National Institute for Health and Care Excellence

FINAL

Thyroid disease: assessment and management

[M] Management of subclinical thyrotoxicosis

NICE guideline NG145

Intervention evidence review underpinning recommendations 1.8.1 to 1.8.5 in the guideline. See also evidence review N

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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1.1 Review question: What is the clinical and cost effectiveness of treating subclinical thyrotoxicosis?

1.2 Introduction

Subclinical thyrotoxicosis (SCT), also known as subclinical hyperthyroidism, is a biochemical state in which the serum thyroid stimulating hormone (TSH) is below the reference range, but with normal concentrations of circulating free thyroid hormones (FT4, FT3). There are differences in both aetiology and outcome depending upon whether the serum TSH is in the low but detectable range (0.1-0.4mIU/l) or fully suppressed (<0.1mIU/l). The former is more frequently transient and associated with non-thyroidal illness, drug effects or advanced age. In contrast, some people with SCT and a fully suppressed TSH do have mild thyroid autonomy or early thyrotoxicosis, although the rate of progression to overt hyperthyroidism is low, at only 3-5% annually.

SCT becomes more common with advanced age, affecting around 1% of people over 70 years of age, and 3% of people over 80. Approximately one quarter of people with SCT have a fully suppressed serum TSH, and these warrant the most detailed evaluation.

Symptoms of SCT are not common, but population-based observational studies have shown that it is associated with an adverse prognosis, including increased risk of atrial fibrillation, osteoporotic fracture, circulatory diseases and mortality. However, whether anti-thyroid treatments (such as anti-thyroid drugs or radioiodine) could ameliorate these risks remains essentially untested. Low serum TSH may also be a marker for advanced biological age, further clouding the interpretation of these observational studies. Thus, there remain large areas of uncertainty about the optimal management of people with SCT.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People diagnosed with subclinical thyrotoxicosis (TSH below normal reference ranges, free T3/T4 within normal reference range)
Interventions	Antithyroid drugs Radioactive iodine Surgery
Comparisons	No treatment Placebo
Outcomes	**Critical** • Mortality (dichotomous, ≥1 year) • Quality of life (continuous) **Important (general)** • Thyroid ophthalmopathy (dichotomous) • Euthyroidism (dichotomous) • Hypothyroidism (dichotomous) • Relapse of hyperthyroidism (dichotomous) • Cardiovascular morbidity (ischaemic heart disease, dichotomous) • Arrhythmia (dichotomous)

	• Osteoporosis (dichotomous) • Cognitive impairment (dichotomous) • Pain (continuous) • Symptom scores (continuous) • Patient/family/carer experience (continuous) • Healthcare contacts (rates/dichotomous) **Important (surgical)** • Recurrent laryngeal nerve damage (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Bleeding (dichotomous) • Infection (dichotomous) **Important (pharmacological)** • Agranulocytosis (dichotomous) • Liver failure (dichotomous) • Minor drug related adverse effects (dichotomous) • Teratogenesis (dichotomous) **Important (radioactive iodine)** • Infertility (dichotomous) • Malignancy (dichotomous) • Thyrotoxic storm (dichotomous) • Growth abnormalities (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) Teratogenesis (dichotomous)
Study design	RCTs, non-randomised cohort studies to be considered if adjusted for key confounders (age, co-existing conditions, baseline TSH, size of goitre) and insufficient RCTs evidence found, on an intervention by intervention basis

1.3.1 Included studies

As per the protocol, given the lack of randomised controlled trials, non-randomised studies were also considered for inclusion for this evidence review. No relevant clinical studies assessing the impact of treating subclinical thyrotoxicosis were identified.

See also the study selection flow chart in Appendix C:.

1.3.2 Excluded studies

See the excluded studies list in Appendix G:.

1.4 Economic evidence

1.4.1 Included studies

No relevant health economic studies were identified.

1.4.2 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 inAppendix G:.

1.4.3 Health economic modelling

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

1.4.4 Resource costs

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

Table 2: UK costs of treatments for subclinical thyrotoxicosis

Intervention	*Unit cost*
Carbimazole tablets 5mg daily (a)	Annual cost £148
Surgery (Thyroid Procedures with CC Score 0-4+)(b)	£3,689
Fixed radioactive iodine (c)	£286.32
Calculated radioactive iodine (d)	£453.32

Source: NHS reference costs 2016-17, total HRG schedule [1].

(a) Maintenance dose 5mg to15mg daily, £148-£445 cost per year, respectively.

(b) Weighted average of all 3 combined thyroid procedures with CC scores 0-1, 2-3, 4+(KA09C, KA09D, KA09E) including excess bed days and the average length of stay is 1.6 days

(c) Cost of oral delivery of radiotherapy for thyroid ablation, cost code RN51Z

(d) Total additional costs added to the fixed dose, include uptake measurements with probe, USS and calculation report = £167

1.5 Evidence statements

1.5.1 Clinical evidence statements

- No relevant published evidence was identified.

1.5.2 Health economic evidence statements

- No relevant economic evaluations were identified.

1.6 The committee's discussion of the evidence

1.6.1 Interpreting the evidence

1.6.1.1 The outcomes that matter most

The committee agreed that the critical outcomes for this review were mortality and quality of life. Important outcomes for all interventions included thyroid ophthalmopathy, euthyroidism, hypothyroidism, relapse of hyperthyroidism, cardiovascular morbidity, arrhythmia, osteoporosis, cognitive impairment, pain, symptom scores, experience of care, and healthcare contacts. Important intervention-specific outcomes were recurrent laryngeal nerve damage, hypocalcaemia, hypoparathyroidism, bleeding, infection, agranulocytosis, liver failure, minor drug related adverse effects, teratogenesis, infertility, malignancy, thyrotoxic storm, growth abnormalities.

There was no clinical evidence identified in this review.

1.6.1.2 The quality of the evidence

There was no clinical evidence identified in this review.

1.6.1.3 Benefits and harms

Given the lack of evidence around a benefit for treatment in the general SCT population, the committee made consensus recommendations about a group that would be most likely to potentially obtain a benefit.

The committee limited the population who may receive treatment to those in whom depressed TSH was most likely to be related to thyroid disease. Factors suggesting TSH depression is related to thyroid disease include a TSH depressed to the level of being undetectable and FT3 in the upper half of the reference range, a TSH that is depressed persistently and some other evidence of intrinsic thyroid disease.

The committee agreed that the decision to treat SCT is one best made collaboratively between a person with thyroid disease and an endocrinologist. People between the ages of 65 and 80 are likely to be those who may benefit from treatment most, but these are not definitive cut-offs nor are they based on strong evidence. In people under 65 a person is likely to be at low risk from the subclinical thyrotoxicosis and that treatment may be initiated should the condition become clinical. In the committee's experience, in people over the age of 80 there is a high chance that a low TSH is related to advanced age or co-morbidities.

The preference of the person with thyroid disease is obviously of critical importance, this is relevant for all recommendations but particularly where uncertainty of benefit is notable. If a person is experiencing symptoms, it is possible that treatment of the SCT may reduce symptoms. If the FT3 concentration is in the upper half of the reference range, although this is still normal, it may suggest that progression to clinical thyrotoxicosis is more likely and therefore that treatment may be beneficial. If there is an absence of other causes (particularly medication) for a depressed TSH then this lends further credence to the likelihood of the TSH finding being related to intrinsic thyroid disease. The committee noted that osteoporosis, heart disease and arrhythmia may be long term adverse events associated with SCT, therefore if these co-existing conditions are present, treatment of the SCT may be beneficial to prevent exacerbation.

1.6.2 Cost effectiveness and resource use

There was no health economic evidence identified for this review question. Unit costs were presented for all the interventions considered.

The potential treatments for subclinical thyrotoxicosis includes ATD, radioactive iodine and, in rare cases, surgery. These range in cost from £148 per year for the ATDs to £3, 689 for thyroid surgery. However, if patients benefit from treatment, intervention costs may be justified by reductions in long-term adverse events associated with SCT such as osteoporosis, heart disease and arrhythmia or by improvement in health for the patient. However, given no clinical evidence was identified in this area cost effectiveness is uncertain. The committee chose therefore to make recommendations that highlight who would be most likely to benefit from treatment based on their clinical experience with the aim of better targeting treatment. In addition, the committee recommended specialist advise to be sought for children as small changes in their health might have big impact on development and growth and reduce patients' quality of life, hence increasing downstream costs.

The committee highlighted that there is large variation in current practice in the management of subclinical thyrotoxicosis as some people are given antithyroid drugs, radioactive iodine, or surgery which is very rare and many people are given no treatment. The committee agreed that the recommendations may reduce inappropriate treatment and therefore may be cost saving to the NHS.

Given the uncertainty around the management of subclinical thyrotoxicosis, a research recommendation was also made.

References

1. Department of Health. NHS reference costs 2016-17. 2017. Available from: https://www.gov.uk/government/collections/nhs-reference-costs Last accessed: 15/02/2019

2. 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 treating subclinical thyrotoxicosis?
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 treating subclinical thyrotoxicosis
IV	Eligibility criteria – population / disease / condition / issue / domain	People diagnosed with subclinical thyrotoxicosis (TSH below normal reference ranges, free T3/T4 within normal reference range)
V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	Antithyroid drugs Radioactive iodine Surgery
VI	Eligibility criteria – comparator(s) / control or reference (gold) standard	No treatment Placebo
VII	Outcomes and prioritisation	**Critical** • Mortality (dichotomous, ≥1 year) • Quality of life (continuous) **Important (general)** • Thyroid ophthalmopathy (dichotomous) • Euthyroidism (dichotomous) • Hypothyroidism (dichotomous) • Relapse of hyperthyroidism (dichotomous) • Cardiovascular morbidity (ischaemic heart disease, dichotomous) • Arrhythmia (dichotomous) • Osteoporosis (dichotomous) • Cognitive impairment (dichotomous) • Pain (continuous) • Symptom scores (continuous) • Patient/family/carer experience (continuous) • Healthcare contacts (rates/dichotomous) **Important (surgical)** • Recurrent laryngeal nerve damage (dichotomous)

		• Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Bleeding (dichotomous) • Infection (dichotomous) **Important (pharmacological)** • Agranulocytosis (dichotomous) • Liver failure (dichotomous) • Minor drug related adverse effects (dichotomous) • Teratogenesis (dichotomous) **Important (radioiodine)** • Infertility (dichotomous) • Malignancy (dichotomous) • Thyrotoxic storm (dichotomous) • Growth abnormalities (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Teratogenesis (dichotomous) Minimum duration as for the minimum duration for inclusion of studies unless specified.
VIII	Eligibility criteria – study design	• Minimum follow-up of 3 months • RCTs • Non-randomised cohort studies to be considered if adjusted for key confounders (age, co-existing conditions, baseline TSH, size of goitre) and insufficient RCTs evidence found, on an intervention by intervention basis
IX	Other inclusion exclusion criteria	• Excluding studies in pregnancy • Excluding studies aimed specifically at treating thyroid eye disease

X	Proposed sensitivity / subgroup analysis, or meta-regression	**Stratifications**
		• Age – young children (0-4), children and young people (4-18), adults (>18-65), older adults (>65)
		• TSH level - <0.1mIU/L, between 0.1mIU/L and lower limit of reference range
		
		Subgroup analyses
		• Gender (male only vs female only)
		• Age subdivisions (4-12, 12-18, 18-50, 50-65, 65-85, >85)
		• Submodalities of treatment from clinical thyrotoxicosis review:
		  ○ Radioactive iodine (fixed vs calculated, w/ATD vs without ATD)
		  ○ Antithyroid drugs (Carbimazole/methimazole vs propylthiouracil, Block and replace vs titration regimen, 6-<12 months vs 12-18 months vs >18 months)
		  ○ Surgery (Total vs subtotal vs near total (Dunhill) vs one sided only (hemithyroidectomy/lobectomy/isthmectomy))

XI	Selection process – duplicate screening / selection / analysis	• No duplicate screening was deemed necessary for this question, for more information please see the separate Methods report for this guideline.
XII	Data management	• Endnote was used for bibliography, citations, sifting and reference management

	(software)	
XIII	Information sources – databases and dates	• Medline, Embase and the Cochrane Library
XIV	Identify if an update	Not an update
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10074
XVI	Highlight if amendment to previous protocol	Not an amendment
XVII	Search strategy – for one database	For details please see Appendix B:.
XVIII	Data collection process – forms / duplicate	Not applicable
XIX	Data items – define all variables to be collected	For details please see evidence tables in Appendix C:(clinical evidence tables) or Appendix E: (health economic evidence tables).
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 of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the

		manual.
XXVII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 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).[2] **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 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Medline (Ovid) search terms

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

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

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

Embase (Ovid) search terms

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

35.	meta-analysis/
36.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
37.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
38.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
39.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
40.	(search* adj4 literature).ab.
41.	(medline or pubmed or cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or science citation index or bids or cancerlit).ab.
42.	cochrane.jw.
43.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
44.	or/34-43
45.	Clinical study/
46.	Observational study/
47.	family study/
48.	longitudinal study/
49.	retrospective study/
50.	prospective study/
51.	cohort analysis/
52.	follow-up/
53.	cohort*.ti,ab.
54.	52 and 53
55.	(cohort adj (study or studies or analys* or data)).ti,ab.
56.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
57.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
58.	(before adj2 after adj2 (study or studies or data)).ti,ab.
59.	or/45-51,54-58
60.	exp case control study/
61.	case control*.ti,ab.
62.	or/60-61
63.	59 or 62
64.	cross-sectional study/
65.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
66.	or/64-65
67.	59 or 66
68.	59 or 62 or 66
69.	23 and (33 or 44 or 68)
70.	limit 69 to English language

Cochrane Library (Wiley) search terms

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

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

B.2 Health Economics literature search strategy

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

Table 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.

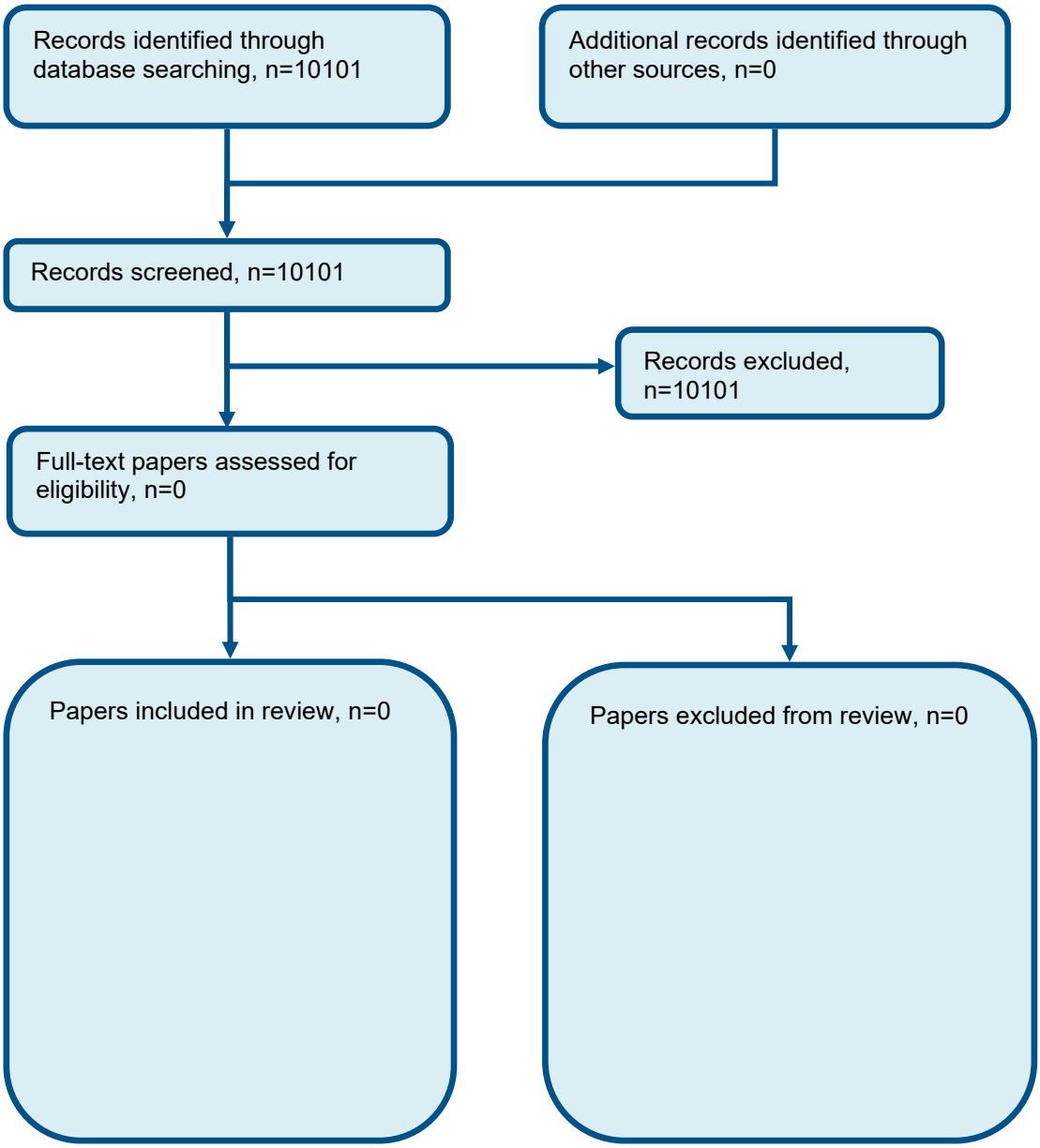
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 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

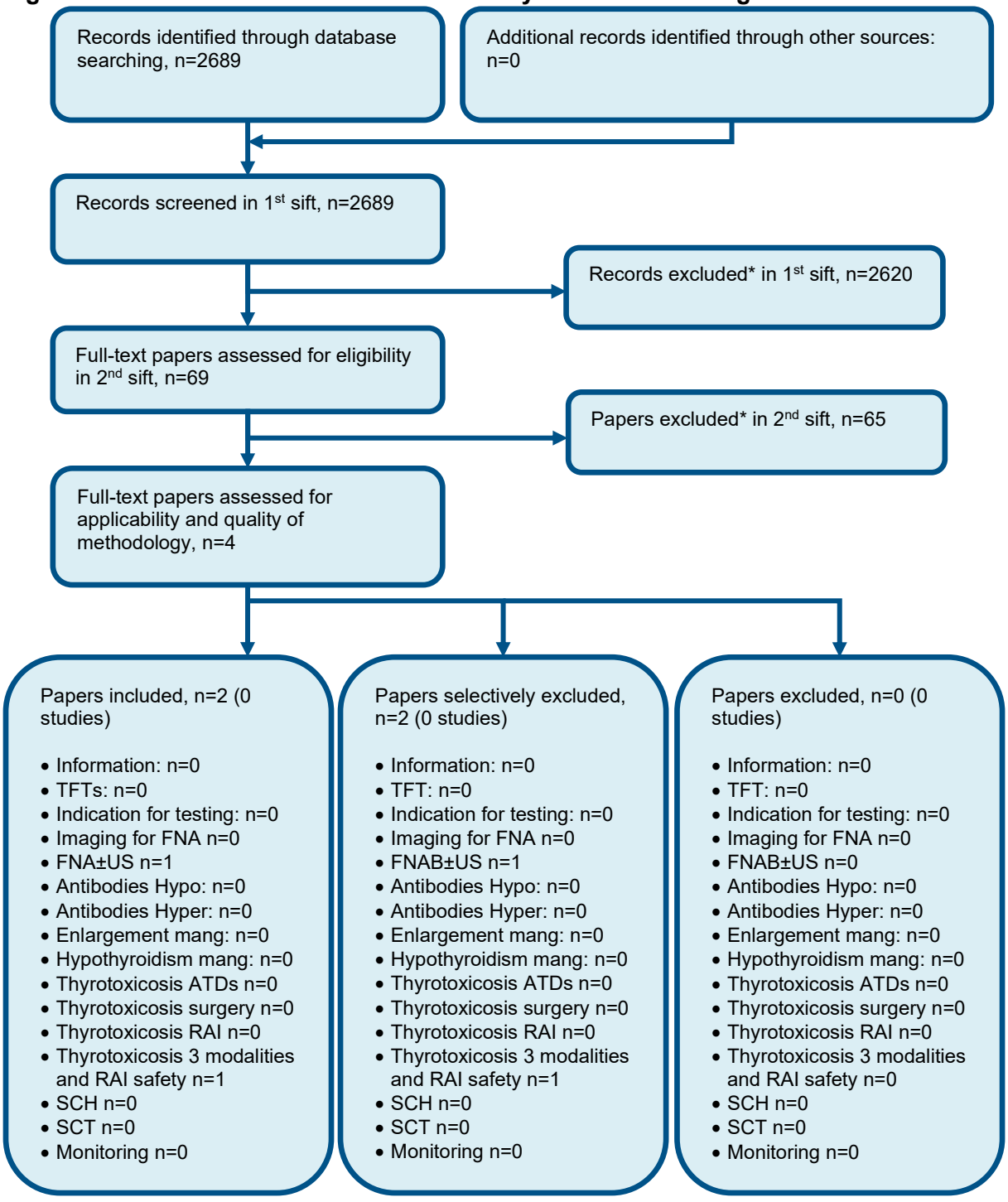
Appendix C: Clinical evidence selection

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



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

None

G.2 Excluded health economic studies

None

Appendix H: Research recommendations

Research question: What is the clinical and cost effectiveness of treatment (antithyroid drugs or radioactive iodine) for improving long-term health outcomes for people with subclinical hyperthyroidism?

Why this is important:

Subclinical hyperthyroidism affects 1% of people in their 70s and 3% of those in their 80s, and in some reflects a state of mild thyroid overactivity or autonomy. SCT is associated with an increased risk of atrial fibrillation, excess cardiovascular and all-cause mortality, osteoporosis and dementia in several large population-based observational surveys. Importantly, many cases of subclinical hyperthyroidism are transient and resolve spontaneously, and it is likely that TSH falls 'physiologically' with increasing multimorbidity which may explain some or all of the associations with adverse outcomes.

Most people with subclinical thyrotoxicosis are asymptomatic so have little to gain in terms of subjective benefit from any treatment. However, an important question is whether treatment of the mild thyroid overactivity/autonomy in subclinical hyperthyroidism could improve outcomes, for instance prevent atrial fibrillation, dementia, mortality. Current practice is generally to treat most patients with TSH <0.05mIU/l, however this is based predominantly on consensus and no evidence exists to demonstrate a benefit of treatment.

Criteria for selecting high-priority research recommendations:

PICO question	Population: Adults over 70 with persistent TSH <0.05 for >3 months , normal FT4 & FT3 Intervention(s): Carbimazole 5mg daily for 5 years or 1 dose of 400MBq ^{131}I-radioiodine Comparison: Placebo daily for 5 years Outcome(s): Atrial fibrillation, major acute cardiovascular events (MACE), mortality, bone mineral density, cognition.
Importance to patients or the population	If treatment of subclinical hyperthyroidism is shown to have clinical benefits, this would be useful for people with SCT. If treatment is shown to have no benefit, inappropriate treatment could be reduced.
Relevance to NICE guidance	Currently, there is no evidence to support benefit of any treatment for subclinical hyperthyroidism, so the NICE guidance suggests consideration of treating groups most likely to have intrinsic thyroid disease. A randomised clinical trial would give a clear steer to treat or not to treat, depending upon the result. This will address the lack of evidence supporting any format of treatment of subclinical hyperthyroidism available to guide the management of people with this condition.
Relevance to the NHS	The health benefits in the comorbid elderly could be significant, potentially resulting in reduced disability and dependency in older people
National priorities	Multimorbidity and chronic conditions are a national priority, and subclinical hyperthyroidism is intrinsic to people with these states.
Current evidence base	There are 2 reported controlled studies of therapy for subclinical hyperthyroidism, the biggest recruited 28 patients and reported only on bone density outcomes (Mudde AH 1994; Faber J 1998). A third study in France (PIRATHES; NCT00213720) has recruited 300 subclinical hyperthyroidism patients and randomised them to receive radioiodine treatment or not, with a primary endpoint of AF. The outcomes of this study will be known in 2020.

	Currently there is no strong evidence to support any form of treatment for people with subclinical hyperthyroidism.
Equality	The trial would be specific to older adults (≥70 years of age) as treatment of subclinical hyperthyroidism might be of particular benefit to this age stratum considering the risks associated with subclinical hyperthyroidism that are particularly relevant to older adults
Study design	A randomised control trial/study design using antithyroid drugs or radioactive iodine (RAI) vs placebo may be acceptable. Atrial fibrillation, MACE and other outcomes would be of interest
Feasibility	Two other prospective large studies of RAI for subclinical hyperthyroidismhave failed to recruit (UK MRC study “TRISH” and one in the Netherlands), because the median age of subclinically hyperthyroid individuals is 79 or 80 and few are willing to ‘randomly’ have a RAI dose at this age. ‘Equipoise’ does not sit well when the proposed treatment is radioactive. There are serious feasibility issues with studies of subclinical hyperthyroidismthat have recruited largely asymptomatic people from practice or hospital databases and offered them RAI. A new national approach using ATDs might be feasible.
Other comments	None
Importance	Medium: the research is relevant to the recommendations in the guideline, but the research recommendations are not key to future updates.