effectiveness evidence

No studies were identified for this review.

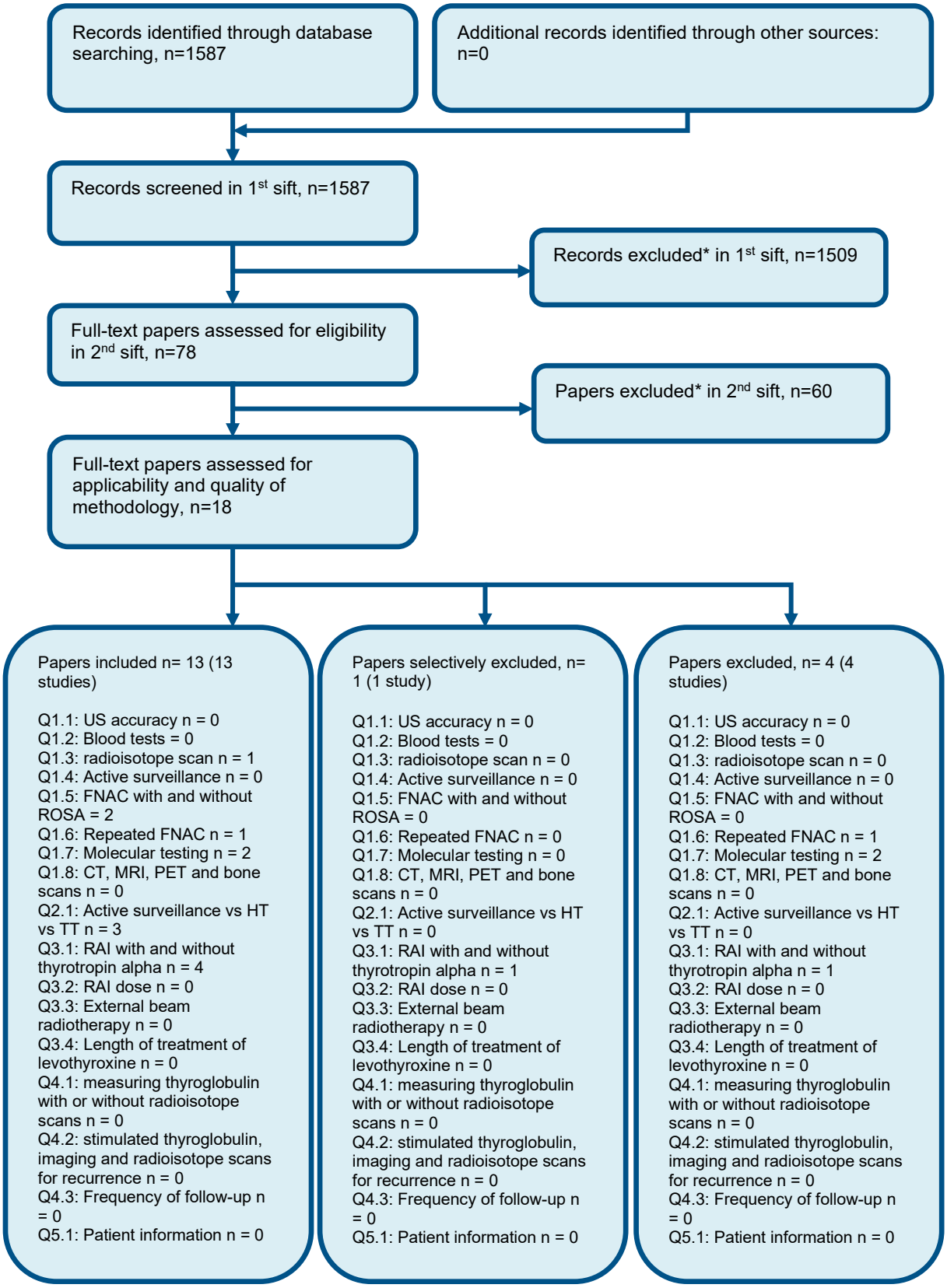
Appendix E – Forest plots

No studies were identified for this review.

Appendix F – GRADE tables

No studies were identified for this review

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
Abo-Touk 2015[1]	Inappropriate comparison – not comparing length of administration for TSH suppression
Chen 2004[2]	Inappropriate comparison / no relevant outcomes – compares outcomes for pre / post-menopausal women with controls (euthyroid); not comparing length of administration for TSH suppression
Del Duca 2015[3]	Inappropriate comparison / population – only a minority with previous DTC / not comparing length of administration for TSH suppression
Diamond 1991[4]	Inappropriate comparison / no relevant outcomes – pre / postmenopausal women compared to healthy controls; not comparing length of administration for TSH suppression
Diessl 2012[5]	Inappropriate comparison – non comparative study (single cohort); no relevant outcomes
Fujiyama 1995[6]	Inappropriate population – participants not treated with RAI
Kim 2015[7]	Inappropriate population– participants not treated with RAI
Ko 2014[8]	Inappropriate population – participants with DTC excluded
Kung 1993[9]	Inappropriate comparison / no relevant outcomes – postmenopausal women compared to healthy controls; not comparing length of administration for TSH suppression
Miccoli 2020[10]	Systematic review – references checked
Park 2017[12]	Inappropriate population – participants not treated with RAI
Pujol 1996[13]	Inappropriate comparison – non comparative study (single cohort)
Schneider 2012[14]	Inappropriate population – DTC / non-toxic goitre compared with healthy controls
Soydal 2019[15]	Inappropriate comparison / no relevant outcomes – assessing time taken to develop Osteoporosis

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.

Appendix J – Research recommendations – full details

J.1.1 Research recommendation

For people with differentiated thyroid cancer who have had surgery and RAI, what is the optimal length of TSH suppression?

J.1.2 Why this is important

In patients with differentiated thyroid cancer who have had initial treatment and RAI, there is a need to supress TSH levels to help prevent recurrence or spread. Although continued suppression for an unlimited time might appear sensible, this may be expensive and have side effects that impair quality of life. On the other hand, an overly short period of suppression might allow recurrence and spread to occur. There should therefore be an optimal duration, but there are currently no data available suggesting the optimal duration of such suppression. The committee agreed that the ideal evidence would be derived by an RCT comparing:

- Treatment length of <5 years
- Treatment length of 5-10 years
- Treatment length of >10 years

This could be stratified by the TSH-suppressing strategy used (T4 levothyroxine *versus* levothyroxine and liothyronine *versus* liothyronine alone), which would help to answer the secondary question of the optimal method of supressing TSH.

It is highly likely that the optimal duration will depend on patient characteristics, and so analysis should also be stratified by patient factors that the researchers think will influence outcomes.

J.1.3 Rationale for research recommendation

Importance to 'patients' or the population	Whilst TSH suppression reduces the probability of recurrence and spread, it also carries harms and costs, and so an optimal duration of suppression will exist for each patient. A research study designed to evaluate the optimal duration of suppression is therefore of great relevance to patients.
Relevance to NICE guidance	The efficacy of different durations of TSH suppression has been considered in this guideline, but we did not find any RCTs evaluating them. The development of such RCTs is therefore required.
Relevance to the NHS	If an optimal duration can be derived this may improve patient outcomes and reduce costs for the NHS.
National priorities	Whilst TSH suppression reduces the probability of recurrence and spread, it also

	carries harms and costs, and so an optimal duration of suppression will exist for each patient. A research study designed to evaluate the optimal duration of suppression is therefore of great relevance to patients.
Current evidence base	There is currently no RCT evidence.
Equality considerations	None known

1

2 ### J.1.4 Modified PICO table

3

Population	People with differentiated thyroid cancer who have had surgery and RAI
Intervention	• Treatment length of <5 years • Treatment length of 5-10 years • Treatment length of >10 years
Comparator	To each other (see above)
Outcome	Quality of life, recurrence, progression, mortality
Study design	RCT
Timeframe	Long term
Additional information	This could be stratified by the TSH-suppressing strategy used (T4 levothyroxine versus levothyroxine and liothyronine versus liothyronine alone), which would help to answer the secondary question of the optimal method of supressing TSH. It is highly likely that the optimal duration will depend on patient characteristics, and so analysis should also be stratified by patient factors that the researchers think will influence outcomes.

4

5