National Institute for Health and Care Excellence

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Draft

Thyroid cancer

[J] Evidence review for RAI vs no RAI

NICE guideline <number>

Evidence reviews underpinning recommendations 1.3.15 to 1.3.17 and the research recommendation in the NICE guideline

June 2022

Draft for Consultation

These evidence reviews were developed by National Guideline Centre

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The recommendations in this guideline represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, professionals are expected to take this guideline fully into account, alongside the individual needs, preferences and values of their patients or service users. The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Local commissioners and/or providers have a responsibility to enable the guideline to be applied when individual health professionals and their patients or service users wish to use it. They should do so in the context of local and national priorities for funding and developing services, and in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities. Nothing in this guideline should be interpreted in a way that would be inconsistent with compliance with those duties.

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ISBN:

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1 Radioactive iodine versus no radioactive iodine

1.1 Review question

1.1.1 What is the clinical and cost effectiveness of radioactive iodine (RAI) ablation/treatment versus no RAI ablation/treatment in different population groups, characterised by stage, type of differentiated cancer, existence of vascular infiltration and gender?

1.1.2 Introduction

For the past 70 years it has become routine practice to treat most patients with differentiated thyroid cancer with radioactive iodine (RAI). This treatment would be offered to those patients who had received a "total thyroidectomy" and would be used to remove or "ablate" any residual thyroid cells. The less common advantage of this treatment is that any residual thyroid cancer cells remaining which cannot be seen will be removed as an adjuvant treatment. The most common reason forgiving RAI is to ensure there is no more normal non-cancerous thyroid cells left after surgery. This then means a blood test called thyroglobulin may be more accurately used to monitor the patient in the follow-up period as this should fall to zero or a negligible level after surgery and RAI ablation. The disadvantage is that patients will need to take lifelong thyroid replacement therapy and there can be other side effects such as chronic dry mouth. Whilst there is consensus that those with very small and pathologically low risk differentiated thyroid cancers probably do not need RAI and those with extensive tumours and pathologically high-risk tumours will always need RAI, there remains a question concerning those patients whose tumours are between these two categories. In these patients, does RAI ablation provide a survival benefit and justify possible side effects and the need for life-long thyroid hormone replacement. This review seeks to determine the patient groups who are most suitable for RAI after surgery.

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 for differentiated thyroid cancer. People will need to have had total or near total thyroidectomy. Exclusion: Children under 16
Intervention	Radioactive iodine ablation/treatment
Comparison	No radioactive iodine ablation/treatment
Outcomes	• mortality • quality of life (any validated tools) • local cancer progression • incidence of distant metastases • cancer recurrence • salivary gland disorders • second primary malignancy Time of follow up: longest available
Study design	RCTs and SRs or RCTs

1.1.4 Methods and process

The purpose of this review is not simply to evaluate if radioactive iodine ablation/treatment (RIA) is superior to no RAI, because it is well established that RAI is indeed superior to no RAI in some groups of patients. A more meaningful clinical question would seek to identify the groups for which RIA is beneficial. Therefore, the underlying aim of this review is to identify the groups who will benefit, and who will not benefit, from being given RAI. This will be achieved by identifying the population groups in which radioactive iodine /treatment leads to better overall outcomes than no radioactive iodine treatment and identifying the populations where there is either no relative benefit of RAI, or where RAI poses a relative harm. This should permit recommendations for RAI to be given to the populations who will benefit the most, and to avoid the harms of unnecessary RAI prescription in the populations where the benefits are less apparent.

These population groups have been defined by the four characteristics of stage, gender, type of differentiated cancer (papillary vs follicular), each of which will be evaluated through independent stratified analyses in the review. For example, for the characteristic of 'stage', studies that have participants that are predominantly lower stage disease will be placed in the 'lower stage' stratum and studies that have participants that are predominantly higher stage disease will be placed in the 'higher stage' stratum. Outcomes of RAI vs no RAI in each of these strata will then be compared to help evaluate the stage of disease most appropriate for RAI.

This rather indirect review methodology has the limitation that there may be insufficient studies in all of the possible population categories to permit useful conclusions, but the alternative approach is felt to be more problematical. The alternative approach would look for cohort studies that evaluate the risk factors for a good (or bad) outcome from RAI. Although initially more intuitive, such an alternative approach might be even more severely limited.

These limitations might occur because any associations between risk factor and outcome might be independent of whether radioactive iodine is given or not and would therefore not inform us of the groups most in need of radioactive iodine or the groups where radioactive iodine should not be given. For example, if the factor is 'stage' we will probably find that lower stage patients undergoing RAI have better absolute survival than higher stage patients undergoing RAI, spuriously suggesting that because lower stage patients end up doing better, they should be preferentially managed with RAI. However, this misses the point that we would expect lower stage patients to do better because of their superior prognosis, regardless of whether RAI is given or not. In reality it might be the higher stage patients who would benefit most from having RAI, because they would experience a greater *improvement* in their condition, even if their *absolute attainment* at follow up is inferior to people in the lower stages. Therefore, what we would really want to know is, 'what is the factor associated with the best *improvement* in the chosen outcome'? This might be possible for continuous outcomes like quality of life because you can chart the changes occurring at baseline to follow up, by taking the values at baseline as the non-RAI condition. However, for the majority of outcomes that are binary, such as mortality or recurrence, everyone starts the study at baseline with the same non-RAI condition of 'alive', or 'no recurrent disease yet'. This lack of resolution at baseline means any differences in states of health at baseline are not considered, and so changes occurring from the pre-RAI condition to post-RAI condition are not charted in a way that allows us to determine group differences in *improvement*. Because the absolute attainment at follow up may be more influenced by the underlying prognosis associated with the characteristic under investigation, and the real benefits or harms of RAI in this population group may be occluded by the lack of consideration of changes occurring from the non-RAI condition, this method may lead to spurious conclusions. In contrast, the strength of our chosen methodology is that RAI is compared to

no RAI in all strata, thus allowing an assessment of the benefits of RAI (with reference to no RAI) for that stratum that is independent of confounding prognostic effects.

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

A search was conducted for randomised trials comparing the effectiveness of radioactive iodine ablation/treatment to no radioactive iodine ablation/treatment. No randomised trials were found.

1.1.5.2 Excluded studies

See the excluded studies list in Appendix I.

1.1.6 Economic evidence

1.1.6.1 Included studies

No health economic studies were included.

1.1.6.2 Excluded studies

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

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

1.1.7 Summary of included economic evidence

None.

1.1.8 Economic model

This are was not prioritised for an original cost-effectiveness analysis.

1.1.9 Unit costs

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

Resource	Unit costs	Source
Low activity RAI (day care)	£406	NHS Reference Costs 2018-2019, NICE 2015, Committee expert opinion
Low activity RAI	£628	NHS Reference Costs 2018-2019, NICE 2015, Committee expert opinion
High activity RAI	£961	NHS Reference Costs 2018-2019, NICE 2015, Committee expert opinion

1.1.10 Economic evidence statements

No relevant economic evaluations were identified.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1 The outcomes that matter most

Protocol-specified outcomes of mortality, quality of life (any validated tools), local cancer progression, incidence of distant metastases, cancer recurrence, salivary gland disorders and second primary malignancy were all deemed critical and were therefore of equal importance in decision-making.

1.1.11.2 The quality of the evidence

The review found no evidence pertaining to the clinical and cost-effectiveness of RAI ablation or treatment versus no RAI ablation or treatment in different population groups, characterised by stage, type of differentiated cancer, existence of vascular infiltration and gender.

1.1.11.3 Benefits and harms

The committee sought consensus around clinical presentations for which they would definitely offer RAI, and conversely, clinical presentations for which they would definitely not offer RAI.

To determine criteria for an offer of RAI ablation, the committee referred to the exclusion criteria of an ongoing trial, the ION trial, as a starting point for discussion. A consensus was reached that RAI ablation should be offered after an initial total thyroidectomy or after a completion thyroidectomy, when the following criteria are fulfilled: primary tumour at stage T3 or T4 (which describes a size of at least 4cm and extrathyroidal extension), regional lymph node involvement, pathological findings that are associated with a poor prognosis (including multifocal disease), and evidence of distant metastases. The committee decided that this should be a strong 'offer' recommendation because there was consensus, based on clinical experience, that for patients fulfilling these criteria there was very likely to be a benefit strongly outweighing any harms. It was agreed by the committee that pending further evidence, RAI ablation should not be offered in solitary microcarcinoma (that is, T1a, a single papillary thyroid carcinoma of size 1cm or less, in maximum dimension) unless other adverse prognostic features were present. These would include prognostically poor histological subtypes, R1 resection margin and multifocality. This decision was based on the consensus opinion that the harms from RAI might outweigh the benefits unless the adverse prognostic features were present. Furthermore, there was a consensus that this approach represents current clinical practice.

Having defined clinical presentations in which RAI would, and would not be offered, the committee felt that a recommendation to 'consider RAI' would be appropriate for clinical presentations that did not fit into either the 'offer' or 'do not offer' categories. This group can therefore be defined, by exclusion, as a group that does not have any of the following: a primary tumour at stage T3 or T4, regional lymph node involvement, pathological findings that are associated with a poor prognosis, evidence of distant metastases, or a solitary papillary microcarcinoma without adverse prognostic features such as prognostically poor histological subtypes, R1 resection margin and multifocality.

In the absence of appropriate evidence, a research recommendation was made to address the question: 'What is the clinical and cost effectiveness of RAI after total thyroidectomy or hemithyroidectomy followed by completion (total thyroidectomy) for patients at tumour stages 2b or 3, with no adverse pathological features?'

The committee agreed that it is important that up-to-date guidance should be available to clinicians on when to offer RAI. The committee were aware that results from the ION and ESTIMABL2 trials may provide much needed evidence. Although results from these trials

were not able to be considered for the consultation draft of the guideline, it was deemed important that consensus and research recommendations should be made in the interim.

1.11.4 Cost effectiveness and resource use

No health economics analysis was included for this review.

Given the lack of clinical evidence, the committee agreed to make a consensus recommendation based on their experience, offering RAI to people with particularly concerning characteristics and considering RAI in the remaining cases of total thyroidectomy (TT) and completion thyroidectomy (CT). There is currently heterogeneity in practice especially among people considered to be at low and intermediate risk of recurrence. The recommendations, by providing a list of characteristics that should be considered when offering RAI, will likely make the decision-making process more efficient and transparent and therefore enhance the efficiency of the NHS.

The committee were aware that there are ongoing trials, such as ION and ESTIMABL2, looking at long-term outcomes of people with and without RAI. Further health economics analyses based on those trials may be able to shed light on the real cost effectiveness of RAI among people with low or intermediate-risk cancer.

1.11.5 Other factors the committee took into account

The committee discussed equality issues regarding pregnancy, gender and disabilities.

Exposure to radioiodine during pregnancy is harmful to the developing fetus with consequent fetal hypothyroidism and potential cognitive disorders. Pregnancy should therefore be avoided after radioiodine for at least six months to avoid exposure to radioactivity, and to ensure the mother is in remission and with adequate thyroid hormone replacement. If radioiodine is required after delivery, breast feeding should be stopped for at least six weeks. Mothers receiving radioiodine should avoid breast feeding. Therefore, careful consideration is required for these women as to the timing of RAI treatment.

There is some evidence suggesting that radioiodine may adversely affect fertility men. Some centres offer sperm banking for men if multiple doses of radioiodine are planned, particularly if the cumulative planned dose is >13GBq or they are attempting conception within 18 months of treatment. However, this is not offered by all centres.

Overall, the committee agreed there is standard and accepted advice around want to do and recommended that written and verbal information is provided on how treatment may affect conception, pregnancy and fertility. The committee also recommended surgery is deferred until after pregnancy where possible. As radioactive iodine is only given postoperatively then by default it would also be deferred.

In addition, in people who have significant physical and mental co-morbidities and disabilities which may impact on the safe administration of RAI the committee agreed that usual practice is for them to have a patient specific risk assessment and care plan arranged before RAI is administered.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.3.15 to 1.3.17 and the research recommendation on radioactive iodine.

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Appendices

Appendix A – Review protocols

131.12.1 Review protocol for radioactive iodine therapy

Field	Content
PROSPERO registration number	CRD42020213254
Review title	Clinical and cost effectiveness of radioactive iodine (RAI) versus no RAI in different groups of people after surgery. The different population strata will be characterised by stage, type of differentiated cancer, the existence of vascular infiltration, and gender. Of course, the resultant groupings we use for comparison of effects will be interactions of all these strata! That is, if our chosen strata are stage and gender, we would compare (for example) stage 1 male, stage 1 female, stage 2 male, stage 2 female, etc).
Review question	What is the clinical and cost effectiveness of radioactive iodine (RAI) ablation/treatment versus no RAI ablation/treatment in different population groups, characterised by stage, type of differentiated cancer, existence of vascular infiltration and gender?
Objective	To determine the patient groups who are most suitable for RAI
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 for MEDLINE database will be published in the final review.
Condition or domain being studied	Thyroid cancer

Population	Inclusion: People aged 16 or over who have had thyroidectomy for differentiated thyroid cancer. People will need to have had total or near total thyroidectomy. Exclusion: Children under 16
Intervention/Exposure/Test	Radioactive iodine ablation
Comparator/Reference standard/Confounding factors	No radioactive iodine ablation
Types of study to be included	• Systematic reviews • RCTs
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	RAI treatment/ablation is now an established intervention, 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)	• mortality • quality of life (any validated tools) • local cancer progression • incidence of distant metastases • cancer recurrence • salivary gland disorders • second primary malignancy Time of follow up: longest available
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) 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. third review author where necessary.
Strategy for data synthesis	Where possible, data will be meta-analysed. Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5) to combine the data given in all studies for each of the outcomes stated above. A fixed effect meta-analysis, with weighted mean differences for continuous outcomes and risk ratios for binary outcomes will be used, and 95% confidence intervals will be calculated for each outcome. Heterogeneity between the studies in effect measures will be assessed using the I^2 statistic and visually inspected. We will consider an I^2 value greater than 50% indicative of substantial heterogeneity. Sensitivity analyses will be conducted based on pre-specified subgroups using stratified meta-analysis to explore the heterogeneity in effect estimates. If this does not explain the heterogeneity, the results will be presented using random-effects. GRADE pro will be used to assess the quality of each outcome, taking into account individual study quality and the meta-analysis results. The 4 main quality elements (risk of bias, indirectness, inconsistency and imprecision) will be appraised for each outcome. Publication bias is tested for when there are more than 5 studies for an outcome. Other bias will only be taken into consideration in the quality assessment if it is apparent. Where meta-analysis is not possible, data will be presented and quality assessed individually per outcome.

	If sufficient data is available to make a network of treatments, WinBUGS will be used for network meta-analysis.
Analysis of sub-groups	<u>Stratification (up-front stratification of analysis, NOT conditional on heterogeneity of prior meta-analysis)</u> • Stage • Gender • papillary vs follicular • Vascular infiltration vs no infiltration <u>Sub-grouping (conditional stratification if heterogeneity seen in initial unstratified meta-analysis)</u> If serious or very serious heterogeneity (I2>50%) is present within any stratum, sub-grouping will occur according to the following strategy: • Total vs hemi-thyroidectomy • Thyrotrophin vs withdrawal of thyroid replacement in RAI group • Dietary restriction of iodine vs no dietary restrictions • Ablation vs treatment • Longest follow up in study: <1 yr, 1-5 yrs, >5 yrs • Activity low (1Gb) vs higher (3-4 Gb)
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 Vimal Bedia, Senior systematic reviewer Giulia Zuodar, Project manager Dave Wonderling, Head of health economics 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	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=213254
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	
Details of existing review of same topic by same authors	N/A
Additional information	N/A
Details of final publication	www.nice.org.uk

11.12.2 Review protocol health economic evidence

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2005, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[11] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations', then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations', then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion**

The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below.

The health economist will be guided by the following hierarchies.

Setting:

- UK NHS (most applicable).
- OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden).
- OECD countries with predominantly private health insurance systems (for example, Switzerland).
- Studies set in non-OECD countries or in the USA will be excluded before being assessed for applicability and methodological limitations.

Health economic study type:

- Cost–utility analysis (most applicable).
- Other type of full economic evaluation (cost–benefit analysis, cost-effectiveness analysis, cost–consequences analysis).
- Comparative cost analysis.
- Non-comparative cost analyses including cost-of-illness studies will be excluded before being assessed for applicability and methodological limitations.

Year of analysis:

- The more recent the study, the more applicable it will be.
- Studies published in 2005 or later but that depend on unit costs and resource data entirely or predominantly from before 2005 will be rated as ‘Not applicable’.
- Studies published before 2005 will be excluded before being assessed for applicability and methodological limitations.

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

- The more closely the clinical effectiveness data used in the health economic analysis match with the outcomes of the studies included in the clinical review the more useful the analysis will be for decision-making in the guideline.

Appendix B – Literature search strategies

The literature searches for these reviews are detailed below and complied with the methodology outlined in Developing NICE guidelines: the manual, 2014 (updated 2020) https://www.nice.org.uk/process/pmg20/chapter/identifying-the-evidence-literature-searching-and-evidence-submission.

For more information, please see the Methodology review published as part of the accompanying documents for this guideline.

Clinical literature search strategy

This literature search strategy was used for this review:

- What is the clinical and cost effectiveness of radioactive iodine (RAI) ablation/treatment versus no RAI ablation/treatment in different population groups, characterised by stage, type of differentiated cancer, existence of vascular infiltration and gender?

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

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	1946 – 13 January 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, children) English language
Embase (OVID)	1974 – 13 January 2022	Randomised controlled trials Systematic review studies Observational studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts, children) English language
The Cochrane Library (Wiley)	Cochrane Database of Systematic Reviews to Issue 12 of 12, December 2021 Cochrane Central Register of Controlled Trials to Issue 12 of 12, December 2021	Exclusions (clinical trials, conference abstracts)

Database	Dates searched	Search filters and limits applied
Epistemonikos (The Epistemonikos Foundation)	Inception – 13 January 2022	Systematic review Exclusions (Cochrane reviews) English language

1 **Medline (Ovid) search terms**

1.	exp Thyroid Neoplasms/
2.	(thyroid and (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or follicul* or lymphoma* or anaplastic or sarcoma* or medullar* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.
4.	((papillar* or follicul* or medullar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump* or lymphoma*)).ti,ab.
5.	or/1-4
6.	letter/
7.	editorial/
8.	news/
9.	exp historical article/
10.	Anecdotes as Topic/
11.	comment/
12.	case report/
13.	(letter or comment*).ti.
14.	or/6-13
15.	randomized controlled trial/ or random*.ti,ab.
16.	14 not 15
17.	animals/ not humans/
18.	exp Animals, Laboratory/
19.	exp Animal Experimentation/
20.	exp Models, Animal/
21.	exp Rodentia/
22.	(rat or rats or mouse or mice or rodent*).ti.
23.	or/16-22
24.	5 not 23
25.	limit 24 to english language
26.	exp radiotherapy/
27.	radiotherapy dosage/
28.	Iodine Radioisotopes/
29.	radioiodine.ti,ab.
30.	(iodi?e adj2 (radio* or isotope*)).ti,ab.
31.	(iodi?e 131 or 131-I or I-131).ti,ab.
32.	remnant ablation.ti,ab.
33.	(iodi?e adj2 (ablation or treatment* or therap* or medic* or procedure* or intervention*)).ti,ab.
34.	(RAA or RRA or RAI).ti,ab.

35.	or/26-34
36.	25 and 35
37.	randomized controlled trial.pt.
38.	controlled clinical trial.pt.
39.	randomi#ed.ab.
40.	placebo.ab.
41.	randomly.ab.
42.	clinical trials as topic.sh.
43.	trial.ti.
44.	or/37-43
45.	Meta-Analysis/
46.	Meta-Analysis as Topic/
47.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
48.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
49.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
50.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
51.	(search* adj4 literature).ab.
52.	(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.
53.	cochrane.jw.
54.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
55.	or/45-54
56.	Epidemiologic studies/
57.	Observational study/
58.	exp Cohort studies/
59.	(cohort adj (study or studies or analys* or data)).ti,ab.
60.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
61.	((longitudinal or retrospective or prospective or cross sectional) and (study or studies or review or analys* or cohort* or data)).ti,ab.
62.	Controlled Before-After Studies/
63.	Historically Controlled Study/
64.	Interrupted Time Series Analysis/
65.	(before adj2 after adj2 (study or studies or data)).ti,ab.
66.	exp case control study/
67.	case control*.ti,ab.
68.	Cross-sectional studies/
69.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
70.	or/57-70
71.	36 and (44 or 55 or 70)

1 **Embase (Ovid) search terms**

1.	exp Thyroid Cancer/
2.	(thyroid adj3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)).ti,ab.
3.	DTC.ti,ab.

4.	((papillar* or anaplastic) adj2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)).ti,ab.
5.	or/1-4
6.	letter.pt. or letter/
7.	note.pt.
8.	editorial.pt.
9.	case report/ or case study/
10.	(letter or comment*).ti.
11.	(conference abstract or conference paper).pt.
12.	or/6-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice or rodent*).ti.
22.	or/14-21
23.	5 not 22
24.	limit 23 to english language
25.	(exp child/ or exp pediatrics/) not (exp adult/ or exp adolescent/)
26.	24 not 25
27.	exp radiotherapy/
28.	radiotherapy dosage/
29.	radioactive iodine/
30.	radioiodine.ti,ab.
31.	(iodi?e adj2 (radio* or isotope*)).ti,ab.
32.	iodine 131/
33.	(iodi?e 131 or 131-I or I-131).ti,ab.
34.	remnant ablation.ti,ab.
35.	(iodi?e adj2 (ablation or treatment* or therap* or medic* or procedure* or intervention*)).ti,ab.
36.	(RAA or RRA or RAI).ti,ab.
37.	or/27-36
38.	26 and 37
39.	random*.ti,ab.
40.	factorial*.ti,ab.
41.	(crossover* or cross over*).ti,ab.
42.	((doubl* or singl*) adj blind*).ti,ab.
43.	(assign* or allocat* or volunteer* or placebo*).ti,ab.
44.	crossover procedure/
45.	single blind procedure/
46.	randomized controlled trial/
47.	double blind procedure/
48.	or/39-47
49.	systematic review/

50.	Meta-Analysis/
51.	(meta analy* or metanaly* or metaanaly* or meta regression).ti,ab.
52.	((systematic* or evidence*) adj3 (review* or overview*)).ti,ab.
53.	(reference list* or bibliograph* or hand search* or manual search* or relevant journals).ab.
54.	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
55.	(search* adj4 literature).ab.
56.	(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.
57.	cochrane.jw.
58.	((multiple treatment* or indirect or mixed) adj2 comparison*).ti,ab.
59.	or/49-58
60.	Clinical study/
61.	Observational study/
62.	family study/
63.	longitudinal study/
64.	retrospective study/
65.	prospective study/
66.	cohort analysis/
67.	follow-up/
68.	cohort*.ti,ab.
69.	67 and 68
70.	(cohort adj (study or studies or analys* or data)).ti,ab.
71.	((follow up or observational or uncontrolled or non randomi#ed or epidemiologic*) adj (study or studies or data)).ti,ab.
72.	((longitudinal or retrospective or prospective) and (study or studies or review or analys* or cohort* or data)).ti,ab.
73.	(before adj2 after adj2 (study or studies or data)).ti,ab.
74.	exp case control study/
75.	case control*.ti,ab.
76.	cross-sectional study/
77.	(cross sectional and (study or studies or review or analys* or cohort* or data)).ti,ab.
78.	or/60-66,69-77
79.	38 and (48 or 59 or 78)

1 **Cochrane Library (Wiley) search terms**

#1.	MeSH descriptor: [Thyroid Neoplasms] explode all trees
#2.	(thyroid near/3 (cancer* or carcinom* or microcarcinoma* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or node* or nodul* or nodal or lump* or papillar* or swollen or swell* or anaplastic or sarcoma* or cyst* or malignan*)):ti,ab
#3.	DTC:ti,ab
#4.	((papillar* or anaplastic) near/2 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nodul* or node* or lump*)):ti,ab
#5.	#1 or #2 or #3 or #4
#6.	conference:pt or (clinicaltrials or trialsearch):so
#7.	#5 not #6
#8.	MeSH descriptor: [Iodine Radioisotopes] explode all trees
#9.	MeSH descriptor: [Radiotherapy] explode all trees

#10.	MeSH descriptor: [Radiotherapy Dosage] this term only
#11.	radioiodine:ti,ab
#12.	((iodi?e) near/2 (radio* or isotope*)):ti,ab
#13.	(iodi?e-131 or I-131):ti,ab
#14.	remnant ablation:ti,ab
#15.	((iodi?e) near/2 (ablation or treatment* or therap* or medic* or procedure* or intervention*)):ti,ab
#16.	(RAA or RRA or RAI):ti,ab
#17.	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18.	#7 and #17

Epistemonikos search terms

1.	(title:(remnant ablation OR RAI OR RRA OR RAA) OR abstract:(remnant ablation OR RAI OR RRA OR RAA)) OR (title:(thyroid AND (iodine OR iodide)) OR abstract:(thyroid AND (iodine OR iodide)))

Health Economics literature search strategy

Health economic evidence was identified by conducting searches using terms for a broad Thyroid Cancer population. The following databases were searched: NHS Economic Evaluation Database (NHS EED - this ceased to be updated after 31st March 2015), Health Technology Assessment database (HTA - this ceased to be updated from 31st March 2018) and The International Network of Agencies for Health Technology Assessment (INAHTA). Searches for recent evidence were run on Medline and Embase from 2014 onwards for health economics, and all years for quality-of-life studies.

Table 2: Database parameters, filters and limits applied

Database	Dates searched	Search filters and limits applied
Medline (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1946 – 16 December 2021	
Embase (OVID)	Health Economics 1 January 2014 – 16 December 2021	Health economics studies Quality of life studies Exclusions (animal studies, letters, comments, editorials, case studies/reports, conference abstracts) English language
	Quality of Life 1974 – 16 December 2021	
NHS Economic Evaluation Database (NHS EED) (Centre for Research and Dissemination - CRD)	Inception –31st March 2015	
Health Technology Assessment Database (HTA)	Inception – 31st March 2018	

Database	Dates searched	Search filters and limits applied
(Centre for Research and Dissemination – CRD)		
The International Network of Agencies for Health Technology Assessment (INAHTA)	Inception - 16 December 2021	English language

1 **Medline (Ovid) search terms**

1.	exp Thyroid Neoplasms/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter/
6.	editorial/
7.	news/
8.	exp historical article/
9.	Anecdotes as Topic/
10.	comment/
11.	case report/
12.	(letter or comment*).ti.
13.	or/5-12
14.	randomized controlled trial/ or random*.ti,ab.
15.	13 not 14
16.	animals/ not humans/
17.	exp Animals, Laboratory/
18.	exp Animal Experimentation/
19.	exp Models, Animal/
20.	exp Rodentia/
21.	(rat or rats or mouse or mice).ti.
22.	or/15-21
23.	4 not 22
24.	limit 23 to english language
25.	economics/
26.	value of life/
27.	exp "costs and cost analysis"/
28.	exp Economics, Hospital/
29.	exp Economics, medical/
30.	Economics, nursing/
31.	economics, pharmaceutical/
32.	exp "Fees and Charges"/
33.	exp budgets/
34.	budget*.ti,ab.
35.	cost*.ti.

36.	(economic* or pharmaco?economic*).ti.
37.	(price* or pricing*).ti,ab.
38.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
39.	(financ* or fee or fees).ti,ab.
40.	(value adj2 (money or monetary)).ti,ab.
41.	or/25-40
42.	24 and 41
43.	quality-adjusted life years/
44.	sickness impact profile/
45.	(quality adj2 (wellbeing or well being)).ti,ab.
46.	sickness impact profile.ti,ab.
47.	disability adjusted life.ti,ab.
48.	(qal* or qtime* or qwb* or daly*).ti,ab.
49.	(euroqol* or eq5d* or eq 5*).ti,ab.
50.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
51.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
52.	(hui or hui1 or hui2 or hui3).ti,ab.
53.	(health* year* equivalent* or hye or hyes).ti,ab.
54.	discrete choice*.ti,ab.
55.	rosser.ti,ab.
56.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
57.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
58.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
59.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
60.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
61.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
62.	or/52-70
63.	24 and 62

1 **Embase (Ovid) search terms**

1.	exp Thyroid Cancer/
2.	(thyroid adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)).ti,ab.
3.	((papillar* or follicul* or medullary or anaplastic) adj4 (cancer* or carcinom* or tumo?r* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)).ti,ab.
4.	or/1-3
5.	letter.pt. or letter/
6.	note.pt.
7.	editorial.pt.
8.	case report/ or case study/
9.	(letter or comment*).ti.
10.	or/5-9
11.	randomized controlled trial/ or random*.ti,ab.
12.	10 not 11
13.	animal/ not human/
14.	nonhuman/

15.	exp Animal Experiment/
16.	exp Experimental Animal/
17.	animal model/
18.	exp Rodent/
19.	(rat or rats or mouse or mice).ti.
20.	or/12-19
21.	4 not 20
22.	limit 21 to english language
23.	health economics/
24.	exp economic evaluation/
25.	exp health care cost/
26.	exp fee/
27.	budget/
28.	funding/
29.	budget*.ti,ab.
30.	cost*.ti.
31.	(economic* or pharmaco?economic*).ti.
32.	(price* or pricing*).ti,ab.
33.	(cost* adj2 (effectiv* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
34.	(financ* or fee or fees).ti,ab.
35.	(value adj2 (money or monetary)).ti,ab.
36.	or/23-35
37.	22 and 36
38.	quality-adjusted life years/
39.	"quality of life index"/
40.	short form 12/ or short form 20/ or short form 36/ or short form 8/
41.	sickness impact profile/
42.	(quality adj2 (wellbeing or well being)).ti,ab.
43.	sickness impact profile.ti,ab.
44.	disability adjusted life.ti,ab.
45.	(qal* or qtime* or qwb* or daly*).ti,ab.
46.	(euroqol* or eq5d* or eq 5*).ti,ab.
47.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
48.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
49.	(hui or hui1 or hui2 or hui3).ti,ab.
50.	(health* year* equivalent* or hye or hyes).ti,ab.
51.	discrete choice*.ti,ab.
52.	rosser.ti,ab.
53.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
54.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
55.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
56.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
57.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
58.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
59.	or/37-58
60.	22 and 59

1

1 **NHS EED and HTA (CRD) search terms**

#1.	MeSH DESCRIPTOR Thyroid Neoplasms EXPLODE ALL TREES
#2.	((thyroid NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or papillar* or follicul* or lymphoma* or anaplastic)))
#3.	(((papillar* or follicul* or medullary or anaplastic) NEAR4 (cancer* or carcinom* or tumour* or tumor* or neoplasm* or metast* or adenoma* or adenocarcinom* or nod* or lump* or lymphoma*)))
#4.	#1 OR #2 OR #3

2 **INHATA search terms**

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

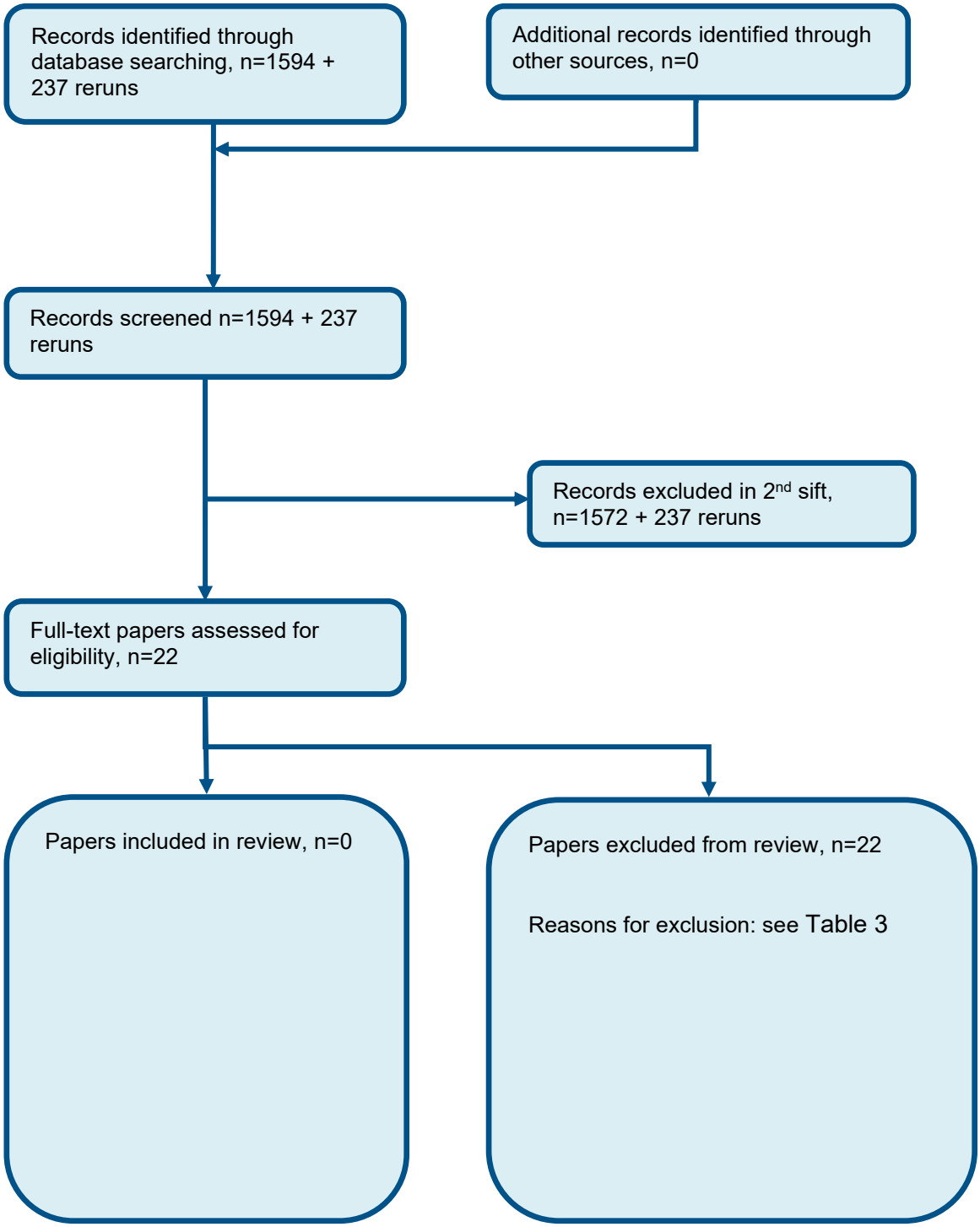
3

4

5

Appendix C – Effectiveness evidence study selection

Figure 1: Flow chart of clinical study selection for the review of RAI vs no RAI



Appendix D – Effectiveness evidence

No evidence found.

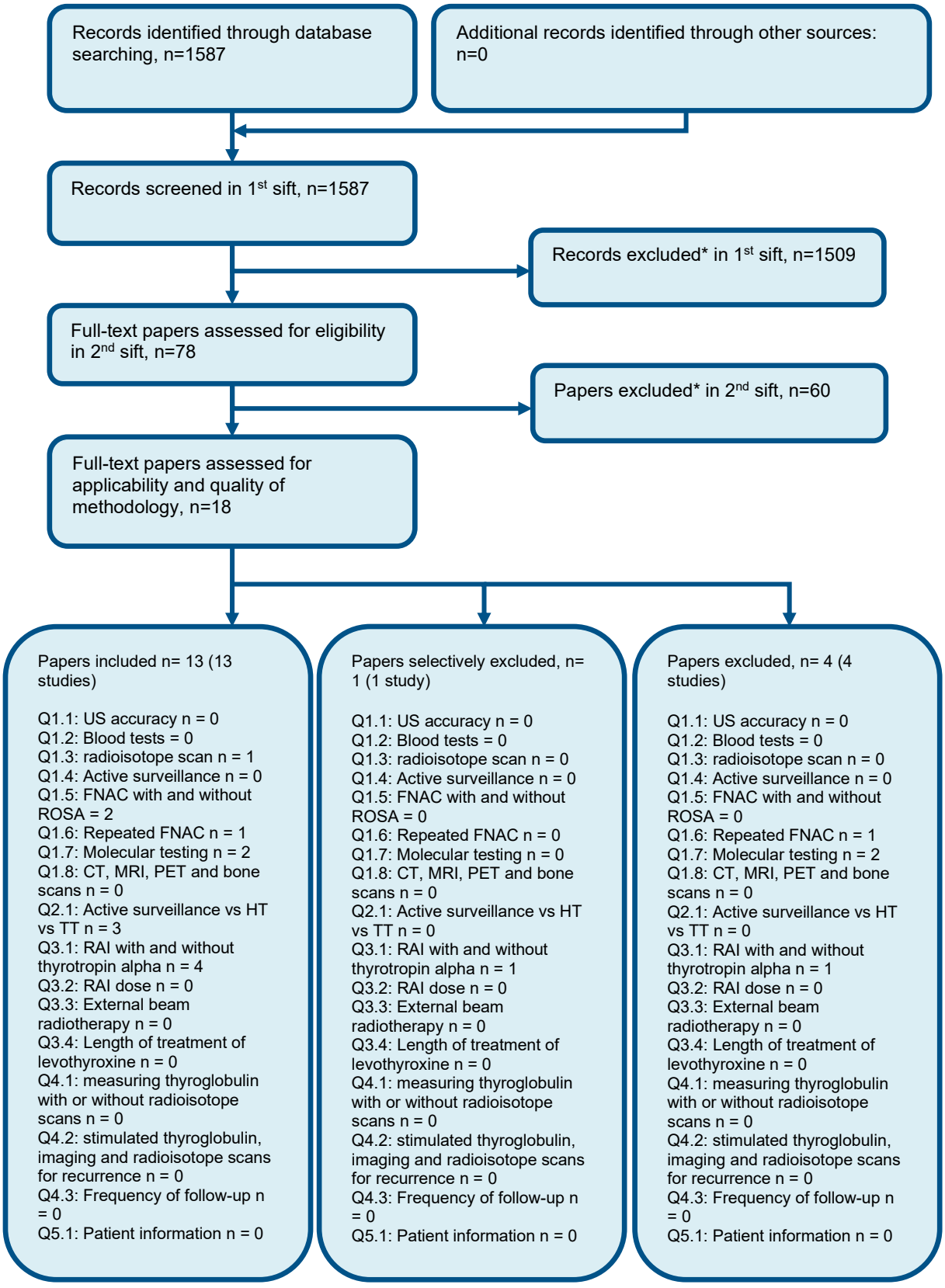
Appendix E – Forest plots

No evidence found

Appendix F – GRADE and/or GRADE-CERQual tables

No evidence found.

Appendix G – Economic evidence study selection



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

Appendix H – Economic evidence tables

None.

Appendix I – Excluded studies

I.1 Clinical studies

Table 3: Studies excluded from the clinical review

Reference	Reason for exclusion
Andresen, 2017[1]	systematic review- references checked
Bal, 2006[2]	non randomised
Banerjee, 2018[3]	non randomised
Goldsmith, 2011[4]	systematic review - references checked
Kim, 2013[5]	non randomised
Lamartina, 2015[6]	opinion piece on the cons of radioiodine ablation
Laupa, 1993[7]	comparator from a different population (head and neck cancer)
Lazaro, 2018[8]	non randomised
Mallick, 2012[10]	wrong comparison (comparing doses)
Mallick, 2012[9]	study protocol for ongoing trial
Pacini, 2005[12]	systematic review - references checked
Piccardo, 2020[13]	systematic review - references checked
Reiners, 2011[14]	systematic review - references checked
Sacks, 2010[15]	systematic review - references checked
Sawka, 2004[18]	systematic review - references checked
Sawka, 2004[19]	systematic review - references checked
Sawka, 2008[16]	abstract
Sawka, 2013[17]	systematic review - references checked
Verburg, 2017[20]	systematic review - references checked
Yang, 2019[21]	systematic review - references checked
Yin, 2018[22]	non randomised; although 'random grouping' was mentioned once in the text, this was the only reference to randomisation and so it was deemed likely that this study was probably a non-randomised trial.
Zaman, 2013[23]	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.

Appendix J – Research recommendations

J.1 Research recommendation

What is the clinical and cost effectiveness of radioactive iodine (RAI) after total thyroidectomy or hemithyroidectomy followed by completion thyroidectomy for people with tumour stages 2b or 3, with no adverse pathological features?

J.1.1 Why this is important

The committee agreed that RAI should be offered after total thyroidectomy or completion hemithyroidectomy for higher primary tumour stages (T3B, T4A and T4B stage), regional lymph node involvement, adverse pathological features, or distant metastatic disease (M1). However, they were less clear about the benefits and harms for patients who had had a total thyroidectomy or completion hemithyroidectomy but who were at lower tumour stages (2b or 3), without adverse pathological features. For this reason, a 'consider' recommendation was made. The committee agreed that this clinical uncertainty, which could feed into potential harm for some patients, should be resolved by further research work. An RCT is required to provide high quality evidence. The committee believe that an RCT restricted to this specific group would be both feasible and ethical, because there is genuine uncertainty about the benefits and harms of RAI for these people; given this potential equipoise, there should be relatively few concerns with randomising people to 'no RAI'.

J.1.2 Rationale for research recommendation

Importance to 'patients' or the population	RAI has both benefits and harms for the patient, and it is essential to know the precise balance of benefits and harms for this patient group so that appropriate clinical decisions can be made, which will maximise benefits and minimise harms.
Relevance to NICE guidance	The efficacy of RAI for different patient groups has been considered in this guideline, but we did not find any RCTs. The development of such RCTs is therefore required.
Relevance to the NHS	Reduction of potential harms from RAI through better knowledge and understanding of its effects on specific patient groups is essential.
National priorities	None known
Current evidence base	There is currently no RCT evidence of the benefits of RAI.
Equality considerations	None known

J.1.3 Modified PICO table

Population	People at tumour stages 2b or 3, with no adverse pathological features who have had

	total thyroidectomy or hemithyroidectomy followed by completion (total thyroidectomy)
Intervention	RAI
Comparator	Usual care
Outcome	Quality of life, progression, recurrence, mortality
Study design	RCT
Timeframe	Long term
Additional information	None

1

2