National Institute for Health and Care Excellence

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Draft

Thyroid Cancer

[M] Evidence review for TSH suppression vs no suppression

NICE guideline <number>

Evidence reviews underpinning recommendations 1.4.1 to 1.4.4 in the NICE guideline

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Draft for Consultation

These evidence reviews were developed by National Guideline Centre

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ISBN:

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1 TSH suppression vs no TSH suppression

1.1 Review question

1.1.1 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?

1.1.2 Introduction

TSH suppression with supraphysiological doses of levothyroxine has been employed in the treatment of thyroid cancer for many years. It is aimed at inhibiting the stimulatory effect of TSH on any residual thyroid cancer cells persisting after surgery and radioiodine ablation. This approach, whilst potentially reducing the risk of recurrence or progression is not without long term adverse effects. These include an increased risk of cardiovascular morbidity and mortality as well as a higher incidence of osteoporosis and fractures.

In recent years it has been proposed that TSH suppression therapy may be of little benefit and potentially harmful in certain patient groups. This review seeks to determine those patient groups who are most suitable for TSH suppression.

1.1.3 Summary of the protocol

For full details see the review protocol in Appendix A.

Table 1: PICO characteristics of review question

Population	Inclusion: People aged 16 or over who have had thyroidectomy and RAI for differentiated thyroid cancer. People will need to have had total or near total thyroidectomy. Exclusion: Children under 16
Intervention(s)	TSH suppression (using high doses of levothyroxine [T4] or other TSH-lowering agents, such as 'armour thyroid' [T4 + liothyronine] or liothyronine alone)
Comparison(s)	No TSH suppression. (Note that patients, in the absence of functioning thyroid tissue, will still receive levothyroxine doses sufficient to prevent hypothyroidism, although unless actual TSH suppression is indicated the doses will not be sufficient to reduce TSH levels below normal levels)
Outcomes	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • mortality • quality of life (any validated tools) • thyroglobulin levels • local cancer progression • incidence of distant metastases • cancer recurrence • osteoporosis • cardiac complications (reported or composite outcomes allowed) • second primary malignancy • time of follow up: longest available but minimum of 3 years
Study design	• Systematic reviews • RCTs

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

One randomised study was included in the review.[1] The characteristics of this study are summarised in Table 2, and evidence from this study is summarised in the clinical evidence summary in Table 3.

The included study compared TSH suppression with Levothyroxine to no additional suppression (to maintain TSH levels at a normal range). This study was put into the high risk stratum as the majority of the population were at high risk of recurrence according to the AMES assessment.

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

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Abo-Touk 2015[1]	Levothyroxine TSH suppression (T4): L-T4 was given at an initial dose of 100µg/d for patients with body weight under 50kg, 150 µg/d for patients weighting 50-70kg and 200µg/d for patients weighing 70kg or more. Serum levels of free T4, free T3 and TSH were done every 4 weeks. The daily dose of LT4 is then adjusted in the patients of this group to suppression TSH levels below 0.1µU/ml. (n=76) No additional TSH suppression: TSH suppression therapy - L-T4 was given at an initial dose of 100µg/d for patients with body weight under 50kg, 150 µg/d for patients weighting 50-70kg and 200µg/d for patients weighing 70kg or more. Serum levels of free T4, free T3 and TSH were done every 4 weeks. The daily dose of LT4 is then adjusted in the patients of this group to normal range (0.27 - 4.2 µU/ml). (n=72)	Patients aged from 18 - 70 with operable differentiated thyroid carcinoma Age <45: 96; ≥45: 52. Gender (M:F): 30/118 T4 suppression: Ames risk of recurrence: Low - 26; high – 50 No additional suppression: Ames risk of recurrence: low - 30; high – 42 Egypt	• Cancer recurrence • Mortality	Postoperatively radioiodine therapy was given when the patient with a completely resected tumour had a significant potential for recurrence. Patients were treated with about 50 - 100 mCi of radioiodine. In case of incomplete tumour resection, 150 - 200 mCi was administered

See Appendix D for full evidence tables.

1.1.7 Summary of the effectiveness evidence

Table 3: Clinical evidence summary: Levothyroxine vs no additional suppression

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with No additional suppression (mixed stratum)	Risk difference with TSH suppression (95% CI)
Cancer Recurrence	148 (1 study) 24-86 months	⨁⨁⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.44 (0.18 to 1.09)	181 per 1000	101 fewer per 1000 (from 148 fewer to 16 more)
Mortality	148 (1 study) 24-86 months	⨁⨀⨀⨀ VERY LOW[1,2] due to risk of bias, imprecision	RR 0.32 (0.07 to 1.51)	83 per 1000	38 fewer per 1000 (from 52 fewer to 29 more)

1 Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
2 Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

See Appendix F for full GRADE table

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 Summary of included economic evidence

None.

1.1.10 Economic model

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

1.1.11 Cost-consequence analysis

A cost-consequence analysis was conducted to compare the costs of offering TSH suppression or TSH adjustment therapy (where TSH is adjusted to normal value) to people who underwent surgery due to differentiated thyroid carcinoma, as described in the randomised trial included in the clinical review[1]. Achieving TSH suppression (mU/L= 0.1) requires a higher dosage of Levothyroxine (L-T4) compared to adjusting TSH to normal values (mU/L= 0.5 – 6.2). The dosages required to achieve the two states were estimated from the literature and are presented in table 4 for a person weighting 80kg. Cost per mg was calculated using British National Formulary (2020) and Prescription Cost Analysis 2020. The resulting cost per year indicates that people achieving TSH suppression has an incremental pharmaceutical cost per patient of £11.

Table 4: Dosage and cost of L-T4 for TSH suppression and TSH adjustment

TSH aim	Dosage (80 kg)	Cost per year	Source
TSH suppression (mU/L= 0.1)	204.8 mg per day	£62	BNF 2020[27] Prescription cost analysis 2020[22] Burmeister 1992[14]
TSH adjustment (mU/L= 0.5 – 6.2)	168.8 mg per day	£51	

The clinical review based on the included RCT[1] found that TSH suppression therapy compared to TSH adjustment therapy reduces, although not statistically significantly, the risk of dying and cancer recurrence (respectively, RR: 0.24, 0.03 to 2.07; RR:0.44, 0.18 to 1.09). See also Table 3 in section 1.1.6. Probabilities in the baseline arm (TSH adjustment) were converted into yearly probabilities and a cost-consequence analysis with a time horizon of 1 year was performed. Costs of FNAC See table 5 for the parameters used in the cost-consequence analysis.

Table 5: Cost-consequence analysis

Parameter	Value	Source
1 year risk of recurrence without TSH suppression	0.043	Calculated from Abu-Touk 2015[1]

Parameter	Value	Source
1 year mortality risk without TSH suppression	0.013	Calculated from Abu-Touk 2015[1]
Risk ratio for recurrence	0.44	Abu-Touk 2015[1]
Risk ratio for mortality	0.24	Abu-Touk 2015[1]
Yearly cost		
TSH suppression therapy	£61.52	BNF 2020[27] Prescription cost analysis 2020[22] Burmeister 1992[14]
TSH adjustment therapy	£50.71	BNF 2020[27] Prescription cost analysis 2020[22] Burmeister 1992[14]
FNAC	£299	NHS Reference Costs 2019-2020{NHS England and NHS Improvement, 2020 #1938}
Thyroidectomy	£4,791	NHS Reference Costs 2019-2020{NHS England and NHS Improvement, 2020 #1938}

The analysis found that in a cohort of 1000 patients, TSH suppression would prevent 24 recurrent cancers and 10 deaths during a time period of 12 months. Assuming that a recurrent cancer will require a FNAC assessment and a new thyroidectomy, each recurrence will cost to the NHS around £5,090 (this estimation does not include possible adjuvant treatments such as RAI).

The results of the cost-consequence analysis are presented in table 6.

Table 6: Cost analysis results (per 1,000 people)

Strategy	N° of recurrence	N° of death	Cost (per patient)
TSH suppression	19	13	£159
TSH adjustment	43	3	£272
Difference (Suppression – adjustment)	-24	-10	-£113

This analysis showed that TSH suppression therapy is potentially cost saving compared with TSH adjustment therapy. Although the cost of the levothyroxine required to achieve TSH suppression is higher due to the higher dosage needed, fewer recurrent cancers in the TSH supressed group leads to important savings outweighing the additional pharmaceutical cost. On average, offering TSH suppression therapy instead of TSH adjustment therapy leads to savings for the NHS equal to £113 per patient.

This analysis should be interpreted with caution. The effectiveness is based on the single RCT included in the clinical review[1] which, although found improvement in mortality and recurrence, did not achieve statistically significancy in neither of these outcomes. Moreover, the analysis is a cost analysis only and, as such, does not include any quality of life (QoL) aspect. People under TSH suppression therapy may have impaired QoL if compared with people with a normal level of TSH and are at higher risk of osteoporosis and cardiac complications, although the committee noted that with new suppression regimes people have no QoL impairment and very low risk of adverse events. Regardless of the quality of life of

people in the two arms, the very high effect on mortality found in Abo-Touk 2015[1] should ultimately lead to higher QALYs in the TSH-supressed group.

In conclusion, this cost analysis found that TSH suppression therapy is cost saving compared to TSH adjustment therapy. The analysis should be interpreted with caution as the effectiveness is based on a single RCT with very high uncertainty.

1.1.12 Economic evidence statements

No relevant economic evaluations were identified.

1.1.13 The committee's discussion and interpretation of the evidence

1.1.13.1 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.

1.1.13.2 The quality of the evidence

For the 'TSH suppression versus no TSH suppression' review, only one paper was found. This was found to be at very serious risk of bias because of probable selection, performance and detection bias. Selection bias was likely due to a failure to report allocation concealment, performance bias was likely due to an inability to report blinding of patients and health care providers to the treatment being provided, and detection bias was probable due to no evidence that outcome assessors had been blinded to treatment allocation. Overall quality was further compromised by imprecision of estimates for both outcomes, leading to a final GRADE rating of very low.

1.1.13.3 Benefits and harms

The evidence involved a single study. The intention had been to stratify the analysis of data in this review to reveal patient groupings who might gain more (or less) clinical benefit from TSH suppression. There had been four stratification strategies, in terms of risk [very low risk/ low risk /high risk /persistent disease], ethnicity [white/ Asian/Black/Other/Mixed], gender [male/female] and age [<55 years/>55 years]. In contrast to the usual method of stratification, where all permutations of all strategies would interact to form a multitude of possible sub-strata, it had been decided to run each stratification strategy independently, to avoid slicing the total number of papers into excessively small sub-groups. It had been hoped that such a stratification methodology might yield useful information on which categories of risk, ethnicity, gender or age group are independently associated with best results from TSH suppression. Thus, the aim of this review was not solely to evaluate the efficacy of TSH suppression but also to evaluate the patient groupings for whom it would be most suitable. In this way, it was hoped it would effectively answer the question, 'who needs TSH suppression?'.

Unfortunately, the existence of only one study meant that it was not possible to put this stratification methodology to use.

The evidence suggested a benefit for TSH suppression over no TSH suppression in terms of reduced cancer recurrence and reduced mortality which the committee considered to be clinically important benefits. However, this evidence was from a single small study and the evidence was graded as very low quality partly due to uncertainty in the effect estimates, and there was no accompanying evidence assessing potential harms or risks associated with TSH suppression such as osteoporosis or cardiac complications. Although the sample in this study were mostly female, the risk levels and the age categories were mixed, and ethnicity was unreported, so it was not possible to associate the results with any particular risk, age or ethnicity stratum. Because the evidence base was weak, and lacked information on harms, the committee decided to form recommendations largely through consensus. This consensus opinion reflects current clinical practice and also mirrors the low quality evidence.

Who to offer TSH suppression

It was agreed that patients with very low risk thyroid cancers such as microcarcinomas, or those who do not need RAI, should not be offered TSH suppression. Low risk thyroid cancers were defined by the committee as follows. A low risk thyroid cancer would have no evidence of clinical lymph node metastases, no evidence of aggressive histology, no evidence of vascular invasion, no evidence of incomplete macroscopic tumour resection, and no evidence of distant metastases. The tumour would be intrathyroid with absent macroscopic extra-thyroid extension. In patients treated with radioiodine, there would be no uptake outside the thyroid bed on post-therapeutic whole-body scan. In the case of a low risk follicular thyroid cancer, the tumour would be well-differentiated with capsular invasion only or less than four foci of vascular invasion. A solitary papillary microcarcinoma would be considered very low risk. For such patients with such low risk cancers the risks of recurrence or mortality are believed to be so low that TSH suppression would benefit only a very small number of people. Given that the adverse effects of TSH suppression on bone and cardiac health would affect a far greater proportion of people, the balance of benefits and harms was agreed to strongly indicate avoidance of TSH suppression in this group.

In contrast, the committee agreed that the situation would be different for those patients who had been given total thyroidectomy and RAI, as these treatments are only provided when the perceived risks of recurrence, spread or mortality are higher. For such patients the balance of benefits and harms would shift towards an overall benefit for TSH suppression, as although the risks of recurrence, spread and mortality without TSH suppression might still be lower than the adverse effects experienced with TSH suppression, the overall impact of thyroid cancer progression would still exceed the impact of the treatment complications. Therefore, for such patients, TSH suppression may be offered to maintain TSH levels below 0.1mIU/L.

Assessing and managing response to TSH suppression

After initiating this treatment, the patient's response to the suppression should be monitored. The committee agreed that this should be done by dynamic risk stratification between 9 and at 12 months after initial treatment to consider reducing the levels of TSH suppression. If the person responed well, suppression could be reduced to achieve a TSH level of between 0.3 and 2.0 IU/L. This is on the basis that initial treatments and TSH suppression had probably eliminated the cancer and that further high levels of suppression would possibly cause more harm than good. If, on the other hand, the response at 1 year were poor, with persistent biochemical or structural disease, then the high levels of suppression (<0.1 mIU/L) should be continued, on the basis that the benefits of continued treatment would outweigh the possible harms. For an intermediate level of response at 1 year, a compromise approach should be taken, with an intermediate level of suppression adopted (0.1-0.5 mIU/L), on the basis that a lower level of suppression might lead to a net increase in harm arising from the condition, whilst a higher level of suppression might lead to a net increase in harm arising from TSH

suppression. Furthermore, based on clinical experience, the committee agreed that all patient's comorbidities need to be taken into consideration when planning TSH suppression. Significant comorbidities, particularly those of a cardiac nature, may mean that total suppression or a low normal level of TSH should be avoided. In this way, TSH suppression treatment should be stratified according to response to the treatment and comorbidities.

The committee therefore used consensus to make different recommendations about TSH suppression across different risk strata. The conclusion was that TSH suppression was definitely indicated for those at higher risk and could be avoided for those at lowest risk. However, the committee did not make any consensus recommendations based on age, gender or ethnicity. This was because the committee did not feel that there were any compelling reasons, in the absence of any evidence, to suggest that the balance of benefits and harms of TSH suppression should vary across age, gender or ethnic groups.

1.1.13.4 Cost effectiveness and resource use

No health economic evidence was found for this question.

The one trial included in the clinical review, although at serious risk of bias, showed that offering levothyroxine at a TSH suppression dosage can potentially reduce cancer recurrence and mortality. As TSH suppression requires a higher dosage of levothyroxine compared to no TSH suppression therapy, the cost of the intervention is uncertain.

A cost comparison analysis was undertaken and presented to the committee comparing the cost and potential outcomes of TSH suppression vs no TSH suppression using UK sources for unit cost and the trial included in the clinical review for treatment effectiveness. The analysis showed that the higher levothyroxine required for achieving TSH suppression would increase the cost of thyroxine by £11 a year. However, savings due to preventing cancer recurrences are expected to highly outweigh the small additional costs leading to a saving estimated to be £113 per patient per year. This analysis was based on a single RCT with a serious risk of bias and imprecision, as it failed to reach statistically significance in either of the study's outcomes. Moreover, it does not account for potential adverse events of TSH suppression therapy. The committee noted that TSH suppression therapy does not reduce people quality of life although it can increase the risk of osteoporosis or cardiac complications.

The committee decided to recommend TSH suppression therapy to people who underwent total thyroidectomy and RAI. This reflects current practice in England and it is supported by the very low quality evidence provided, which found TSH suppression to be potentially cost saving and to reduce recurrence and mortality. The committee recommended to reduce TSH suppression to people with excellent improvement as assessed by Dynamic Risk Stratification (DRS), which allows to predict risk of recurrence. This recommendation should reduce the number of people with low risk of recurrence under a strict TSH suppression therapy, thus saving cost for the NHS and reducing the risk of TSH suppression adverse events like osteoporosis and cardiac complications.

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.

1.1.13.5 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.

1.1.14 Recommendations supported by this evidence review

This evidence review supports recommendations 1.4.1 to 1.4.4.

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Appendices

Appendix A – Review protocols

A.1 Review protocol for TSH suppression vs no TSH suppression

Field	Content
PROSPERO registration number	Not registered
Review title	Clinical and cost effectiveness of thyroid stimulating hormone (TSH) suppression versus no TSH suppression in different groups of people after thyroidectomy and radioactive iodine (RAI). The different population strata will be characterised by recurrence risk, ethnicity, gender and age
Review question	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?
Objective	To determine the patient groups who are most suitable for TSH suppression
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. 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 RAI for differentiated thyroid cancer. People will need to have had total or near total thyroidectomy. Exclusion: Children under 16
Intervention/Exposure/Test	TSH suppression (using high doses of levothyroxine [T4] or other TSH-lowering agents, such as 'armour thyroid' [T4 + liothyronine] or liothyronine alone)
Comparator/Reference standard/Confounding factors	No TSH suppression. (Note that patients, in the absence of functioning thyroid tissue, will still receive levothyroxine doses sufficient to prevent hypothyroidism, although unless actual TSH suppression is indicated the doses will not be sufficient to reduce TSH levels below normal levels)
Types of study to be included	Published NMAs and IPDs will be considered for inclusion. • Systematic reviews • RCTs Non-randomised studies (any controlled studies such as prospective or retrospective cohorts, or case control studies, with appropriate adjustment for plausible confounders) will be excluded

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	TSH suppression is now an established intervention for this review population, but there is concern that it may not always be given to the people who will benefit the most and may also sometimes be given to people who may not benefit and may even be harmed. Therefore there is a need for a systematic review to allow an evidence-based recommendation in this area.
Primary outcomes (critical outcomes)	All outcomes are considered equally important for decision making and therefore have all been rated as critical: • mortality • quality of life (any validated tools) • thyroglobulin levels • local cancer progression • incidence of distant metastases • cancer recurrence • osteoporosis • cardiac complications (reported or composite outcomes allowed) • second primary malignancy Time of follow up: longest available but minimum of 3 years

Secondary outcomes (important outcomes)	None
Data extraction (selection and coding)	EndNote will be used for reference management, sifting, citations and bibliographies. All references identified by the searches and from other sources will be screened for inclusion. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies (see Developing NICE guidelines: the manual section 6.4). 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 • 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)

	• Non randomised study, including cohort studies: Cochrane ROBINS-I (if a lack of any RCTs necessitate dropping down to non-randomised studies)
Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.

	If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
Analysis of sub-groups	Stratification (up-front stratification of analysis, NOT conditional on heterogeneity of prior meta-analysis) • very low risk/ low risk /high risk /persistent disease • Ethnicity (white/white other, Asian, Black, Other/Mixed) • Gender • Age (<55, ≥55) The above strata will also have an unknown/mixed category (mixed where one category makes up <75% of total) Sub-grouping (conditional stratification if heterogeneity seen in initial unstratified meta-analysis) If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategy: • Duration of TSH supplementation (<5, 5-10 and >10 yrs) • Level of TSH suppression (low normal vs very low vs extremely low)
Type and method of review	☒ Intervention ☐ Diagnostic ☐ Prognostic

	☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)
Language	English
Country	England
Named contact	**Named contact** National Guideline Centre **Organisational affiliation of the review** National Institute for Health and Care Excellence (NICE) and the National Guideline Centre
Review team members	From the National Guideline Centre: Carlos Sharpin, Guideline lead Mark Perry, Senior systematic reviewer Alfredo Mariani, Health economist Lina Gulhane, Head of Information specialists
Funding sources/sponsor	This systematic review is being completed by the National Guideline Centre which receives funding from NICE.

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

Keywords	None
Details of existing review of same topic by same authors	N/A
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).{National Institute for Health and Care Excellence, 2014 #23} **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.

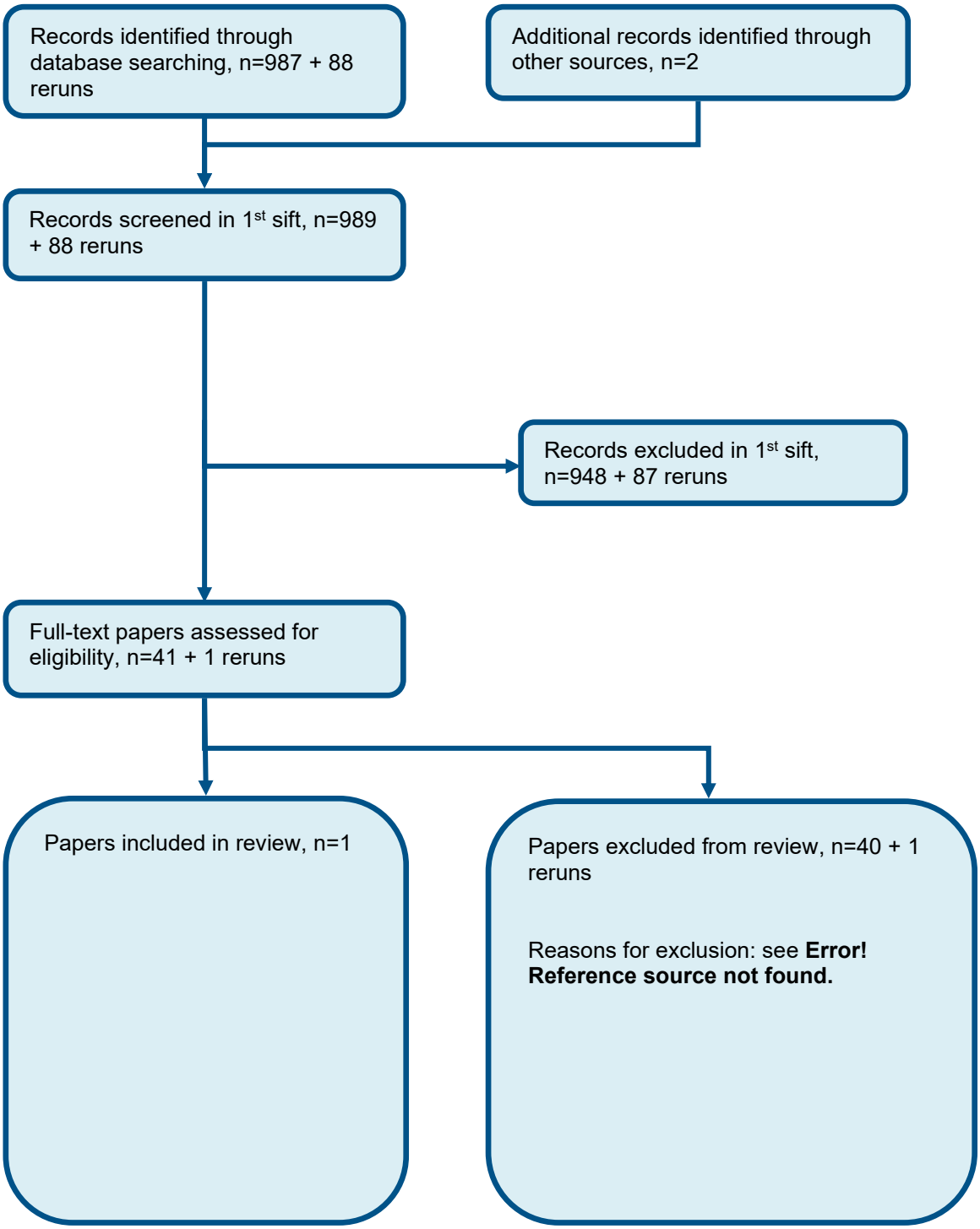
Quality and relevance of effectiveness data used in the health economic analysis:

	• 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

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of Levothyroxine TSH suppression vs no additional suppression



1 # Appendix D – Effectiveness evidence

Study	Abo-touk 2015[1]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	n/a (n=148)
Countries and setting	Conducted in Egypt; Setting: Department of clinical oncology and nuclear medicine, faculty of medicine, Mansoura University, Egypt
Line of therapy	3rd line
Duration of study	Intervention + follow up: up to 86 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Other - mixed
Subgroup analysis within study	Not applicable
Inclusion criteria	Patients aged from 18 - 70 with pathologically confirmed operable differentiated thyroid carcinoma who presented to the department during November 2006 and December 2010. All patients were aimed to be treated with total or near total thyroidectomy and lymph node surgery was performed according to their presentation.
Exclusion criteria	Patients with a maximum diameter or primary tumour 1cm or smaller (microcarcinoma) as measured by preoperative ultrasonography or postoperative data, distant metastasis, grave's disease, ischemic heart disease or arrythmia, or severe osteoporosis were excluded.
Recruitment/selection of patients	Patients aged from 18 - 70 with pathologically confirmed operable differentiated thyroid carcinoma who presented to the department during the study period
Age, gender and ethnicity	Age - Other: <45: 96; ≥45: 52. Gender (M:F): 30/118. Ethnicity: n/a

Further population details	
Indirectness of population	No indirectness
Interventions	(n=76) Intervention 1: TSH suppression - high dose Levothyroxine (T4). TSH suppression therapy - L-T4 was given at an initial dose of 100µg/d for patients with body weight under 50kg, 150 µg/d for patients weighting 50-70kg and 200µg/d for patients weighing 70kg or more. Serum levels of free T4, free T3 and TSH were done every 4 weeks. The daily dose of LT4 is then adjusted in the patients of this group to suppression TSH levels below 0.1µU/ml. Duration of study (Nov 2006 - December 2010). Concurrent medication/care: daily intake of calcium (1200mg/day) and vitamin D (1000 units/day). Postoperatively radioiodine therapy was given when the patient with a completely resected tumour had a significant potential for recurrence. Patients were treated with about 50 - 100 mCi of radioiodine. In case of incomplete tumour resection, 150 - 200 mCi was administered. . Indirectness: No indirectness Further details: 1. Duration of TSH supplementation: 2. Level of TSH suppression: Comments: Ames risk of recurrence: Low - 26; high - 50 (n=72) Intervention 2: No TSH suppression - No additional TSH suppression. TSH suppression therapy - L-T4 was given at an initial dose of 100µg/d for patients with body weight under 50kg, 150 µg/d for patients weighting 50-70kg and 200µg/d for patients weighing 70kg or more. Serum levels of free T4, free T3 and TSH were done every 4 weeks. The daily dose of LT4 is then adjusted in the patients of this group to normal range (0.27 - 4.2 µU/ml). Duration of study (Nov 2006 - December 2010). Concurrent medication/care: daily intake of calcium (1200mg/day) and vitamin D (1000 units/day). Postoperatively radioiodine therapy was given when the patient with a completely resected tumour had a significant potential for recurrence. Patients were treated with about 50 - 100 mCi of radioiodine. In case of incomplete tumour resection, 150 - 200 mCi was administered. Indirectness: No indirectness Further details: 1. Duration of TSH supplementation: 2. Level of TSH suppression: Comments: Ames risk of recurrence: low - 30; high - 42
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: HIGH DOSE LEVOTHYROXINE (T4) versus NO ADDITIONAL TSH SUPPRESSION

Protocol outcome 1: mortality at Define
- Actual outcome for Other - mixed: Mortality at 54 months; Group 1: 2/76, Group 2: 6/72
Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover -

Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0 Protocol outcome 2: cancer recurrence at Define - Actual outcome for Other - mixed: Cancer recurrence at 54 months; Group 1: 6/76, Group 2: 13/72 Risk of bias: All domain – Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life at Define; Thyroglobulin levels at Define; local cancer progression at Define; Incidence of distant metastases at Define; Osteoporosis at Define; Cardiac complications at Define; second primary malignancy at Define

Appendix E – Forest plots

E.1 Levothyroxine suppression vs no additional suppression

Figure 2: Cancer recurrence

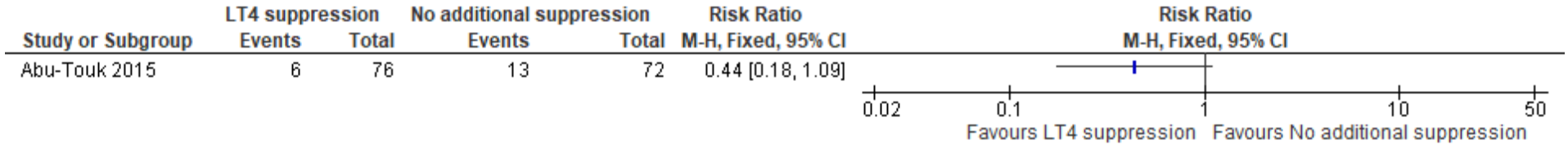
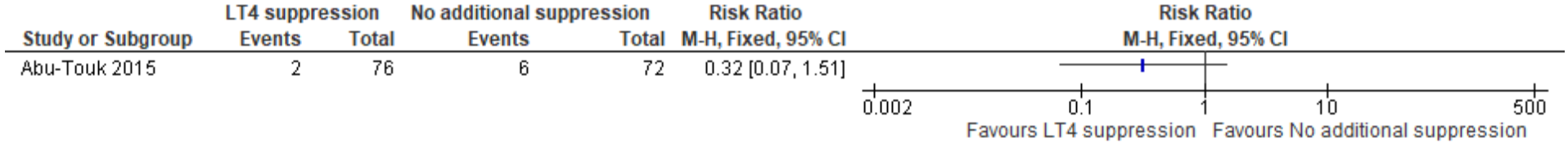


Figure 3: Mortality



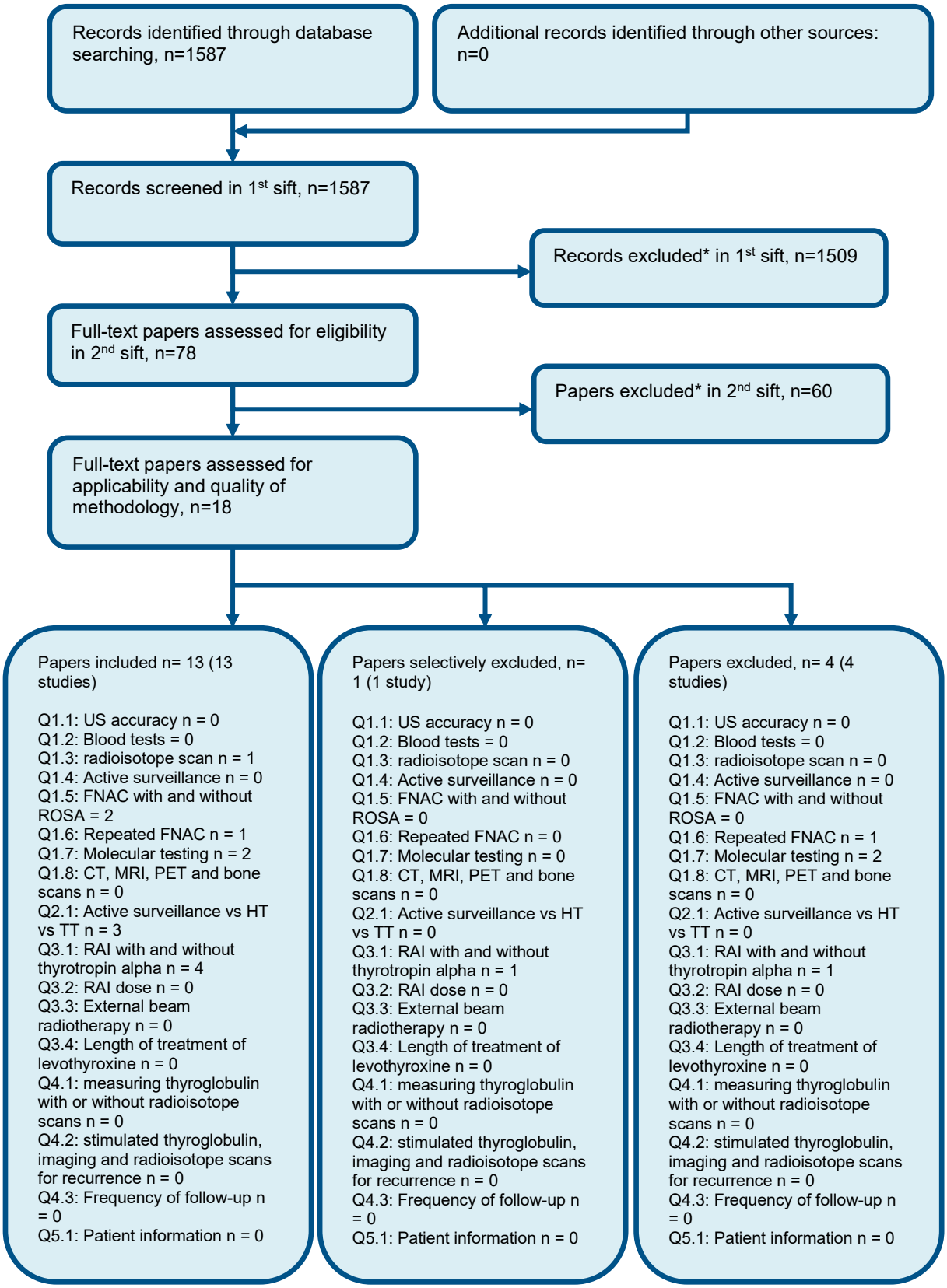
Appendix F – GRADE tables

Table 7: Clinical evidence profile: Levothyroxine suppression vs no additional suppression

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	T4 suppression	No additional suppression	Relative (95% CI)	Absolute		
Cancer Recurrence (follow-up 24-86 months)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	6/76 (7.9%)	18.1%	RR 0.44 (0.18 to 1.09)	101 fewer per 1000 (from 148 fewer to 16 more)	⊕⊕OO VERY LOW	CRITICAL
Mortality (follow-up 24-86 months)												
1	randomised trials	Very serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	2/76 (2.6%)	8.3%	RR 0.32 (0.07 to 1.51)	38 fewer per 1000 (from 52 fewer to 29 more)	⊕OOO VERY LOW	CRITICAL

[1] Downgraded by 1 increment if the majority of the evidence was at high risk of bias, and downgraded by 2 increments if the majority of the evidence was at very high risk of bias
[2] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

None.

1 Appendix I – Excluded studies

2 I.1 Clinical studies

3 **Table 8: Studies excluded from the clinical review**

Reference	Reason for exclusion
Anonymous 2018[26]	Paper not in English
Ahmed 2013[2]	Incorrect study design – objective to determine correct dose of Levothyroxine according to lean body mass
Akirov 2019[3]	Systematic Review – references checked
Almodovar Ruiz 2000[4]	Paper not in English
Appelhof 2005[5]	Incorrect population – primary autoimmune hypothyroid (thyroidectomy excluded)
Boguszewski 1998[6]	Incorrect population – patients with palpable thyroid nodule only
Brancatella 2020[7]	Literature review – references checked
Brun 2021[8]	Incorrect study design – validation study to determine dosage of Levothyroxine, no relevant outcomes.
Bunevicius 2002[9]	Incorrect population – Grave's disease
Bunevicius 1997[10]	Paper not available
Bunevicius 1998[11]	Paper not available
Bunevicius 2000[12]	Incorrect study design – cross over study
Burgos 2020[13]	Incorrect study design – investigating side effects of discontinuing TSH suppression
Celi 2010[15]	Incorrect study design – cross over study
Clyde 2003[16]	Incorrect population – only one participant with thyroid cancer
Eustatia-Rutten 2006[17]	Incorrect study design – follow up period too short (6 months)
Faber 1994[18]	Incorrect study design – cross sectional observational study
Fischman 2018[19]	Paper not in English
Fussey 2017[20]	Literature review – references checked
Greenspan 1999[21]	Systematic Review – references checked
Helfand 1990[23]	Literature review – references checked
Hennessey 2018[24]	Literature review – references checked
Iakovou 2010[25]	Incorrect study design – case control study
Lee 2021[28]	Incorrect study design – study protocol only
Lee, 2021[29]	Non-randomised
Lee 2019[30]	Systematic Review – references checked
Ma 2009[31]	Systematic Review – references checked
Mendonca Monteiro de Barros 2016[32]	Incorrect study design – cross sectional observational study
Quan 2002[33]	Systematic Review – references checked
Regalbuto 2007[34]	Incorrect study design – cohort study (no discussion or clarity on randomization)
Saravanan 2005[35]	Incorrect population – participants with thyroid cancer were excluded
Schaffler 2010[36]	Literature review – references checked
Sugitani 2010[37]	Incorrect population – participants did not undergo RAI treatment

Reference	Reason for exclusion
Sugitani 2011[38]	Incorrect population – participants did not undergo RAI treatment
Valle 2013[39]	No relevant outcomes – objective of study to determine dosages for TSH suppression cut off point
van Vliet 2018[40]	Incorrect study design – cohort study investigating gene association
Vera 2016[41]	Incorrect study design – case control study
Vestergaard 2005[42]	Incorrect study design – case control study
Wang 2020[43]	Systematic Review – references checked
Yamazaki 2012[44]	Incorrect study design – investigating lithium adjuvant post thyroidectomy
Yoon 2019[45]	Systematic Review – references checked

I.2 Health Economic studies

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

None.