National Institute for Health and Care Excellence

FINAL

Thyroid disease: assessment and management

[D] Tests for people with confirmed primary hypothyroidism

NICE guideline NG145

Intervention evidence review underpinning recommendations 1.3.1 and 1.3.2 in the guideline

2019

FINAL

Developed by the National Guideline Centre, hosted by the Royal College of Physicians

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, where appropriate, their carer or guardian.

Local commissioners and 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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1 Antibodies in hypothyroidism

1.1 Review question: What is the clinical and cost effectiveness of antibody testing during investigation of hypothyroidism?

1.2 Introduction

The commonest cause of hypothyroidism is autoimmune thyroid disease, which is associated with the presence of circulating thyroid antibodies. Therefore, tests for thyroid autoantibodies, including Thyroid peroxidase antibody(TPO-Ab) and Thyroglobulin antibody (TG-Ab), may be useful to confirm autoimmunity as the cause in a patient with hypothyroidism. Furthermore, in patients with subclinical hypothyroidism, the presence of thyroid antibodies (in particular, TPO-Ab) is associated with an increased risk of progression to overt hypothyroidism. Despite the potential value of testing thyroid antibodies in hypothyroidism, there is uncertainty in terms of which antibodies should be tested when determining the cause of hypothyroidism, when the test should be carried out and if the test should be repeated. Currently, there is no national standard on the topic, resulting in a wide variation in the clinical practice.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People being investigated for hypothyroidism (confirmed as having hypothyroidism via thyroid stimulating hormone (TSH) +/- thyroid hormone results)
Interventions	• Testing for anti-thyroid peroxidase (TPO) at diagnosis • Repeated testing for anti-TPO • Testing for anti-thyroglobulin at diagnosis • Repeated testing for anti-thyroglobulin
Comparisons	Not testing for anti-TPO or anti-thyroglobulin Any testing strategy above vs any other strategy
Outcomes	**Critical** • Mortality (dichotomous, ≥1 year) • Quality of life (continuous) **Important** • Patient/family/carer experience of care (continuous) • Healthcare contacts (rates/dichotomous) • Symptom scores (continuous) • Change in management (rates/dichotomous)
Study design	• Minimum follow-up of 3 months • RCTs Non-randomised cohort studies to be considered if adjusted for key confounders (age, sex, co-existing conditions) and insufficient RCTs evidence found

1.4 Clinical evidence

1.4.1 Included studies

No relevant clinical studies comparing different antibody assessment strategies in hypothyroidism were identified.

1.4.2 Excluded studies

See the excluded studies list in Appendix G:.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

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

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

1.5.3 Health economic modelling

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

1.5.4 Resource costs

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

Table 2: UK costs of antibody testing

Test	Unit costs
TPO antibody testing (a)	£12.32
Tg antibody testing (b)	£15.57

Source: Guideline committee members
(a) Average costs obtained from two hospitals.
(b) Cost obtained from one hospital

1.6 Evidence statements

1.6.1 Clinical evidence statements

- No relevant published evidence was identified.

1.6.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

The critical outcomes for this review were quality of life and mortality. The important outcomes for this review were experience of care, healthcare contacts, symptom scores and change in management.

No evidence was identified for any outcomes in this review.

1.7.1.2 The quality of the evidence

No evidence was identified for any outcomes in this review.

1.7.1.3 Benefits and harms

TPO testing may be beneficial in the early investigation of hypothyroidism in elucidating the cause of the hypothyroidism, in other words whether or not it is autoimmune. However, this is largely unlikely to affect the management plan and any non-autoimmune causes are likely to be obvious from the person's clinical history (for example adverse effects of medication or post-treatment for thyroid cancer). The committee agreed that TPO testing can be beneficial both in terms of fully informing people with thyroid disease about their condition and in some circumstances aiding with treatment adherence. It was also noted that TPO testing may be beneficial in cases of diagnostic uncertainty as to whether a person has clinically relevant thyroid disease, for example in subclinical hypothyroidism or where TSH is only marginally elevated.

Some healthcare professionals perform repeated TPO tests. The committee agreed that this is not a useful strategy as it does not provide additional information beyond that in TSH or FT4 testing. For children, repeated TPO test at the point of transition from child to adult services may be useful. It is not uncommon for a period of temporary drug withdrawal to be instituted at this point and TPO testing can be helpful in confirming the diagnosis at this stage, guiding the long term treatment plan under adult services and reminding the person with thyroid disease of the underlying disease process.

1.7.2 Cost effectiveness and resource use

No health economic evidence was identified for this question. The unit costs for the TPO test was obtained from two NHS hospitals and were presented to the committee. The TPO cost was estimated to be £12.32. It was noted that costs vary as pathology laboratories may add a handling fee to these costs.

The committee noted, from their experience, that the more informed the patient is about their condition the more likely they are to comply with treatment, resulting in better management and improved quality of life. Hence, the test was seen to have benefit and is not likely to have a resource impact. The committee also highlighted the importance of not repeating the test, except in children at the time of transitioning to adult services, as it does not provide any additional information and increases costs to the NHS.

References

1. Barbesino G, Tomer Y. Clinical utility of TSH receptor antibodies. Journal of Clinical Endocrinology and Metabolism. 2013; 98(6):2247-2255

2. Downs H, Meyer AA, Flake D, Solbrig R. Clinical inquiries: How useful are autoantibodies in diagnosing thyroid disorders? Journal of Family Practice. 2008; 57(9):615-6

3. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [updated October 2018]. London. National Institute for Health and Care Excellence, 2014. Available from: http://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview

Appendices

Appendix A: Review protocols

Table 3:

ID	Field	Content
I	Review question	What is the clinical and cost effectiveness of antibody testing during investigation of hypothyroidism?
II	Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	To determine the clinical and cost effectiveness of antibody testing during investigation of hypothyroidism. Antibody testing diagnoses Hashimoto's thyroiditis as the cause of hypothyroidism. However this diagnosis does not substantially affect management. Therefore this review seeks to identify what benefits or harms the diagnosis brings and the cost of this strategy.
IV	Eligibility criteria – population / disease / condition / issue / domain	People being investigated for hypothyroidism (confirmed as having hypothyroidism via TSH +/- thyroid hormone results)
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Testing for anti-TPO at diagnosis Repeated testing for anti-TPO Testing for anti-thyroglobulin at diagnosis Repeated testing for anti-thyroglobulin
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	Not testing for anti-TPO or anti-thyroglobulin Any testing strategy above vs any other strategy
VII	Outcomes and prioritisation	**Critical** Mortality (dichotomous, ≥1 year)

		Quality of life (continuous) **Important** Patient/family/carer experience of care (continuous) Healthcare contacts (rates/dichotomous) Symptom scores (continuous) Change in management (rates/dichotomous)
VIII	Eligibility criteria – study design	Minimum follow-up of 3 months RCTs Non-randomised cohort studies to be considered if adjusted for key confounders (age, sex, co-existing conditions) and insufficient RCTs evidence found
IX	Other inclusion exclusion criteria	-
X	Proposed sensitivity / subgroup analysis, or meta-regression	**Stratifications** Age – infants (<4), children and young people (4-18), adults (>18-65), older adults (>65) **Subgroup analyses** Age subdivisions (4-12, 12-18, 18-50, 50-65, 65-85, >85)
XI	Selection process – duplicate screening / selection / analysis	A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline.
XII	Data management (software)	EndNote was used for reference management, sifting, citations and bibliographies.
XIII	Information sources – databases and dates	Medline, Embase and Cochrane Library
XIV	Identify if an update	Not an update
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10074

XVI	Highlight if amendment to previous protocol	Not an amendment
XVII	Search strategy – for one database	For details please see Appendix B:
XVIII	Data collection process – forms / duplicate	Not applicable
XIX	Data items – define all variables to be collected	For details please see health economic evidence tables in Appendix E:.
XX	Methods for assessing bias at outcome / study level	Not applicable
XXI	Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details please see the introduction to the evidence review.
XXVI	Describe contributions	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and

	of authors and guarantor	chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 4: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B: below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[3] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded then a health economic evidence table will not be completed and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

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

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 5: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 07 January 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 07 January 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 1 or 12 CENTRAL to 2019 Issue 1 or 12	None

Medline (Ovid) search terms

1.	exp hypothyroidism/ or thyroiditis, autoimmune/
2.	(thyroid adj3 (defic* or insuffic* or underactiv*)).ti,ab.
3.	(hypothyr* or hypo-thyr* or autoimmune thyroiditis).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.	exp autoantibodies/
26.	anti-TPO.ti,ab.
27.	((anti thyroid or antithyroid or TPO) adj2 (peroxidase or antibod* or autoantibod*)).ti,ab.
28.	((iodide adj2 peroxidase) or thyroperoxidase or microsomal antigen*).ti,ab.
29.	(antithyroglobulin* or anti thyroglobulin* or thyroglobulin antibod*).ti,ab.
30.	(anti-Tg or TgAb or anti TgAb).ti,ab.
31.	or/25-30
32.	randomized controlled trial.pt.
33.	controlled clinical trial.pt.
34.	randomi#ed.ti,ab.
35.	placebo.ab.
36.	randomly.ti,ab.
37.	Clinical Trials as topic.sh.
38.	trial.ti.
39.	or/32-38
40.	Meta-Analysis/
41.	exp Meta-Analysis as Topic/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(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.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	Epidemiologic studies/
52.	Observational study/
53.	exp Cohort studies/
54.	(cohort adj (study or studies or analys* or data)).ti,ab.
55.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
56.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
57.	Controlled Before-After Studies/
58.	Historically Controlled Study/
59.	Interrupted Time Series Analysis/

60.	(before adj2 after adj2 (study or studies or data)).ti,ab.
61.	or/51-60
62.	exp case control study/
63.	case control*.ti,ab.
64.	or/62-63
65.	61 or 64
66.	Cross-sectional studies/
67.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	or/66-67
69.	61 or 68
70.	61 or 64 or 68
71.	24 and 31
72.	71 and (39 or 50 or 70)

Embase (Ovid) search terms

1.	exp hypothyroidism/ or autoimmune thyroiditis/
2.	(thyroid adj3 (defic* or insuffic* or underactiv*)).ti,ab.
3.	(hypothyr* or hypo-thyr* or autoimmune thyroiditis).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.	exp autoantibody/
24.	anti-TPO.ti,ab.
25.	((anti thyroid or antithyroid or TPO) adj2 (peroxidase or antibod* or autoantibod*)).ti,ab.
26.	((iodide adj2 peroxidase) or thyroperoxidase or microsomal antigen*).ti,ab.
27.	(antithyroglobulin* or anti thyroglobulin* or thyroglobulin antibod*).ti,ab.
28.	(anti-Tg or TgAb or anti TgAb).ti,ab.
29.	or/23-28
30.	random*.ti,ab.
31.	factorial*.ti,ab.

32.	(crossover* or cross over*).ti,ab.
33.	((doubl* or singl*) adj blind*).ti,ab.
34.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
35.	crossover procedure/
36.	single blind procedure/
37.	randomized controlled trial/
38.	double blind procedure/
39.	or/30-38
40.	systematic review/
41.	meta-analysis/
42.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
43.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
44.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
45.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
46.	(search* adj4 literature).ab.
47.	(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.
48.	cochrane.jw.
49.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
50.	or/40-49
51.	Epidemiologic studies/
52.	Observational study/
53.	exp Cohort studies/
54.	(cohort adj (study or studies or analys* or data)).ti,ab.
55.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
56.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
57.	Controlled Before-After Studies/
58.	Historically Controlled Study/
59.	Interrupted Time Series Analysis/
60.	(before adj2 after adj2 (study or studies or data)).ti,ab.
61.	or/51-60
62.	exp case control study/
63.	case control*.ti,ab.
64.	or/62-63
65.	61 or 64
66.	Cross-sectional studies/
67.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
68.	or/66-67
69.	61 or 68
70.	61 or 64 or 68
71.	22 and 29 and (39 or 50 or 70)

Cochrane Library (Wiley) search terms

#1.	MeSH descriptor: [Hypothyroidism] explode all trees
#2.	MeSH descriptor: [Thyroiditis] explode all trees
#3.	(thyroid near/3 (defic* or insuffic* or underactiv*)):ti,ab
#4.	(hypothyr* or hypo-thyr* or autoimmune thyroiditis):ti,ab
#5.	(or #1-#4)
#6.	MeSH descriptor: [Autoantibodies] explode all trees
#7.	anti-TPO:ti,ab
#8.	((anti thyroid or antithyroid or TPO) near/2 (peroxidase or antibod* or autoantibod*)):ti,ab
#9.	((iodide near/2 peroxidase) or thyroperoxidase or microsomal antigen*):ti,ab
#10.	(antithyroglobulin* or anti thyroglobulin* or thyroglobulin antibod*):ti,ab
#11.	(anti-Tg or TgAb or anti TgAb):ti,ab
#12.	(or #6-#11)
#13.	#5 and #12

B.2 Health Economics literature search strategy

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

Table 6: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5

7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.
17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.

51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	quality-adjusted life years/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.
61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/54-72
74.	26 and (43 or 53 or 73)

Embase (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis*.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/

18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/
27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	statistical model/
40.	exp economic aspect/
41.	39 and 40
42.	*theoretical model/
43.	*nonbiological model/
44.	stochastic model/
45.	decision theory/
46.	decision tree/
47.	monte carlo method/
48.	(markov* or monte carlo).ti,ab.
49.	econom* model*.ti,ab.
50.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
51.	or/41-50
52.	quality adjusted life year/
53.	"quality of life index"/
54.	short form 12/ or short form 20/ or short form 36/ or short form 8/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.

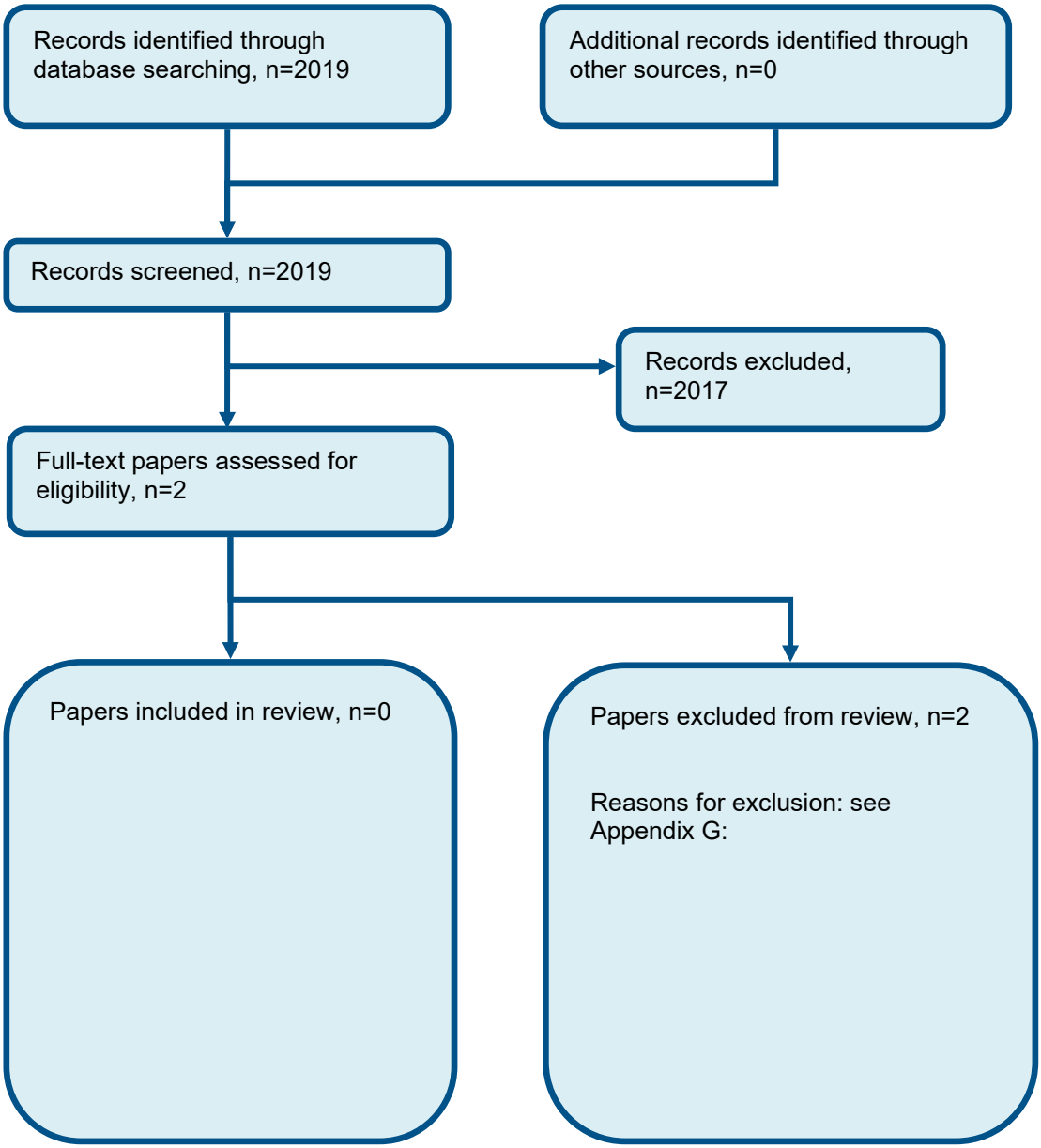
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.
61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/52-72
74.	24 and (38 or 51 or 73)

NHS EED and HTA (CRD) search terms

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

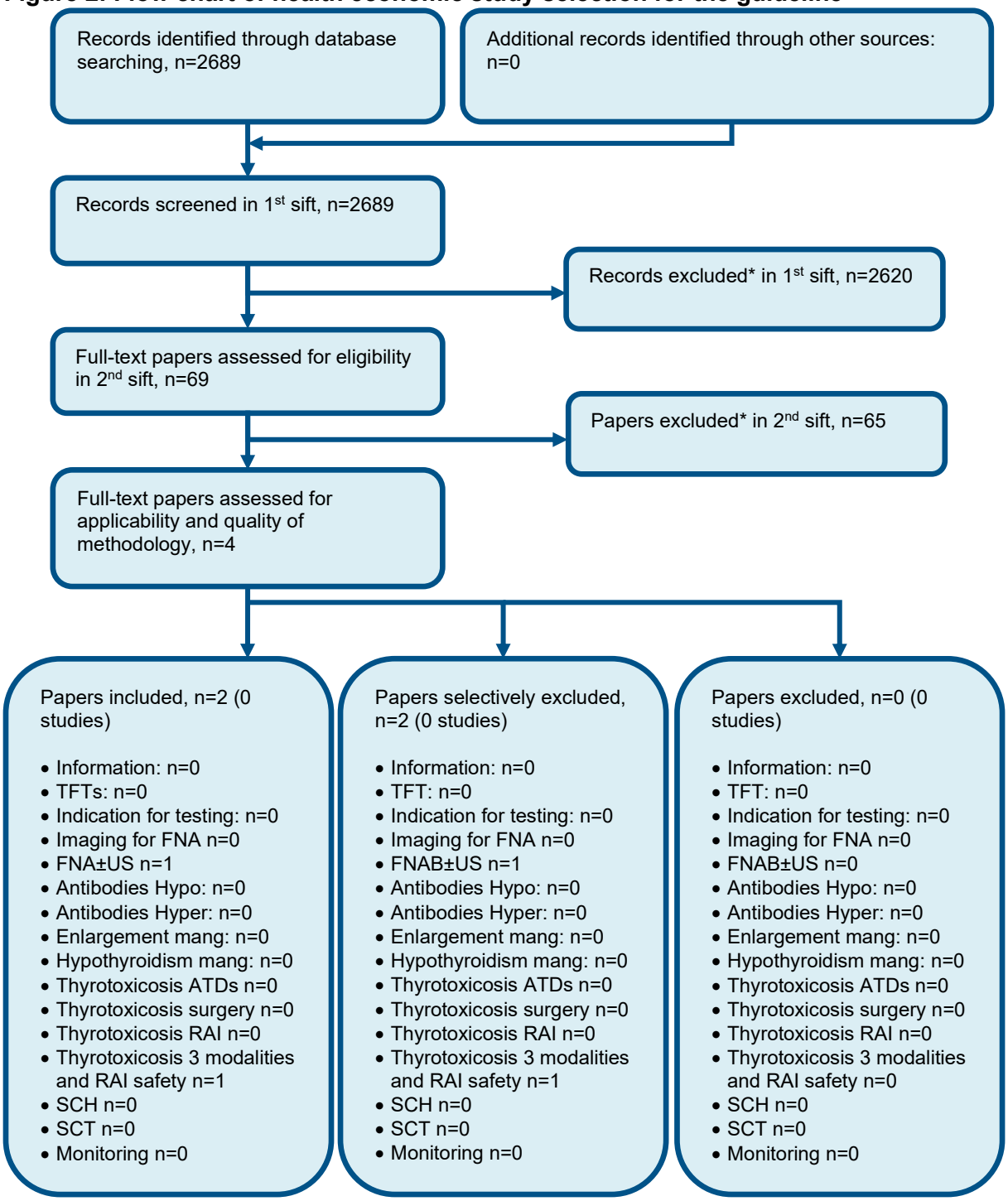
Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of antibodies in hypothyroidism



Appendix D: Health economic evidence selection

Figure 2: Flow chart of health economic study selection for the guideline



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

Appendix E: Health economic evidence tables

None

Appendix F:Health economic analysis

None

Appendix G: Excluded studies

G.1 Excluded clinical studies

Table 7: Studies excluded from the clinical review

Reference	Reason for exclusion
Barbesino 2013[1]	Non-systematic review
Downs 2008[2]	Non-systematic review

G.2 Excluded health economic studies

None