National Institute for Health and Care Excellence

FINAL

Thyroid disease: assessment and management

[L] Management of thyrotoxicosis: radioactive iodine options

NICE guideline NG145

Intervention evidence review underpinning recommendations 1.6.10 to 1.6.20 in the guideline. See also evidence reviews I, J, K and D

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1.1 Review question: When radioactive iodine is used, what is the most clinically and cost-effective way of using this treatment to treat thyrotoxicosis (for example different dosing strategies)?

1.2 Introduction

Radioactive iodine has been used to treat thyrotoxicosis for many years. The attractions of this therapy include the fact that it is relatively cheap. Administration is straight-forward although guidelines that limit exposure to ionising radiation need to be followed when using radioactive agents and there is variation between centres in terms of when this modality is considered to be an appropriate therapeutic option. Some units are more proactive than others and consider this treatment more readily in the context of the younger patient and the individual with complicating factors such as thyroid eye disease. Some units administer a 'set' dose of radio-iodine in the context of the patient with thyrotoxicosis whilst other units calculate the dose on an individual basis. Establishing the circumstances and threshold for using this treatment is an important area because the therapeutic options for patients who fail to respond to anti-thyroid drug are limited.

1.3 PICO table

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

Table 1: PICO characteristics of review question

Population	People requiring/opting for radioactive iodine (RAI) treatment for thyrotoxicosis
Interventions	RAI dose - calculated strategy RAI dose - fixed strategy RAI with ATDs RAI alone
Comparisons	Any of the above versus any other
Outcomes	**Critical** Mortality (dichotomous, ≥1 year) Quality of life (continuous) **Important** Thyroid ophthalmopathy (dichotomous) Euthyroidism (dichotomous) Hypothyroidism (dichotomous) Relapse of hyperthyroidism (dichotomous) Cardiovascular morbidity (ischaemic heart disease, dichotomous) Arrhythmia (dichotomous) Osteoporosis (dichotomous) Cognitive impairment (dichotomous) Pain (continuous) Symptom scores (continuous) Patient/family/carer experience (continuous) Healthcare contacts (rates/dichotomous)

	Agranulocytosis (dichotomous) Liver failure (dichotomous) Minor drug related adverse effects (dichotomous) Teratogenesis (dichotomous) Infertility (dichotomous) Malignancy (dichotomous) Thyrotoxic storm (dichotomous) Growth abnormalities (dichotomous) Hypocalcaemia (dichotomous) Hypoparathyroidism (dichotomous)
Study design	RCTs, non-randomised cohort studies to be considered if adjusted for key confounders (age, co-existing conditions, baseline T4, size of goitre) and insufficient RCTs evidence found, on an intervention by intervention basis

The focus of the comparison between RAI with or without ATDs was whether, once the decision to use RAI had been made, a short course of ATDs either before or after RAI, impacted clinical outcomes. The focus was not on a comparison of long term combination therapy with ATDs and RAI versus RAI alone.

A key issue for consideration in this area was how the administered activity of radioactive iodine should be chosen. This review focused on comparisons between radioactive iodine use when administered activity was chosen based on a full assessment of the likely dose that would be absorbed by the thyroid gland (in other words involving a formal assessment of the size of the thyroid gland and a test of the amount of radioactive iodine uptake) and use when the administered activity involved little or no personalisation to the individual (in other words a single administered activity for all people, in some cases with a higher activity chosen for those with clinically obvious larger goitres). The review uses calculated and fixed strategies respectively as short hand for these two categories.

1.4 Clinical evidence

1.4.1 Included studies

Thirteen RCTs were included in the review;[5, 17, 22, 31, 35, 38, 44, 46, 50, 52, 67, 75, 79] these are summarised in Table 2 below. Evidence from these studies is summarised in the clinical evidence summary below (Table 3).

Seven studies compared radioactive iodine with pre or post antithyroid drug treatment with radioactive iodine alone. Four of these studies gave antithyroid drugs before radioactive iodine treatment, two studies gave the antithyroid drugs after radioactive iodine treatment, one study gave antithyroid drugs both before and after radioactive iodine treatment.

Six studies compared radioactive iodine with a calculated strategy with radioactive iodine with a fixed strategy.

All studies were in adults. No studies were identified in children or older adults specifically. Ten studies were either exclusively in people with Graves' disease or in populations in which the majority had Graves' disease. Two studies were in populations in which the majority had toxic multinodular goitre. One study did not describe the breakdown of the cause of thyrotoxicosis in its population.

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:.

1.4.2 Excluded studies

See the excluded studies list in Appendix J:.

1.4.3 Summary of clinical studies included in the evidence review

Table 2: Summary of studies included in the evidence review

Study	Intervention and comparison	Population	Outcomes	Comments
Andrade 2001[5]	RAI with ATDs, n = 29 30g/d MMI given until euthyroidism, RAI given 4 days after discontinuation of MMI RAI alone, n = 32 Calculated activity, 200uCi/g thyroid tissue divided by fractional 24-hr RAI uptake	Adults (mean 37, SD 7) Graves' disease No previous RAI or surgery, no information on previous ATD treatment Brazil	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism 1 year follow-up	Ophthalmopathy at baseline not stated
Bonnema 2004[17]	RAI with ATDs, n = 40 PTU given until euthyroidism, RAI (calculated strategy, 1 dose unless persistent at 9 months) given 4 days after discontinuation of PTU RAI alone, n = 41 calculated strategy, 1 dose unless persistent at 9 months	Adults (mean 59, SD 11) 71% toxic nodular goitre, 29% Graves' disease No previous RAI or surgery, no ATDs within 3 months of study start Denmark	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism 1 year follow-up	Ophthalmopathy at baseline not stated
Canto 2016[22]	RAI calculated strategy, n = 61 (160µCi/g x thyroid weight x 10^{-3})/24hr RAIU RAI fixed strategy, n = 61 9.9mCi of I^{131} if gland <40g, 14.9mCi of I^{131} if gland <40g	Adults (mean 36, SD 12) Graves' disease 75% no previous treatment Philippines	Relapse/persistence of hyperthyroidism 6 month follow-up	26% with ophthalmopathy at baseline Calculated strategy based on ultrasound and thyroid scan 2 + 24 hours after dose of I^{131}

Study	Intervention and comparison	Population	Outcomes	Comments
Gamstedt 1986[31]	RAI with ATDs, n = 17 MMI 10mg 3x daily, given for 7 weeks before RAI, discontinued for 1 week, restarted for 11 weeks after. RAI given at fixed dose of 350MBq, repeated at 3 months as required RAI alone, n = 23	Adults (mean 59, SD 12) Graves' disease No previous radioactive iodine treatment Sweden	Hypothyroidism Ophthalmopathy 12 month follow-up	No ophthalmopathy at baseline
Goolden 1969[35]	RAI with ATDs, n = 83 Carbimazole given for 2-4 months, stopped 3-5 days before RAI treatment. Single RAI treatment on calculated strategy (150uCi/g if gland <70g, gland >70g aimed for 300uCi/g). RAI alone, n = 98	Adults (age not stated) Cause not stated No information on previous treatment United Kingdom	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism 12 month follow-up	Ophthalmopathy at baseline not stated
Hamilton 1952[38]	RAI with ATDs, n = 15 PTU 100mg 3x a day, given 1 week after RAI treatment and continued for 2 weeks. Dose of RAI 'estimated' from degree of toxicity and size of gland, average 4mc RAI alone, n = 22	Adults (mean 48, range 19-68) Graves' disease No information on previous treatment USA	Relapse/persistence of hyperthyroidism 7 month follow-up	Ophthalmopathy at baseline not stated
Jaiswal 2014[44]	RAI calculated strategy, n = 20 (100µCi/g x thyroid weight x 10^{-3})/24hr RAIU	Adults (mean 42, SD 12) Graves' disease	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism	Ophthalmopathy at baseline not stated Calculated strategy based on

Study	Intervention and comparison	Population	Outcomes	Comments
	RAI fixed strategy, n = 20 5mCi of I^{131}	Majority previously received ATDs India	3 month follow-up	ultrasound and thyroid scan 2 + 24 hours after dose of I^{131}
Jarlov 1995[46]	RAI calculated strategy, n = 78 ATDs to euthyroidism before RAI, stopped 4 days before, 7 days after resumed for 3 weeks. 3.7MBq/g of thyroid mass for diffuse glands/solitary hot adenoma or 5.55MBq/g for multinodular glands, corrected for 100% 24hr RAI uptake RAI fixed strategy, n = 85 ATDs as for calculated. Palpation size <30ml, 185MBq. 30-60ml, 370MBq. >60ml 555MBq	Adults (mean 65, range 26-85) 30% Graves' disease, 57% TMNG, 13% hot adenomas All received ATDs before and after RAI treatment Denmark	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism 1 year follow-up	Excluded patients with clinically relevant ophthalmopathy Calculated strategy based on ultrasound and thyroid scan 2 + 24 hours after dose of I^{131}
Kung 1995[50]	RAI with ATDs, n = 80 RAI calculated strategy, 1-3 doses as required. ATDs given post-RAI treatment, 6 months of block and replace with MMI (or PTU if MMI not tolerated) RAI alone, n = 79	Adults (mean 47, SD 10) Graves' disease 76% no previous treatment Hong Kong	Ophthalmopathy Relapse/persistence of hyperthyroidism Minor adverse events Thyroid storm 4.6 years mean follow-up	Ophthalmopathy at baseline not stated
Leslie 2003[52]	RAI calculated strategy, n = 43 Combination of high	Adults (mean 41, SD 14)	Euthyroidism Hypothyroidism	45% with ophthalmopathy at baseline

Study	Intervention and comparison	Population	Outcomes	Comments
	(4.44MBq/g thyroid) and low (2.96MBq/g thyroid arms, calculated per formula dose x RAIU% x 0.01 x volume (g^{-1}) RAI fixed strategy, n = 45 Combination of low (235mBq) and high (350mBq) arms	Graves' disease Excluded those with previous RAI treatment, 'most' had received ATDs before RAI Canada	Relapse/persistence of hyperthyroidism 6.6 years mean follow-up	Calculated strategy based on clinical estimate of size and thyroid scan 2 + 24 hours after dose of I^{131}
Miranda-Padua 2014[67]	Calculated RAI, n = 18 160uCi/g x thyroid gland weight x 100/24hr RAIU %, stop ATDs 8 days before RAI Fixed RAI, n = 27 Grade 0 goitre = 185 MBq, 1 = 259MBq, 2 = 370MBq, 3 = 444MBq	Adults (>18, no other details) Graves' disease No previous surgery or RAI, no information on use of ATDs previously Philippines	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism 6 months follow-up	Ophthalmopathy at baseline not stated
Peters 1995[75]	Calculated RAI, n = 110 'Usually' given ATDs beforehand to achieve euthyroidism, RAI calculated to deliver 100Gy using thyroid volume and iodine uptake. ATDs permitted after treatment for 2-3 months Fixed RAI, n = 100 As above but fixed 555MBq Radioactive iodine used	Adults (median 52, range 30-80) Graves' disease 77% previously failed either surgery or ATDs (80% ATDs) Germany	Euthyroidism Hypothyroidism Relapse/persistence of hyperthyroidism 6 months follow-up	42% ophthalmopathy at baseline Calculated strategy based on ultrasound and thyroid scan 2 + 24 hours after dose of I^{131}

Study	Intervention and comparison	Population	Outcomes	Comments
Pirnat 2011[79]	RAI with ATDs, n = 50 Fixed dose of RAI 550MBq, 10mg/d MMI given for 2-12 months to achieve euthyroidism, stopped 7 days before RAI treatment, one dose only RAI alone, n = 59 Fixed dose of RAI 550MBq, one dose only	Adults (mean 45, SD 13) Graves' disease Excluded those with previous RAI treatment or surgery Slovenia	Relapse/persistence of hyperthyroidism 1 years follow-up	Ophthalmopathy at baseline not stated

See Appendix D: for full evidence tables.

1.4.4 Quality assessment of clinical studies included in the evidence review

Table 3: Clinical evidence summary: Radioactive iodine with antithyroid drugs vs radioactive iodine alone

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RAI	Risk difference with RAI + ATDs (95% CI)
Ophthalmopathy	198 (2 studies) 1-4.6 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias, imprecision	Peto OR 0.13 (0.01 to 2.13)	13 per 1000	11 fewer per 1000 (from 12 fewer to 14 more)
Euthyroidism	322 (3 studies) 1 years	⨁⨁⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.02 (0.86 to 1.20)	660 per 1000	13 more per 1000 (from 92 fewer to 132 more)
Hypothyroidism	361 (4 studies) 1 years	⨁⊖⊖⊖ VERY LOW1,2 due to risk of bias,	RR 0.91 (0.67 to 1.24)	367 per 1000	33 fewer per 1000 (from 121 fewer to 88 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with RAI	Risk difference with RAI + ATDs (95% CI)
		imprecision			
Relapse/persistence of hyperthyroidism	627 (6 studies) 0.5-4.6 years	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	RR 1.38 (1.08 to 1.78)	187 per 1000	71 more per 1000 (from 15 more to 146 more)
Minor adverse events	159 (1 study) 4.6 years	⊕⊕⊕⊖ MODERATE1 due to risk of bias	Peto OR 7.79 (1.53 to 39.6)	0 per 1000	70 more per 1000 (from 10 more to 140 more)[3]
Thyroid storm	159 (1 study) 4.6 years	⊕⊕⊖⊖ LOW1,2 due to risk of bias, imprecision	Not estimable	0 per 1000	Not estimable [4]

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
3 Zero events in control arm
4 Zero events in either arm

Table 4: Clinical evidence summary: calculated strategy vs fixed strategy

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fixed strategy	Risk difference with Calculated strategy (95% CI)
Euthyroidism	539 (5 studies) 3 months - 6 years	⊕⊖⊖⊖ VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	RR 1.07 (0.72 to 1.57)	245 per 1000	17 more per 1000 (from 69 fewer to 140 more)

Outcomes	No of Participants (studies) Follow up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with Fixed strategy	Risk difference with Calculated strategy (95% CI)
	(5 studies) 3 months - 6 years	VERY LOW1,2,3 due to risk of bias, inconsistency, imprecision	(0.54 to 1.33)	400 per 1000	64 fewer per 1000 (from 184 fewer to 132 more)
Relapse/persistence of hyperthyroidism	661 (6 studies) 3 months - 6 years	⊕⊕⊖⊖ LOW1,3 due to risk of bias, imprecision	RR 1.3 (1.04 to 1.63)	276 per 1000	83 more per 1000 (from 11 more to 174 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 or 2 increments because the point estimate and or the confidence intervals varied widely across studies, unexplained by subgroup analysis
3 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 tables.

1.5 Economic evidence

1.5.1 Included studies

No relevant health economic studies were identified.

1.5.2 Excluded studies

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

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

1.5.3 Health economic modelling

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

1.5.4 Resource costs

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

Table 5: UK costs of radioactive iodine

Intervention	Unit cost	
Carbimazole 5mg tablets (a)	£148 per annum	
Radioactive iodine fixed strategy (b)	£286.32	
Radioactive iodine calculated strategy (c)	Procedures (pre and post therapy)	Unit costs
	Uptake measurement with probe ~15 mins Band 7	£10
	USS for volume calculation	£62
	Calculations, verification, report: ~ 3 hours Band 7	£75
	Total additional cost to fixed dose	£147 (d)

Abbreviations: USS, Ultrasound scan
Source: BNF, Date, December 2017[47].(NHS reference costs 2016-17, total HRG schedule) [28].
(a) Maintenance dose of 5mg daily cost reported
(b) Cost of oral delivery of radiotherapy for thyroid ablation, cost code RN51Z
(c) Estimation obtained from committee specialists
(d) Total cost = £433.32

1.6 Evidence statements

1.6.1 Clinical evidence statements

1.6.1.1 Radioactive iodine with antithyroid drugs vs Radioactive iodine alone

No clinically important difference was found for ophthalmopathy (2 studies, very low quality), euthyroidism (3 studies, low quality), hypothyroidism (4 studies, very low quality), relapse/persistence of hyperthyroidism (6 studies, low quality), minor adverse events (1 study, moderate quality), thyroid storm (1 study, low quality).

No evidence was identified for other outcomes.

1.6.1.2 Calculated strategy vs fixed strategy

No clinically important difference was found for euthyroidism (5 studies, very low quality), hypothyroidism (5 studies, very low quality), relapse/persistence of hyperthyroidism (6 studies, low quality).

No evidence was identified for other outcomes.

1.6.2 Health economic evidence statements

No relevant economic evaluations were identified.

1.7 The committee's discussion of the evidence

1.7.1 Interpreting the evidence

1.7.1.1 The outcomes that matter most

Mortality and quality of life were critical outcomes for this review. Ophthalmopathy, euthyroidism, hypothyroidism, relapse of hyperthyroidism, cardiovascular morbidity, arrhythmia, osteoporosis, cognitive impairment, pain, symptom scores, experience of care, healthcare contacts, agranulocytosis, liver failure, minor drug related adverse events, teratogenesis, infertility, malignancy, thyrotoxic storm, growth abnormalities, hypocalcaemia and hypoparathyroidism were important outcomes.

1.7.1.2 The quality of the evidence

The quality of the evidence ranged from moderate to very low quality. In general, the evidence was downgraded for risk of bias and imprecision. No studies reported the critical outcomes of mortality or quality of life.

The committee noted that the trials comparing fixed with calculated activity had a number of limitations, they were generally small single centre studies that used administered activities that were lower than typically used in the UK currently. There was also variability between the studies in terms of the precise approach to their calculations and their fixed dose strategies, a number of the fixed strategies involved some form of variability typically based on an informal clinical assessment of thyroid gland size but importantly no assessment of radionuclide uptake. The committee agreed this was generally in line with what is done in the UK.

1.7.1.3 Benefits and harms

1.7.1.3.1 With or without antithyroid drugs

The evidence identified in this review found no clinically important difference between using antithyroid drugs alongside radioactive iodine or using radioactive iodine alone.

The committee noted that in their experience, people have typically been prescribed a course of antithyroid drugs to control thyrotoxicosis before starting radioactive iodine. This is partly because antithyroid drugs are more readily available in primary care and also because they provide an immediate control of symptoms for people with severe thyrotoxicosis. There is also some concern that radioactive iodine in people with previously uncontrolled thyrotoxicosis may briefly exacerbate the thyrotoxicosis, although this was not a finding in the evidence in this review.

The committee agreed that there are some populations, based on their experience, in which there may be no need for antithyroid drug treatment before radioactive iodine, for example young adults and people with mild thyrotoxicosis.

1.7.1.3.2 Calculated vs fixed

The evidence identified in this review found no clinically important difference between a calculated and a fixed strategy in terms of euthyroidism, hypothyroidism and relapse/persistence of hyperthyroidism.

The committee noted that a fixed strategy would result in a range of doses actually being received by the thyroid gland and that this range would be dictated by the size of each person's gland, their personal uptake percentage and other factors. While the evidence showed that using a more sophisticated calculation based approach did not have a clinically important difference for people, this evidence was only for 3 outcomes and low to very low quality evidence.

In the experience of the committee, currently in the UK the majority of radioactive iodine is given in a fixed dose manner. The dose given ranges from 400-800MBq, but in general most committee members were familiar with centres using 500-600MBq. The actual dose given was not the focus of this review, only which of these two overall strategies was most appropriate.

The committee heard that generally the US uses a similar approach to the UK but elsewhere in Europe a calculated approach is more common.

The committee noted higher fixed doses were chosen in order to reduce the likelihood of treatment failure as people opting for radioactive iodine were typically seeking definitive treatment and did not tend to agree to subsequent doses of radioactive iodine if the first was not effective. The committee also agreed that for people with thyroid disease, remaining euthyroid post-treatment as opposed to hypothyroid has quality of life and treatment burden benefits (avoiding the need for long term levothyroxine treatment), although there is some evidence (not a focus of this review) that long term cardiovascular outcomes are better for those who remain hypothyroid.

The committee agreed that a calculated approach would lead to a narrower range of radiation absorbed by the thyroid gland and therefore could result in better treatment outcomes, however on the basis of the evidence collected in this review, this has not been definitively demonstrated. The committee discussed the general principles around the use of radiation and noted that the use of radiation without an understanding of the absorbed dose is not advised, however they also agreed that this less sophisticated approach is current practice in the UK.

Members of the committee had differing views on how to translate the evidence into recommendations. Some members believed there was sufficient evidence of no difference between the options to make a weak recommendation to use a fixed strategy on the grounds of the costs of interventions. Other members believed that the limitations of the clinical evidence, combined with regulatory prerogatives about the use of radiation generally, made a recommendation to use a fixed strategy inappropriate and justified a calculated strategy. Overall the committee agreed that consensus on a recommendation could not be reached and therefore agreed that a research recommendation was necessary in order to gather further evidence around the potential benefit of a calculated strategy.

1.7.2 Cost effectiveness and resource use

There was no health economic evidence identified in this review on the most cost effective way of using radioactive iodine (RAI) to treat thyrotoxicosis. The committee considered

potential resource use implications alongside the clinical evidence to inform their judgements regarding cost effectiveness.

There is an additional cost of using ATDs with RAI, (£148 per year) compared to RAI alone. The clinical evidence did not clearly support a benefit of RAI with ATDs over RAI alone, however the trials did not reflect the reality of the NHS where people might be awaiting a RAI appointment, which could take several months, or the fact that drugs may be given to help patients with severe thyrotoxicosis to stabilise, before RAI can be administered. The committee sensed that in these cases giving people ATDs is likely to be beneficial, leading to early treatment, better long-term health outcomes, and possibly reduced later expenditure on avoidable complications by administered RAI without unnecessary delays. In addition, the initial cost difference is likely to be offset by these benefits.

Furthermore, the review looked at different RAI strategies; a fixed strategy versus a calculated strategy. The average cost of a fixed strategy was £286.32 (NHS Reference cost code RN51Z) and a calculated strategy was estimated to be £433.32. A calculated strategy includes a pre and post uptake measurement with a thyroid probe and an ultrasound scan.The committee noted that the pre and post uptake measurements are repeated routinely but due to the variation in practice it was difficult to quantify the number of repeats generally required and therefore the cost of a calculated strategy was estimated with one probe measurements pre and post. Overall, a calculated strategy was more expensive than a fixed strategy with no clinically important difference in benefits and so it is unclear if it is cost effective. A research recommendation was made by the committee to determine which RAI strategy is likely to be clinical and cost effective (fixed versus calculated strategy).

1.7.3 Other factors the committee took into account

The committee discussed the timing of antithyroid drugs prior to radioactive iodine. They agreed that treatment with antithyroid drugs before radioactive iodine would minimise the rise in circulating thyroid hormone levels following this treatment and so reduce the symptoms of thyrotoxicosis. They were also were keen to emphasise this was not a full (12 to 18 month) course of antithyroid drugs and that the duration would be dictated by individual circumstances. However, based on their clinical experience the committee agreed that a period of 5 to 7 days between antithyroid drugs and radioactive iodine was usually appropriate.

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Appendices

Appendix A: Review protocols

Table 6:

ID	Field	Content
I	Review question	What is the clinical and cost effectiveness of using radioactive iodine vs antithyroid drugs (ATD) vs surgery to treat thyrotoxicosis secondary to Graves' disease? What is the clinical and cost effectiveness of using radioactive iodine vs surgery to treat thyrotoxicosis secondary to toxic nodular goitre? When antithyroid drugs are used, what is the most clinically and cost-effective way of using these drugs to treat thyrotoxicosis (for example choice of drugs, different treatment regimens)? When radioactive iodine is used, what is the most clinically and cost-effective way of using this treatment to treat thyrotoxicosis (for example different dosing strategies)? When surgery is indicated, what is the most clinically and cost-effective way of using surgery to treat thyrotoxicosis (for example total vs subtotal thyroidectomy)?
II	Type of review question	Intervention A review of health economic evidence related to the same review question was conducted in parallel with this review. For details see the health economic review protocol for this NICE guideline.
III	Objective of the review	Provide clinically and cost effective recommendations on how to manage thyrotoxicosis
IV	Eligibility criteria – population / disease / condition / issue / domain	People diagnosed with thyrotoxicosis (TSH below normal reference ranges, free T3/T4 above normal reference range)

V	Eligibility criteria – intervention(s) / exposure(s) / prognostic factor(s)	• Radioactive iodine
		  ○ Fixed administered activity strategy vs calculated absorbed radiation dose strategy
		  ○ Pre-/post- treatment with ATD vs no pre-/post- treatment
		• Antithyroid drugs
		  ○ Carbimazole/methimazole vs propylthiouracil
		  ○ Block and replace (including levothyroxine) vs titration regimen
		  ○ Duration of treatment: 6-<12 months vs 12-18 months vs >18 months
		• Surgery
		  ○ Total thyroidectomy vs subtotal thyroidectomy vs near total (Dunhill) thyroidectomy vs one sided only (hemithyroidectomy/lobectomy/isthmectomy)

VI	Eligibility criteria – comparator(s) / control or	• Comparisons between modalities • Comparisons between sub-modalities

	reference (gold) standard	
VII	Outcomes and prioritisation	**Critical** • Mortality (dichotomous, ≥1 year) • Quality of life (continuous) **Important (general)** • Thyroid ophthalmopathy (dichotomous) • Euthyroidism (dichotomous) • Hypothyroidism (dichotomous) • Relapse of hyperthyroidism (dichotomous) • Cardiovascular morbidity (ischaemic heart disease, dichotomous) • Arrhythmia (dichotomous) • Osteoporosis (dichotomous) • Cognitive impairment (dichotomous) • Pain (continuous) • Symptom scores (continuous) • Patient/family/carer experience (continuous) • Healthcare contacts (rates/dichotomous) **Important (surgical)** • Recurrent laryngeal nerve damage (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Bleeding (dichotomous) • Infection (dichotomous) **Important (pharmacological)** • Agranulocytosis (dichotomous) • Liver failure (dichotomous) • Minor drug related adverse effects (dichotomous) • Teratogenesis (dichotomous) **Important (radioiodine)** • Infertility (dichotomous) • Malignancy (dichotomous) • Thyrotoxic storm (dichotomous) • Growth abnormalities (dichotomous) • Hypocalcaemia (dichotomous) • Hypoparathyroidism (dichotomous) • Teratogenesis (dichotomous) Minimum duration as for the minimum duration for inclusion of studies unless specified.
VIII	Eligibility criteria – study design	• Minimum follow-up of 3 months • RCTs • Non-randomised cohort studies to be considered if adjusted for key confounders (age, co-existing conditions, baseline T4, size of goitre) and insufficient RCTs evidence found, on an intervention by intervention basis
IX	Other inclusion / exclusion criteria	• Excluding studies in pregnancy • Excluding studies aimed specifically at treating thyroid eye disease • Excluding studies in context of thyroid malignancy
X	Proposed	**Stratifications**

	sensitivity / subgroup analysis, or meta-regression	• Age – young children (0-4), children and young people (4-18), adults (>18-65), older adults (>65) • For antithyroid drugs vs radioactive iodine vs surgery - Cause of thyrotoxicosis (Graves' disease, toxic nodular goitre, thyroiditis) • Treatment stage – naïve/general (non-naïve, downgraded for indirectness), second line (remain symptomatic despite previous treatment, as defined by studies) **Subgroup analyses** • Gender (male only vs female only) • Age subdivisions (4-12, 12-18, 18-50, 50-65, 65-85, >85) • Comparison not under investigation (for example for block and replace vs titration, if some studies use methimazole and others use propylthiouracil)
XI	Selection process – duplicate screening / selection / analysis	• A sample of at least 10% of the abstract lists were double-sifted by a senior research fellow and discrepancies rectified, with committee input where consensus could not be reached, for more information please see the separate Methods report for this guideline.
XII	Data management (software)	• Pairwise meta-analyses were performed using Cochrane Review Manager (RevMan5). • GRADEpro was used to assess the quality of evidence for each outcome. • Endnote was used for bibliography, citations, sifting and reference management
XIII	Information sources – databases and dates	• Medline, Embase and the Cochrane Library
XIV	Identify if an update	Not an update
XV	Author contacts	https://www.nice.org.uk/guidance/indevelopment/gid-ng10074
XVI	Highlight if amendment to previous protocol	Not an amendment
XVII	Search strategy – for one database	For details please see Appendix B:.
XVIII	Data collection process – forms / duplicate	A standardised evidence table format will be used and published as Appendix D: of the evidence report.
XIX	Data items – define all variables to be collected	For details please see evidence tables in Appendix D: (clinical evidence tables) or Appendix H: (health economic evidence tables).
XX	Methods for assessing bias at outcome / study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group

		http://www.gradeworkinggroup.org/
XXI	Criteria for quantitative synthesis	For details please see section 6.4 of Developing NICE guidelines: the manual.
XXII	Methods for quantitative analysis – combining studies and exploring (in)consistency	For details please see the separate Methods report for this guideline.
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual.
XXIV	Confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual.
XXV	Rationale / context – what is known	For details please see the introduction to the evidence review.
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the National Guideline Centre (NGC) and chaired by Sarah Fishburn in line with section 3 of Developing NICE guidelines: the manual. Staff from NGC undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
XXVII	Sources of funding / support	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXVIII	Name of sponsor	NGC is funded by NICE and hosted by the Royal College of Physicians.
XXIX	Roles of sponsor	NICE funds NGC to develop guidelines for those working in the NHS, public health and social care in England.
XXX	PROSPERO registration number	Not registered

Table 7: Health economic review protocol

Review question	All questions – health economic evidence
Objectives	To identify health economic studies relevant to any of the review questions.
Search criteria	• Populations, interventions and comparators must be as specified in the clinical review protocol above. • Studies must be of a relevant health economic study design (cost–utility analysis, cost-effectiveness analysis, cost–benefit analysis, cost–consequences analysis, comparative cost analysis). • Studies must not be a letter, editorial or commentary, or a review of health economic evaluations. (Recent reviews will be ordered although not reviewed. The bibliographies will be checked for relevant studies, which will then be ordered.) • Unpublished reports will not be considered unless submitted as part of a call for evidence. • Studies must be in English.
Search strategy	A health economic study search will be undertaken using population-specific terms and a health economic study filter – see Appendix B: below.
Review strategy	Studies not meeting any of the search criteria above will be excluded. Studies published before 2003, abstract-only studies and studies from non-OECD countries or the USA will also be excluded. Each remaining study will be assessed for applicability and methodological limitations using the NICE economic evaluation checklist which can be found in appendix H of Developing NICE guidelines: the manual (2014).[70] **Inclusion and exclusion criteria** • If a study is rated as both 'Directly applicable' and with 'Minor limitations' then it will be included in the guideline. A health economic evidence table will be completed, and it will be included in the health economic evidence profile. • If a study is rated as either 'Not applicable' or with 'Very serious limitations' then it will usually be excluded from the guideline. If it is excluded, then a health economic evidence table will not be completed, and it will not be included in the health economic evidence profile. • If a study is rated as 'Partially applicable', with 'Potentially serious limitations' or both then there is discretion over whether it should be included. **Where there is discretion** The health economist will make a decision based on the relative applicability and quality of the available evidence for that question, in discussion with the guideline committee if required. The ultimate aim is to include health economic studies that are helpful for decision-making in the context of the guideline and the current NHS setting. If several studies are considered of sufficiently high applicability and methodological quality that they could all be included, then the health economist, in discussion with the committee if required, may decide to include only the most applicable studies and to selectively exclude the remaining studies. All studies excluded on the basis of applicability or methodological limitations will be listed with explanation in the excluded health economic studies appendix below. The health economist will be guided by the following hierarchies. *Setting:* • UK NHS (most applicable). • OECD countries with predominantly public health insurance systems (for example, France, Germany, Sweden). • OECD countries with predominantly private health insurance systems (for example, Switzerland).

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

Appendix B: Literature search strategies

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

For more detailed information, please see the Methodology Review.

B.1 Clinical search literature search strategy

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

Table 8: Database date parameters and filters used

Database	Dates searched	Search filter used
Medline (OVID)	1946 – 07 January 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
Embase (OVID)	1974 – 07 January 2019	Exclusions Randomised controlled trials Systematic review studies Observational studies
The Cochrane Library (Wiley)	Cochrane Reviews to 2019 Issue 1 or 12 CENTRAL to 2019 Issue 1 or 12 DARE, and NHSEED to 2015 Issue 2 of 4 HTA to 2016 Issue 2 of 4	None

Medline (Ovid) search terms

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

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

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

Embase (Ovid) search terms

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

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

Cochrane Library (Wiley) search terms

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

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

B.2 Health Economics literature search strategy

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

Table 9: Database date parameters and filters used

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

Medline (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter/
8.	editorial/
9.	news/
10.	exp historical article/
11.	Anecdotes as Topic/
12.	comment/
13.	case report/
14.	(letter or comment*).ti.
15.	or/7-14
16.	randomized controlled trial/ or random*.ti,ab.

17.	15 not 16
18.	animals/ not humans/
19.	exp Animals, Laboratory/
20.	exp Animal Experimentation/
21.	exp Models, Animal/
22.	exp Rodentia/
23.	(rat or rats or mouse or mice).ti.
24.	or/17-23
25.	6 not 24
26.	limit 25 to English language
27.	Economics/
28.	Value of life/
29.	exp "Costs and Cost Analysis"/
30.	exp Economics, Hospital/
31.	exp Economics, Medical/
32.	Economics, Nursing/
33.	Economics, Pharmaceutical/
34.	exp "Fees and Charges"/
35.	exp Budgets/
36.	budget*.ti,ab.
37.	cost*.ti.
38.	(economic* or pharmaco?economic*).ti.
39.	(price* or pricing*).ti,ab.
40.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
41.	(financ* or fee or fees).ti,ab.
42.	(value adj2 (money or monetary)).ti,ab.
43.	or/27-42
44.	exp models, economic/
45.	*Models, Theoretical/
46.	*Models, Organizational/
47.	markov chains/
48.	monte carlo method/
49.	exp Decision Theory/
50.	(markov* or monte carlo).ti,ab.
51.	econom* model*.ti,ab.
52.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
53.	or/44-52
54.	quality-adjusted life years/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.

61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/54-72
74.	26 and (43 or 53 or 73)

Embase (Ovid) search terms

1.	exp thyroid diseases/
2.	hyperthyroid*.ti,ab.
3.	hypothyroid*.ti,ab.
4.	thyrotoxicosis*.ti,ab.
5.	(thyroid adj3 (swell* or dysfunction* or enlarg* or nodule* or node* or disease* or condition* or disorder*)).ti,ab.
6.	or/1-5
7.	letter.pt. or letter/
8.	note.pt.
9.	editorial.pt.
10.	case report/ or case study/
11.	(letter or comment*).ti.
12.	or/7-11
13.	randomized controlled trial/ or random*.ti,ab.
14.	12 not 13
15.	animal/ not human/
16.	nonhuman/
17.	exp Animal Experiment/
18.	exp Experimental Animal/
19.	animal model/
20.	exp Rodent/
21.	(rat or rats or mouse or mice).ti.
22.	or/14-21
23.	6 not 22
24.	limit 23 to English language
25.	health economics/
26.	exp economic evaluation/

27.	exp health care cost/
28.	exp fee/
29.	budget/
30.	funding/
31.	budget*.ti,ab.
32.	cost*.ti.
33.	(economic* or pharmaco?economic*).ti.
34.	(price* or pricing*).ti,ab.
35.	(cost* adj2 (effective* or utilit* or benefit* or minimi* or unit* or estimat* or variable*)).ab.
36.	(financ* or fee or fees).ti,ab.
37.	(value adj2 (money or monetary)).ti,ab.
38.	or/25-37
39.	statistical model/
40.	exp economic aspect/
41.	39 and 40
42.	*theoretical model/
43.	*nonbiological model/
44.	stochastic model/
45.	decision theory/
46.	decision tree/
47.	monte carlo method/
48.	(markov* or monte carlo).ti,ab.
49.	econom* model*.ti,ab.
50.	(decision* adj2 (tree* or analy* or model*)).ti,ab.
51.	or/41-50
52.	quality adjusted life year/
53.	"quality of life index"/
54.	short form 12/ or short form 20/ or short form 36/ or short form 8/
55.	sickness impact profile/
56.	(quality adj2 (wellbeing or well being)).ti,ab.
57.	sickness impact profile.ti,ab.
58.	disability adjusted life.ti,ab.
59.	(qal* or qtime* or qwb* or daly*).ti,ab.
60.	(euroqol* or eq5d* or eq 5*).ti,ab.
61.	(qol* or hql* or hqol* or h qol* or hrqol* or hr qol*).ti,ab.
62.	(health utility* or utility score* or disutilit* or utility value*).ti,ab.
63.	(hui or hui1 or hui2 or hui3).ti,ab.
64.	(health* year* equivalent* or hye or hyes).ti,ab.
65.	discrete choice*.ti,ab.
66.	rosser.ti,ab.

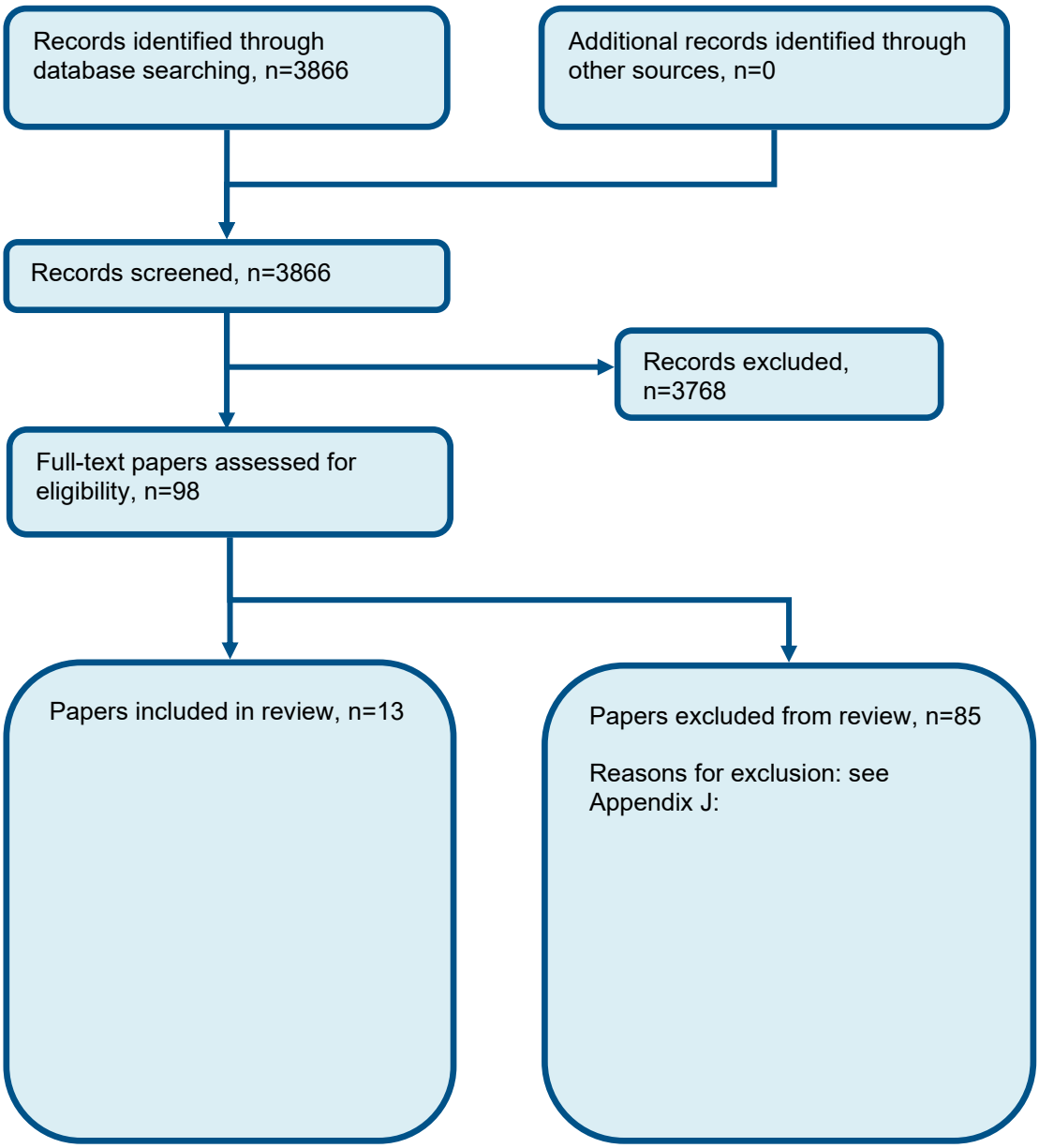
67.	(willingness to pay or time tradeoff or time trade off or tto or standard gamble*).ti,ab.
68.	(sf36* or sf 36* or short form 36* or shortform 36* or shortform36*).ti,ab.
69.	(sf20 or sf 20 or short form 20 or shortform 20 or shortform20).ti,ab.
70.	(sf12* or sf 12* or short form 12* or shortform 12* or shortform12*).ti,ab.
71.	(sf8* or sf 8* or short form 8* or shortform 8* or shortform8*).ti,ab.
72.	(sf6* or sf 6* or short form 6* or shortform 6* or shortform6*).ti,ab.
73.	or/52-72
74.	24 and (38 or 51 or 73)

NHS EED and HTA (CRD) search terms

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

Appendix C: Clinical evidence selection

Figure 1: Flow chart of clinical study selection for the review of thyrotoxicosis (Radioactive iodine)



Appendix D: Clinical evidence tables

Study	Andrade 2001[5]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=61)
Countries and setting	Conducted in Brazil; Setting: Endocrine division at general hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease
Exclusion criteria	Moderate-severe ophthalmopathy, previous treatment with Radioactive iodine or thyroidectomy, severe heart disease, large/compressive goitres
Recruitment/selection of patients	Consecutive patients screened
Age, gender and ethnicity	Age - Mean (SD): 37 (7). Gender (M:F): 6/55. Ethnicity:
Further population details	1. Age: 18-50 2. Gender:
Indirectness of population	No indirectness
Interventions	(n=29) Intervention 1: RAI with ATDs - ATDs before RAI. MMI 30g/d until biochemically euthyroid, MMI then discontinued and RAI given 4 days after discontinuation. RAI given as per RAI alone arm. Duration 1 year follow-up. Concurrent medication/care: No ATDs given after RAI, beta blockers used if tachycardia >120 bpm. Indirectness: No indirectness (n=32) Intervention 2: RAI alone. Calculated activity, 200uCi/g thyroid tissue divided by fractional 24-hr RAI uptake. Duration 1 year follow-up. Concurrent medication/care: As for combined arm. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS BEFORE RAI versus RAI ALONE Protocol outcome 1: Euthyroidism - Actual outcome: Euthyroidism at end of 1 year follow-up at 1 year; Group 1: 9/29, Group 2: 9/32 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 5 total missing during follow-up, distribution not specified; Group 2 Number missing: 0, Reason: 5 total missing during follow-up, distribution not specified Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroidism at end of 1 year follow-up at 1 year; Group 1: 16/29, Group 2: 18/32 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 5 total missing during follow-up, distribution not specified; Group 2 Number missing: 0, Reason: 5 total missing during follow-up, distribution not specified Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome: Hyperthyroidism at end of 1 year follow-up at 1 year; Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0, Reason: 5 total missing during follow-up, distribution not specified; Group 2 Number missing: 0, Reason: 5 total missing during follow-up, distribution not specified	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Bonnema 2004[17]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=81)
Countries and setting	Conducted in Denmark; Setting: Not stated
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves or toxic nodular goiter referred for radioactive iodine therapy
Exclusion criteria	<18, pregnant, anticipation of pregnancy, lactation, suspicion of thyroid malignancy, large or partly intrathoracic goiter, moderate to severe ophthalmopathy, previous radioactive iodine treatment, ATDs in last 3 months before admission
Recruitment/selection of patients	Screened consecutive patients
Age, gender and ethnicity	Age - Mean (SD): 59 (11). Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=40) Intervention 1: RAI with ATDs - ATDs before RAI. PTU dose guided by TFTs, given until stable euthyroidism, then 4 days until RAI, RAI given as calculated strategy (weight, RAI uptake). Duration 1-year follow-up. Concurrent medication/care: Levothyroxine given if hypothyroid, PTU restarted if hyperthyroid after 6 weeks, allowed second RAI dose at 9 months if persistent hyperthyroidism. Indirectness: No indirectness (n=41) Intervention 2: RAI alone. RAI as for combination arm. Duration 1-year follow-up. Concurrent medication/care: As for combination arm. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS BEFORE RAI versus RAI ALONE

Protocol outcome 1: Euthyroidism
- Actual outcome: Euthyroid at end of follow-up at 1 year: Group 1: 20/39, Group 2: 27/41

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Allergic reaction to PTU; Group 2 Number missing: 0 Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroid at end of follow-up at 1 year; Group 1: 6/39, Group 2: 7/41 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Allergic reaction to PTU; Group 2 Number missing: 0 Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome: Hyperthyroid at end of follow-up (or requiring additional ATDs/RAI at 9 months) at 1 year; Group 1: 13/39, Group 2: 7/41 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1, Reason: Allergic reaction to PTU; Group 2 Number missing: 0	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Canto 2016[22]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=122)
Countries and setting	Conducted in Philippines; Setting: General hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves', first RAI session, 18 or older, not pregnant/lactating/considering pregnancy, no co-existing cancer or suspicion of cancer, large or compressive goitres, no previous thyroid surgery, no moderate-severe active ophthalmopathy
Exclusion criteria	Nil else
Recruitment/selection of patients	All referred to nuclear medicine department screened for inclusion
Age, gender and ethnicity	Age - Mean (SD): 36 (12). Gender (M:F): Define. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Indirectness of population	No indirectness
Interventions	(n=61) Intervention 1: Calculated activity. 160uCi/g of thyroid tissue, adjusted for 24-hour RAIU. Duration 6 months follow-up . Concurrent medication/care: Usual care. Indirectness: No indirectness (n=61) Intervention 2: Standard dose. 9.9mCi of I131 if gland <40g, 14.9mCi of I131 if gland <40g. Duration 6 months follow-up. Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCULATED ACTIVITY versus STANDARD DOSE

Protocol outcome 1: Relapse of hyperthyroidism
- Actual outcome: Treatment failure at end of follow-up (neither eu nor hypothyroid) at 6 months; Group 1: 21/61, Group 2: 11/61
Risk of bias: All domain - High, Selection - Low, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low;

Indirectness of outcome: No indirectness ; Group 1 Number missing: , Reason: Only PP analysis available, information lacking on violations; Group 2 Number missing: , Reason: Only PP analysis available, information lacking on violations	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Euthyroidism; Hypothyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Gamstedt 1986[31]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in Sweden; Setting: Not specified
Line of therapy	1st line
Duration of study	Intervention + follow up: 1 year
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	No previous RAI, no ophthalmopathy
Exclusion criteria	None stated
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 59 (12). Gender (M:F): 26:74. Ethnicity: Not stated
Further population details	1. Age: 50-65 2. Gender: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=17) Intervention 1: RAI with ATDs - ATDs before RAI. 7 weeks of MMI 10mg orally, 3 times a day. Withdrawn for a week before RAI. Then restarted the day after RAI and continued for 11 weeks. Duration 1 year follow-up. Concurrent medication/care: 350MBq dose, additional doses given at 3 months if required. Indirectness: No indirectness

	(n=23) Intervention 2: RAI alone. RAI alone . Duration 1 year follow-up. Concurrent medication/care: 350MBq, additional doses given at 3 months if required. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS WITH RAI versus RAI ALONE Protocol outcome 1: Thyroid ophthalmopathy - Actual outcome: Ophthalmopathy confirmed at 12 months at 12 months; Group 1: 0/17, Group 2: 0/22 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 0; Group 2 Number missing: 1, Reason: Suicide Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroidism at 12 months at 12 months; Group 1: 8/17, Group 2: 18/22 Risk of bias: All domain - 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: 1, Reason: Suicide	
Protocol outcomes not reported by the study	Quality of life; Mortality; Euthyroidism; Relapse of hyperthyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	**Goolden 1969[35]**
Study type	RCT (Patient randomised; Parallel)

Number of studies (number of participants)	1 (n=181)
Countries and setting	Conducted in United Kingdom, Unknown, Unknown multicentre; Setting: Nil else stated
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Thyrotoxicosis
Exclusion criteria	Nil else stated
Recruitment/selection of patients	Nil else stated
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: Not stated / Unclear 2. Gender: Not stated / Unclear
Indirectness of population	No indirectness
Interventions	(n=83) Intervention 1: RAI with ATDs - ATDs before RAI. 2-4 months of carbimazole before RAI, carbimazole stopped 3-5 days before RAI. Duration 12 months. Concurrent medication/care: RAI as per other arm . Indirectness: No indirectness (n=98) Intervention 2: RAI alone. No ATDs. Duration 12 months. Concurrent medication/care: Single dose, calculated strategy aimed at 150uCi/g if 70g thyroid or less, if greater then aimed at 300uCi/g. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS BEFORE RAI versus RAI ALONE Protocol outcome 1: Euthyroidism - Actual outcome: Euthyroid at 12 months following RAI at 12 months; Group 1: 63/83, Group 2: 67/98 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroid at 12 months following RAI at 12 months; Group 1: 14/83, Group 2: 13/98 Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome: Hyperthyroid at 12 months following RAI at 12 months; Risk of bias: All domain - Very high, Selection - High, Blinding - High, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	**Hamilton 1952[38]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=37)
Countries and setting	Conducted in USA; Setting: Not stated

Line of therapy	1st line
Duration of study	Intervention + follow up: 7 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease, adults
Exclusion criteria	Nil else stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (range): 48 (19-68). Gender (M:F): 36:64. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Indirectness of population	No indirectness
Interventions	(n=15) Intervention 1: RAI with ATDs - ATDs after RAI. 100mg of 6-propylthiouracil 3x a day, started 1 week after RAI administration. Continued for 2 subsequent weeks only. Duration 7 months. Concurrent medication/care: Dosage of RAI 'estimated' from degree of toxicity and size of gland, average dose 4 mc. Indirectness: No indirectness (n=22) Intervention 2: RAI alone. No medication, no placebo. Duration 7 months. Concurrent medication/care: RAI as for RAI + ATDs arm. Indirectness: No indirectness
Funding	Equipment / drugs provided by industry
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS AFTER RAI versus RAI ALONE	

Protocol outcome 1: Relapse of hyperthyroidism - Actual outcome: Recurrence of hyperthyroidism at 7 months; Group 1: 9/15, Group 2: 7/22 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: 1, Reason: Lost to follow-up	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Euthyroidism; Hypothyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Jaiswal 2014[44]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=40)
Countries and setting	Conducted in India; Setting: India, nuclear medicine centre
Line of therapy	1st line
Duration of study	Intervention + follow up: 3 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease, over 18, no previous RAI
Exclusion criteria	Nil
Recruitment/selection of patients	Not specified
Age, gender and ethnicity	Age - Mean (SD): 42 (12). Gender (M:F): 35:65. Ethnicity: Not stated (set in India)
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	Majority had previously received ATDs, unclear if full course and relapse or just pre-treatment
Indirectness of population	No indirectness
Interventions	(n=20) Intervention 1: Calculated activity. (100uCi/g estimated thyroid weight x thyroid weight x 10^-3)/(24hr RAIU). Duration 3 months follow-up. Concurrent medication/care: Advised to avoid conception for 6 months, no information on number of doses or concurrent drug therapy. Indirectness: No indirectness (n=20) Intervention 2: Standard dose. 5mCi of I131. Duration 3 months follow-up. Concurrent medication/care: As for calculated activity. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCULATED ACTIVITY versus STANDARD DOSE

Protocol outcome 1: Euthyroidism
- Actual outcome for Treatment naive/general population: Euthyroidism at end of follow-up at 3 month follow-up: Group 1: 8/20, Group 2: 4/20

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Majority had received ATDs previously for mean 22 months; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Hypothyroidism - Actual outcome for Treatment naive/general population: Hypothyroidism at end of follow-up at 3 month follow-up; Group 1: 5/20, Group 2: 8/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Majority had received ATDs previously for mean 22 months; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome for Treatment naive/general population: Hyperthyroidism at end of follow-up at 3 month follow-up; Group 1: 7/20, Group 2: 8/20 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: Serious indirectness, Comments: Majority had received ATDs previously for mean 22 months; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	**Jarløv 1995[46]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=221)
Countries and setting	Conducted in Denmark; Setting: Endocrine out-patients' clinic
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Hyperthyroid
Exclusion criteria	<18, pregnant/lactating, previous RAI or SUR, clinically evident ophthalmopathy
Recruitment/selection of patients	Consecutive referrals screened
Age, gender and ethnicity	Age - Mean (range): 65 (26-85). Gender (M:F): 12:88. Ethnicity: Not stated
Further population details	1. Age: 50-65 2. Gender: Not applicable
Indirectness of population	No indirectness
Interventions	(n=78) Intervention 1: Calculated activity. 3.7MBq/g of thyroid mass for diffuse glands/solitary hot adenoma or 5.55MBq/g for multinodular glands, corrected for 100% 24hr RAI uptake. Maximum dose of 740 MBq. Duration 1 year. Concurrent medication/care: All received ATDs to euthyroidism until 4 days before RAI and then 7 days after, for 3 weeks. Majority MMI, some PTU. . Indirectness: No indirectness (n=85) Intervention 2: Standard dose. Palpation size <30ml, 185MBq. 30-60ml, 370MBq. >60ml 555MBq. Duration 1 year. Concurrent medication/care: As for calculated. Indirectness: No indirectness
Funding	Academic or government funding

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCULATED ACTIVITY versus STANDARD DOSE

Protocol outcome 1: Euthyroidism
- Actual outcome: Euthyroid at end of follow-up at 12 months: Group 1: 39/78, Group 2: 49/85

Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: None from 78, Reason: 40 patients did not receive ATD treatment and excluded, 4 patients died, 7 patients lost to follow-up; Group 2 Number missing: None from 85, Reason: 40 patients did not receive ATD treatment and excluded, 4 patients died, 7 patients lost to follow-up Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroid (or requiring levothyroxine) at end of follow-up at 12 months; Group 1: 7/78, Group 2: 6/85 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: None from 78, Reason: 40 patients did not receive ATD treatment and excluded, 4 patients died, 7 patients lost to follow-up; Group 2 Number missing: None from 85, Reason: 40 patients did not receive ATD treatment and excluded, 4 patients died, 7 patients lost to follow-up Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome: Relapse/persistence of hyperthyroidism at end of follow-up at 12 months; Group 1: 32/78, Group 2: 30/85 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: None from 78, Reason: 40 patients did not receive ATD treatment and excluded, 4 patients died, 7 patients lost to follow-up; Group 2 Number missing: None from 85, Reason: 40 patients did not receive ATD treatment and excluded, 4 patients died, 7 patients lost to follow-up	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Kung 1995[50]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=159)
Countries and setting	Conducted in Hong Kong (China); Setting: Hong Kong
Line of therapy	1st line
Duration of study	Intervention + follow up: Average follow-up 4.6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Treatment naive/general population
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease, suppressed TSH
Exclusion criteria	Previous RAI treatment
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 47 (10). Gender (M:F): 25:75. Ethnicity:
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	75% had no previous treatment for Graves' disease, those who had previously received ATDs had not for at least 4 weeks prior to study
Indirectness of population	No indirectness
Interventions	(n=80) Intervention 1: RAI with ATDs - ATDs after RAI. Calculated dose RAI (size of gland, thyroid uptake, 1-3 doses), 4 days after RAI, 6-month course of ATDs (10mg 3x a day MMI unless not tolerated, then PTU), block and replace with T4. Duration Mean follow-up 4.6 years. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=79) Intervention 2: RAI alone. RAI as for other arm. Duration Mean follow-up 4.6 years. Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS AFTER RAI versus RAI ALONE Protocol outcome 1: Thyroid ophthalmopathy	

- Actual outcome for Treatment naive/general population: Onset of severe ophthalmopathy at Average follow-up 4.6 years; Group 1: 0/80, Group 2: 2/79 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 5 in RAI + ATD previous subtotal thyroidectomy vs 1 in RAI alone arm; Group 1 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1; Group 2 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1 Protocol outcome 2: Relapse of hyperthyroidism - Actual outcome for Treatment naive/general population: Relapse/persistence of hyperthyroidism at Average follow-up 4.6 years; Group 1: 40/80, Group 2: 31/79 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 5 in RAI + ATD previous subtotal thyroidectomy vs 1 in RAI alone arm; Group 1 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1; Group 2 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1 Protocol outcome 3: Minor drug related adverse events - Actual outcome for Treatment naive/general population: Minor AEs (skin reaction requiring switch from MMI to PTU) at Average follow-up 4.6 years; Group 1: 6/80, Group 2: 0/79 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 5 in RAI + ATD previous subtotal thyroidectomy vs 1 in RAI alone arm; Group 1 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1; Group 2 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1 Protocol outcome 4: Thyrotoxic storm - Actual outcome for Treatment naive/general population: Thyrotoxic storm at Average follow-up 4.6 years; Group 1: 0/80, Group 2: 0/79 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - High, Crossover - Low; Indirectness of outcome: No indirectness ; Baseline details: 5 in RAI + ATD previous subtotal thyroidectomy vs 1 in RAI alone arm; Group 1 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1; Group 2 Number missing: Unclear, Reason: 5 missing in total due to loss to follow-up in Y1	
Protocol outcomes not reported by the study	Quality of life; Mortality; Euthyroidism; Hypothyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Teratogenesis; Infertility; Malignancy

Study	Leslie 2003[52]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=88)
Countries and setting	Conducted in Canada; Setting: Nil else stated
Line of therapy	1st line
Duration of study	Intervention + follow up: Mean follow-up 6.6 years
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Treatment naive/general population
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease
Exclusion criteria	Previously treated with RAI
Recruitment/selection of patients	All patients being referred to nuclear medicine department were considered
Age, gender and ethnicity	Age - Mean (SD): 41 (14). Gender (M:F): 25:75. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Indirectness of population	No indirectness
Interventions	(n=43) Intervention 1: Calculated activity. Combination of two arms from study (high 4.44 MBq/g thyroid, adjusted for 24hr RAIU and low 2.96Mbq), . Duration 6.6 years mean follow-up . Concurrent medication/care: 'Most' received ATDs before RAI, discontinued 5 days before RAI and only restarted if evidence of persistent hyperthyroidism 6 weeks post treatment. Indirectness: No indirectness (n=45) Intervention 2: Standard dose. Combination of low fixed (235mBq) and high fixed (350mBq) doses. Duration 6.6 years mean follow-up. Concurrent medication/care: As for calculated activity. Indirectness: No indirectness
Funding	Funding not stated

RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCULATED ACTIVITY versus STANDARD DOSE

Protocol outcome 1: Euthyroidism
- Actual outcome for Treatment naive/general population: Euthyroid at end of follow-up at Mean follow-up 6.6 years: Group 1: 4/43, Group 2: 2/45

Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 2: Hypothyroidism - Actual outcome for Treatment naive/general population: Hypothyroid at end of follow-up at Mean follow-up 6.6 years; Group 1: 30/43, Group 2: 31/45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing: Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome for Treatment naive/general population: Hyperthyroid at end of follow-up at Mean follow-up 6.6 years; Group 1: 9/43, Group 2: 12/45 Risk of bias: All domain - Low, Selection - Low, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Miranda-padua 2014[67]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=45)
Countries and setting	Conducted in Philippines; Setting: University hospital in Philippines
Line of therapy	1st line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	At least 18, Graves' disease, symptoms of hyperthyroidism
Exclusion criteria	Poorly controlled hyperthyroidism, compressive symptoms, pregnancy or planned pregnancy, previously treated with RAI/SUR, palpable nodule, congestive heart failure, amiodarone therapy
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Other: Not stated. Gender (M:F): 17:83. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	No information on use of ATDs or ophthalmopathy at baseline
Indirectness of population	Serious indirectness: Poorly controlled hyperthyroidism excluded
Interventions	(n=18) Intervention 1: Calculated activity. 160uCi/g x thyroid gland weight x 100/24hr RAIU %. Duration 3-6 months follow-up. Concurrent medication/care: Reduce dietary iodine uptake one week before RAIU and therapy, stop ATDs 8 days before RAI, only restart if hyperthyroid 2-3 weeks after treatment, can use beta blockers. Indirectness: No indirectness (n=27) Intervention 2: Standard dose. Grade 0 goitre = 185 MBq, 1 = 259MBq, 2 = 370MBq, 3 = 444MBq. Duration 3-6 months. Concurrent medication/care: As for calculated activity. Indirectness: Serious indirectness; Indirectness comment: Not strictly fixed dose
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCULATED ACTIVITY versus STANDARD DOSE	

Protocol outcome 1: Euthyroidism - Actual outcome: Euthyroid at 6 months follow-up at 6 months; Group 1: 7/17, Group 2: 17/26 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 missing from randomisation to follow-up, ~12 missing prior to randomisation, Reason: Not stated; Group 2 Number missing: 1 missing from randomisation to follow-up, ~3 missing prior to randomisation, Reason: Not stated Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroid at 6 months follow-up at 6 months; Group 1: 6/17, Group 2: 6/26 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 missing from randomisation to follow-up, ~12 missing prior to randomisation, Reason: Not stated; Group 2 Number missing: 1 missing from randomisation to follow-up, ~3 missing prior to randomisation, Reason: Not stated Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome: Hyperthyroid at 6 months follow-up at 6 months; Group 1: 4/17, Group 2: 3/26 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 1 missing from randomisation to follow-up, ~12 missing prior to randomisation, Reason: Not stated; Group 2 Number missing: 1 missing from randomisation to follow-up, ~3 missing prior to randomisation, Reason: Not stated	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	**Peters 1995[75]**
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=214)
Countries and setting	Conducted in Germany; Setting: Endocrine centres across Germany
Line of therapy	2nd line
Duration of study	Intervention + follow up: 6 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Failed first line treatment
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease, >30 years old, if 30-40 need to have failed first line therapy (drugs or surgery)
Exclusion criteria	Not stated
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Median (range): 52 (30-80). Gender (M:F): 13:87. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	75% failed previous treatment, majority of those treatments were drugs. All patients were 'usually treated with ATDs to achieve euthyroidism' first
Indirectness of population	No indirectness
Interventions	(n=110) Intervention 1: Calculated activity. RAI calculated to deliver 100Gy, ((22.3 x 100Gy x thyroid volume (mL))/(maximal iodine uptake % x effective iodine half-time (d)))). . Duration 6-month follow-up. Concurrent medication/care: ATDs usually given beforehand for euthyroidism, permitted for couple of months after RAI. Indirectness: No indirectness (n=104) Intervention 2: Standard dose. 555MBq, otherwise as for calculated activity. Duration 6month follow-up. Concurrent medication/care: As for calculated activity. Indirectness: No indirectness
Funding	Academic or government funding
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: CALCULATED ACTIVITY versus STANDARD DOSE	

Protocol outcome 1: Euthyroidism - Actual outcome: Euthyroidism at 6 months follow-up (off ATDs for at least 2 months) at 6 months; Group 1: 37/107, Group 2: 24/98 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not stated; Group 2 Number missing: 6, Reason: Not stated Protocol outcome 2: Hypothyroidism - Actual outcome: Hypothyroidism at 6 months follow-up (off ATDs for at least 2 months) at 6 months; Group 1: 25/107, Group 2: 46/98 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not stated; Group 2 Number missing: 6, Reason: Not stated Protocol outcome 3: Relapse of hyperthyroidism - Actual outcome: Hyperthyroidism at 6 months follow-up (off ATDs for at least 2 months) at 6 months; Group 1: 45/107, Group 2: 28/98 Risk of bias: All domain - Low, Selection - High, Blinding - Low, Incomplete outcome data - Low, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: 3, Reason: Not stated; Group 2 Number missing: 6, Reason: Not stated	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Study	Pirnat 2011[79]
Study type	RCT (Patient randomised; Parallel)
Number of studies (number of participants)	1 (n=109)
Countries and setting	Conducted in Slovenia; Setting: Department of nuclear medicine at teaching hospital
Line of therapy	1st line
Duration of study	Intervention + follow up: 12 months
Method of assessment of guideline condition	Adequate method of assessment/diagnosis
Stratum	Overall
Subgroup analysis within study	Not applicable
Inclusion criteria	Graves' disease
Exclusion criteria	Previously treated with RAI/SUR,
Recruitment/selection of patients	Not stated
Age, gender and ethnicity	Age - Mean (SD): 45 (13). Gender (M:F): Not stated. Ethnicity: Not stated
Further population details	1. Age: 18-50 2. Gender: Not applicable
Extra comments	No information on ophthalmopathy or other previous treatments
Indirectness of population	No indirectness
Interventions	(n=50) Intervention 1: RAI with ATDs - ATDs before RAI. Fixed dose of RAI 550MBq, 10mg/d MMI given for 2-12 months until euthyroidism, stopped 7 days before RAI treatment, one dose of RAI only Fixed dose of RAI 550MBq, 10mg/d MMI given for 2-12 months to achieve euthyroidism, stopped 7 days before RAI treatment, one dose only Fixed dose of RAI 550MBq, 10mg/d MMI given for 2-12

	months to achieve euthyroidism, stopped 7 days before RAI treatment, one dose only . Duration 12 months. Concurrent medication/care: Usual care. Indirectness: No indirectness (n=59) Intervention 2: RAI alone. RAI as for combination arm. Duration 12 months. Concurrent medication/care: Usual care. Indirectness: No indirectness
Funding	Funding not stated
RESULTS (NUMBERS ANALYSED) AND RISK OF BIAS FOR COMPARISON: ATDS BEFORE RAI versus RAI ALONE Protocol outcome 1: Relapse of hyperthyroidism - Actual outcome: Persistent hyperthyroidism at 12 months at 12 months; Group 1: 2/50, Group 2: 2/59 Risk of bias: All domain - High, Selection - High, Blinding - Low, Incomplete outcome data - High, Outcome reporting - Low, Measurement - Low, Crossover - Low; Indirectness of outcome: No indirectness ; Group 1 Number missing: ; Group 2 Number missing:	
Protocol outcomes not reported by the study	Quality of life; Mortality; Thyroid ophthalmopathy; Euthyroidism; Hypothyroidism; Ischaemic heart disease; Heart failure; Arrhythmia; Osteoporosis; Impaired cognitive function; Growth; Pain; Symptom scores; Experience of care; Healthcare contacts; Agranulocytosis; Liver failure; Minor drug related adverse events; Teratogenesis; Infertility; Malignancy; Thyrotoxic storm

Appendix E: Forest plots:

E.1 RAI + ATDs vs RAI

Figure 2: Ophthalmopathy

Study or Subgroup	RAI + ATDs Events	RAI + ATDs Total	RAI Events	RAI Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Gamstedt 1986	0	17	0	22		Not estimable
Kung 1995	0	80	2	79	100.0%	0.13 [0.01, 2.13]
Total (95% CI)		**97**		**101**	**100.0%**	**0.13 [0.01, 2.13]**
Total events	0		2			

Heterogeneity: Not applicable
Test for overall effect: Z = 1.43 (P = 0.15)

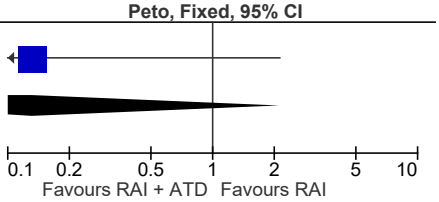


Figure 3: Euthyroidism

Study or Subgroup	RAI + ATDs Events	RAI + ATDs Total	RAI Events	RAI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andrade 2001	9	29	9	32	8.9%	1.10 [0.51, 2.40]
Bonnema 2004	20	39	27	41	27.3%	0.78 [0.53, 1.14]
Goolden 1969	63	83	67	98	63.8%	1.11 [0.93, 1.33]
Total (95% CI)		**151**		**171**	**100.0%**	**1.02 [0.86, 1.20]**
Total events	92		103			

Heterogeneity: Chi² = 2.85, df = 2 (P = 0.24); I² = 30%
Test for overall effect: Z = 0.22 (P = 0.82)

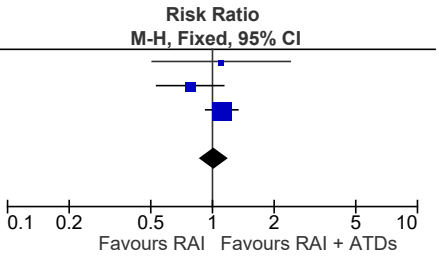


Figure 4: Hypothyroidism

Study or Subgroup	RAI + ATDs Events	RAI + ATDs Total	RAI Events	RAI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andrade 2001	16	29	18	32	33.2%	0.98 [0.63, 1.54]
Bonnema 2004	6	39	7	41	13.2%	0.90 [0.33, 2.45]
Gamstedt 1986	8	17	18	22	30.4%	0.58 [0.33, 0.99]
Goolden 1969	14	83	13	98	23.1%	1.27 [0.63, 2.55]
Total (95% CI)		**168**		**193**	**100.0%**	**0.91 [0.67, 1.24]**
Total events	44		56			

Heterogeneity: Chi² = 3.77, df = 3 (P = 0.29); I² = 20%
Test for overall effect: Z = 0.57 (P = 0.57)

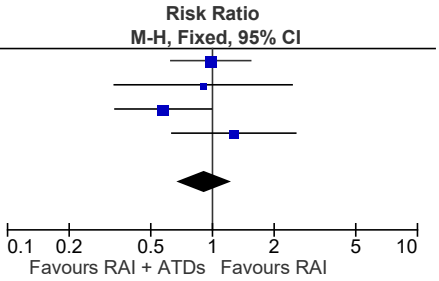


Figure 5: Relapse/persistence of hyperthyroidism

Study or Subgroup	RAI + ATDs Events	RAI + ATDs Total	RAI Events	RAI Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Andrade 2001	4	29	5	32	6.9%	0.88 [0.26, 2.98]
Bonnema 2004	13	39	7	41	9.9%	1.95 [0.87, 4.38]
Goolden 1969	23	83	20	98	26.7%	1.36 [0.80, 2.29]
Hamilton 1952	9	15	7	22	8.3%	1.89 [0.90, 3.95]
Kung 1995	40	80	31	79	45.5%	1.27 [0.90, 1.81]
Pirnat 2011	2	50	2	59	2.7%	1.18 [0.17, 8.08]
Total (95% CI)		**296**		**331**	**100.0%**	**1.38 [1.08, 1.78]**
Total events	91		72			

Heterogeneity: Chi² = 2.14, df = 5 (P = 0.83); I² = 0%
Test for overall effect: Z = 2.53 (P = 0.01)

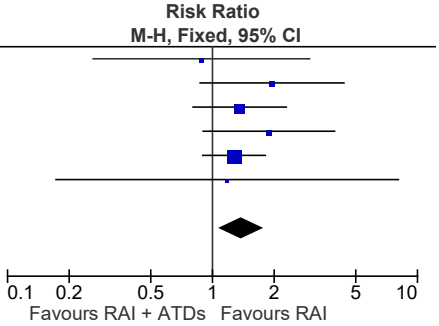


Figure 6: Minor adverse events

Study or Subgroup	RAI + ATDs Events	Total	RAI Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kung 1995	6	80	0	79	100.0%	7.79 [1.53, 39.60]
Total (95% CI)		**80**		**79**	**100.0%**	**7.79 [1.53, 39.60]**
Total events	6		0			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.47 (P = 0.01)

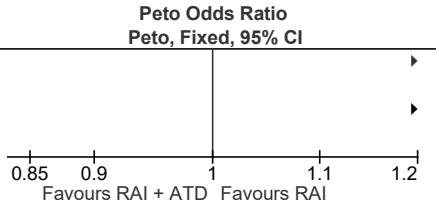
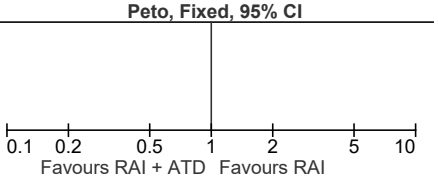


Figure 7: Thyroid storm

Study or Subgroup	RAI + ATDs Events	Total	RAI Events	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Kung 1995	0	80	0	79		Not estimable
Total (95% CI)		**80**		**79**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable



E.2 Calculated strategy vs fixed strategy

Figure 8: Euthyroidism

Study or Subgroup	CAL Events	Total	FIX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Jaiswal 2014	8	20	4	20	10.7%	2.00 [0.72, 5.59]
Jarlov 1995	39	78	49	85	35.7%	0.87 [0.65, 1.16]
Leslie 2003	4	43	2	45	4.9%	2.09 [0.40, 10.85]
Miranda-Padua 2014	7	17	17	26	20.3%	0.63 [0.33, 1.19]
Peters 1995	37	107	24	98	28.4%	1.41 [0.91, 2.18]
Total (95% CI)		**265**		**274**	**100.0%**	**1.07 [0.72, 1.57]**
Total events	95		96			

Heterogeneity: Tau² = 0.09; Chi² = 8.24, df = 4 (P = 0.08); I² = 51%
Test for overall effect: Z = 0.33 (P = 0.74)

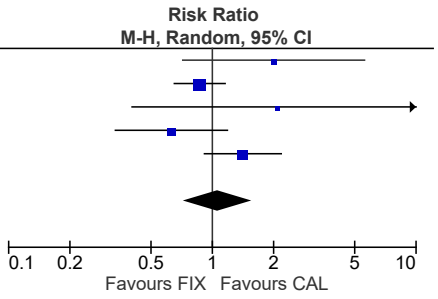


Figure 9: Hypothyroidism

Study or Subgroup	CAL Events	Total	FIX Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Jaiswal 2014	5	20	8	20	14.3%	0.63 [0.25, 1.58]
Jarlov 1995	7	78	6	85	12.3%	1.27 [0.45, 3.62]
Leslie 2003	30	43	31	45	31.6%	1.01 [0.77, 1.34]
Miranda-Padua 2014	6	17	6	26	13.9%	1.53 [0.59, 3.96]
Peters 1995	25	107	46	98	27.9%	0.50 [0.33, 0.74]
Total (95% CI)		**265**		**274**	**100.0%**	**0.84 [0.54, 1.33]**
Total events	73		97			

Heterogeneity: Tau² = 0.15; Chi² = 11.39, df = 4 (P = 0.02); I² = 65%
Test for overall effect: Z = 0.73 (P = 0.46)

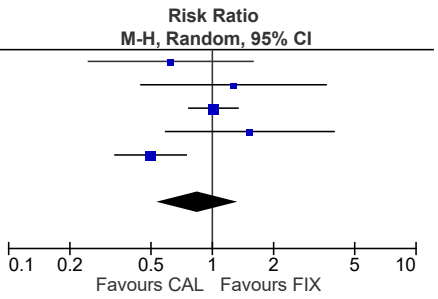
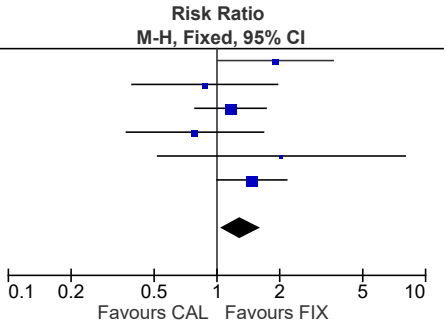


Figure 10: Relapse/persistence of hyperthyroidism

Study or Subgroup	CAL Events	CAL Total	FIX Events	FIX Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Canto 2016	21	61	11	61	12.1%	1.91 [1.01, 3.61]
Jaiswal 2014	7	20	8	20	8.8%	0.88 [0.39, 1.95]
Jarlov 1995	32	78	30	85	31.5%	1.16 [0.79, 1.72]
Leslie 2003	9	43	12	45	12.9%	0.78 [0.37, 1.67]
Miranda-Padua 2014	4	17	3	26	2.6%	2.04 [0.52, 8.00]
Peters 1995	45	107	28	98	32.1%	1.47 [1.00, 2.16]
Total (95% CI)		**326**		**335**	**100.0%**	**1.30 [1.04, 1.63]**
Total events	118		92			

Heterogeneity: Chi² = 5.17, df = 5 (P = 0.40); I² = 3%
Test for overall effect: Z = 2.29 (P = 0.02)



Appendix F: GRADE tables

F.1 Management of Thyrotoxicosis: Radioactive Iodine options

Table 10: Clinical evidence profile: radioactive iodine with antithyroid drugs vs radioactive iodine alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	RAI + ATDs	RAI	Relative (95% CI)	Absolute		
Ophthalmopathy (follow-up mean 4.6 years)												
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/97 (0%)	2.5%	Peto OR 0.13 (0.01 to 2.13)	11 fewer per 1000 (from 12 fewer to 14 more)	⊕OOO VERY LOW	IMPORTANT
Euthyroidism (follow-up 1 years)												
3	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	66%	47%	RR 1.02 (0.86 to 1.20)	13 more per 1000 (from 92 fewer to 132 more)	⊕⊕OO LOW	IMPORTANT
Hypothyroidism (follow-up 1 years)												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	44/168 (26.2%)	36.7%	RR 0.91 (0.67 to 1.24)	33 fewer per 1000 (from 121 fewer to 88 more)	⊕OOO VERY LOW	IMPORTANT
Relapse/persistence of hyperthyroidism (follow-up 1-4.6 years)												
6	randomised	serious[1]	no serious	no serious	serious[2]	none	91/296	18.7%	RR 1.38 (1.08	71 more per 1000 (from	⊕⊕OO	IMPORTANT

	trials		inconsistency	indirectness			(30.7%)		to 1.78)	15 more to 146 more)	LOW	
Minor adverse events (follow-up 4.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	6/80 (7.5%)	0%	Peto OR 7.79 (1.53 to 39.6)	70 more per 1000 (from 10 more to 140 more)[3]	⊕⊕⊕O MODERATE	IMPORTANT
Thyroid storm (follow-up 4.6 years)												
1	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	0/80 (0%)	0%	-	Not estimable-[4]	⊕⊕OO LOW	IMPORTANT

[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
[3] Zero events in control arm
[4] Zero events in either arm

Table 11: Clinical evidence profile: calculated strategy vs fixed strategy

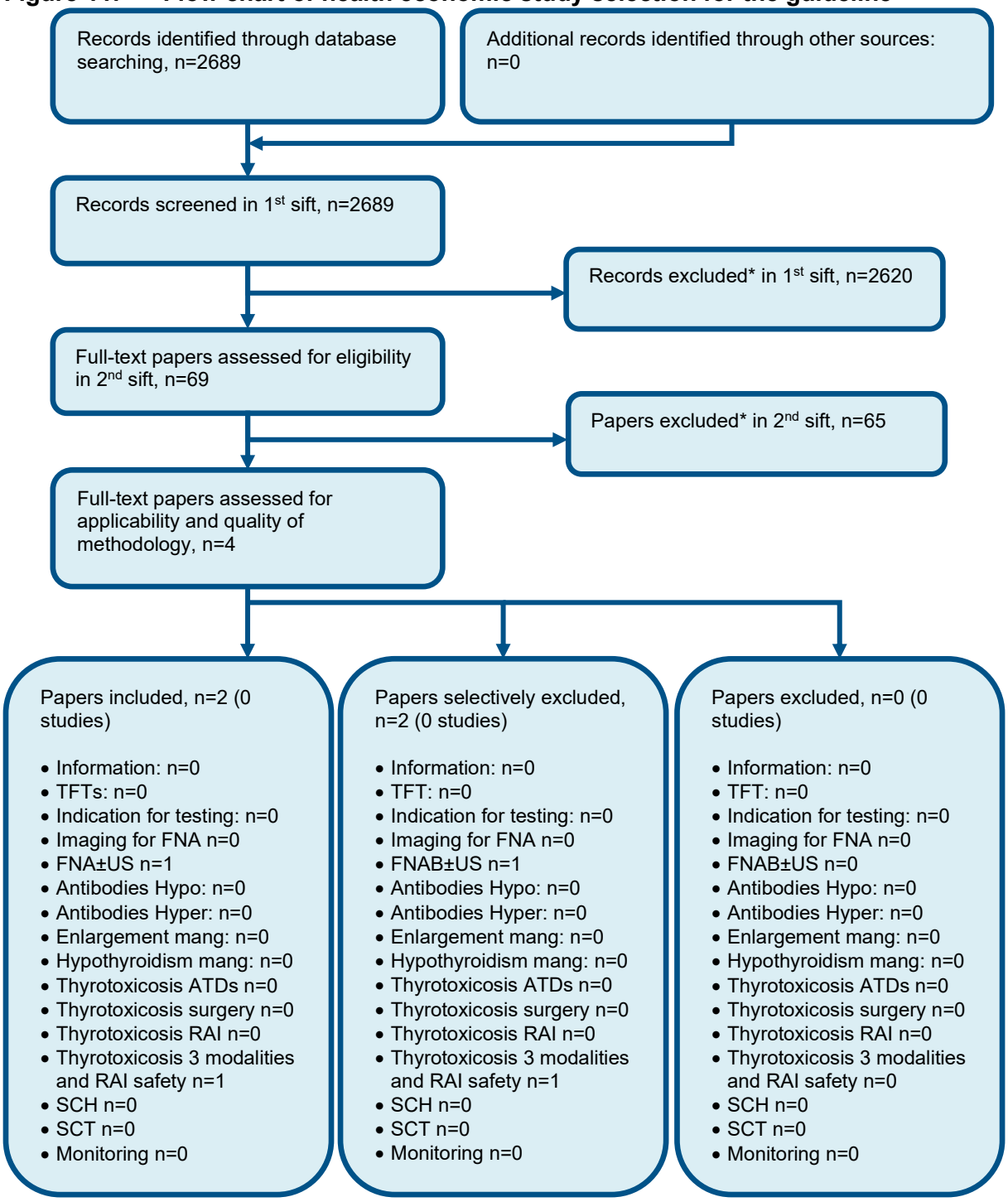
Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Calculated strategy**	**Fixed strategy**	**Relative (95% CI)**	**Absolute**		
Euthyroidism (follow-up 3 months - 6 years)												
5	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	95/265 (35.8%)	24.5%	RR 1.07 (0.72 to 1.57)	17 more per 1000 (from 69 fewer to 140 more)	⊕OOO VERY LOW	IMPORTANT
Hypothyroidism (follow-up 3 months - 6 years)												
5	randomised trials	serious[1]	serious[2]	no serious indirectness	very serious[3]	none	73/265 (27.5%)	40%	RR 0.84 (0.54 to 1.33)	64 fewer per 1000 (from 184 fewer to 132 more)	⊕OOO VERY	IMPORTANT

											LOW	
Relapse/persistence of hyperthyroidism (follow-up 3 months - 6 years)												
6	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	118/326 (36.2%)	27.6%	RR 1.3 (1.04 to 1.63)	83 more per 1000 (from 11 more to 174 more)	⊕⊕OO LOW	IMPORTANT

[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 or 2 increments because the point estimate and or the confidence intervals varied widely across studies, unexplained by subgroup analysis
[3] Downgraded by 1 increment if the confidence interval crossed one MID or by 2 increments if the confidence interval crossed both MIDs

Appendix G: Health economic evidence selection

Figure 11: Flow chart of health economic study selection for the guideline



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

Appendix H: Health economic evidence tables

None

Appendix I: Health economic analysis

None

Appendix J: Excluded studies

J.1 Excluded clinical studies Management of Thyrotoxicosis Radioactive iodine options

Table 12: Studies excluded from the clinical review

Study	Exclusion reason
Abraham 2010[2]	Systematic review is not relevant to review question or unclear PICO
Abraham-nordling 2007[1]	No usable outcomes
Allannic 1990[3]	Incorrect interventions
Andrade 1999[4]	Less than minimum duration
Andrade 2004[6]	Incorrect interventions
Aro 1980[7]	Not in English
Azizi 2012[9]	Wrong study design
Azizi 2018 [8]	NRS where RCTs are available
Barczynski 2012[10]	Incorrect interventions
Barczynski 2010[11]	Abstract only
Barczynski 2018[12]	Incorrect interventions
Bazzi 1993[13]	Incorrect interventions
Benker 1995[15]	Incorrect interventions
Benker 1998[14]	Incorrect interventions
Bonnema 2003[16]	Incorrect interventions
Bonnema 2011[18]	Inappropriate comparison
Braga 2002[19]	Less than minimum duration
Burch 2001[20]	No usable outcomes
Buscemi 2007[21]	Not guideline condition
Chen 2011[23]	Inappropriate comparison
Chen 2014[24]	No additional outcomes to those reported elsewhere
Chi 2005[25]	Inappropriate comparison
Connell 1987[26]	No usable outcomes
De Luca 2018[27]	SR, checked for references
Edmonds 1994[29]	Incorrect interventions
Esfahani 2005[30]	Inappropriate comparison
García-mayor 1992[32]	Incorrect interventions
Glinoer 2001[33]	Incorrect interventions
Goni iriarte 1995[34]	Not in English
Grebe 1998[36]	Incorrect interventions
Hamide 2014[37]	NRS where RCTs are available
Hashizume 1991[39]	NRS without adequate adjustment
He 2004[40]	Incorrect interventions
Hoermann 2002[41]	Incorrect interventions
Homsanit 2001[42]	Incorrect interventions
Howarth 2001[43]	Incorrect interventions
Järhult 2005[45]	Incorrect interventions
Jorde 1995[48]	Incorrect interventions

Study	Exclusion reason
Kallner 1996[49]	Incorrect interventions
Leclere 1994[51]	Not in English
Leung 2017 [53]	SR, checked for references
Li 2016[54]	SR, checked for references
Liu 2015[56]	Incorrect interventions
Liu 2017[55]	Incorrect interventions
Ljunggren 1998[57]	No usable outcomes
Lucas 1997[58]	Incorrect interventions
Ma 2008[59]	SR, checked for references
Ma 2016[60]	SR checked for references
Marcocci 1989[61]	Incorrect interventions
Mashio 1997[62]	Inappropriate comparison
Mastorakos 2003[63]	Incorrect interventions
Maugendre 1999[64]	Incorrect interventions
Mciver 1996[65]	Incorrect interventions
Menconi 2007[66]	No usable outcomes
Müller 2001[68]	Inappropriate comparison
Nakamura 2007[69]	Incorrect interventions
Nedrebo 2002[71]	Incorrect interventions
Noh 2015[72]	Incorrect interventions
Orsini 2012[73]	Inappropriate comparison
Peixoto 2006[74]	Incorrect interventions
Peters 1996[76]	No usable outcomes
Peters 1997[77]	No additional relevant information to master publication
Pfeilschifter 1997[78]	Inappropriate comparison
Pusuwan 2011[80]	Inappropriate comparison
Raber 2000[81]	Incorrect interventions
Reinwein 1993[82]	Inappropriate comparison
Rittmaster 1998[83]	Incorrect interventions
Rokni 2014[84]	SR checked for references
Romaldini 1983[85]	Incorrect interventions
Santos 2004[86]	NRS without adequate adjustment
Santos 2012[87]	Inappropriate comparison
Sapienza 2015[88]	Inappropriate comparison
Schneider 2005[89]	Inappropriate comparison
Singhal 2014[90]	Withdrawn Cochrane review
Steinbach 1979[91]	Incorrect interventions
Taïeb 2016[92]	Incorrect interventions
Thientunyakit 2010[93]	Inappropriate comparison
Tian 2001[94]	Not in English
Unalp 2009[95]	No usable outcomes
Walter 2006[96]	NRS without adequate adjustment
Wang 2016[97]	SR, checked for references
Weetman 1994[98]	Incorrect interventions
Witte 2000[99]	Incorrect interventions

Study	Exclusion reason
Yousefi 2011[100]	Not in English
Yuan 2017[101]	SR, checked for references

J.2 Excluded health economic studies

None

Appendix K: Research recommendations

K.1 Research question:What is the long-term clinical and cost effectiveness, including safety, of radioactive iodine for hyperthyroidism?

K.2 Research question: What is the clinical and cost effectiveness of dosimetry-guided radioactive iodine strategies for hyperthyroidism?

Why this is important:

Radioactive iodine (I-131 NaI) is used to treat benign thyroid disease in approximately 10,000 patients in the UK each year by delivering absorbed doses (radiation) preferentially to the thyroid. This is a widespread and well established treatment. However, despite being used globally for over 50 years there are many uncertainties regarding treatment optimisation and protocols vary widely in different countries. Patient dosimetry is standard practice in many European countries and is considered by many to enable personalised treatments which can more accurately achieve the aim of treatment with minimal activity. Six RCTs have been conducted in various countries to determine the possible role of patient dosimetry but are of low quality and do not reflect current practice or technology. For some patients dosimetry may offer the potential to become euthyroid without ATDs. Patient dosimetry also may be more in line with the new IR(ME)R regulations introduced in 2018, following the Euratom council directive 2013/59.

A clinical trial is necessary to address the issue of the level of activity to administer, the role of radiation dosimetry and the effect on patient quality of life. This trial should use the technology and methodology now available. It is envisaged that a multi-disciplinary working party will be formed, including endocrinologists, nuclear medicine physicians, physicists, radiation oncologists, primary care and patients, to develop a robust trial protocol that will definitively answer these questions.

Criteria for selecting high-priority research recommendations:

PICO question	Population: People requiring/opting for radioactive iodine (RAI) treatment for hyperthyroidism Intervention(s): Administration of Radioactive iodine Comparison: Different levels of administered activity and/or absorbed doses of radioactive iodine delivered to the thyroid gland Outcome(s): To include long-term euthyroidism, relapse of hyperthyroidism, hypothyroidism, quality of life, morbidity including neoplasia and mortality.
Importance to patients or the population	A clinical trial would determine the optimal level of radioactivity to administer, taking into account patient-specific factors including age, volume of thyroid and the absorbed doses delivered. This would maximise the likelihood of achieving the intended treatment outcome while minimising risks related to radiation exposure.
Relevance to NICE guidance	This will address the lack of high quality evidence available to guide optimal management protocols.
Relevance to the NHS	More informed delivery of radiation would ensure clinically and cost effective treatment, improved patient outcomes and a coherent approach to service delivery

National priorities	The NHS Five Year Forward View (2014) aims to address variations in treatment and outcomes. Outcomes from a clinical trial would support a national evidence based approach to treatment.
Current evidence base	Although there are many articles investigating the radiation dosimetry of radioactive iodine treatment, only 6 RCTs have been performed which have significant limitations. Protocols vary in each trial sample sizes are small and follow-up is short.
Equality	The trial would be open to all ages and both sexes although a trial might be of particular benefit to children and young people. Young people will usually have more life years ahead of them and hence more scope for adverse event development.
Study design	RCT or large, well adjusted (e.g. through regression analysis or propensity matching) non-randomised cohort study. To be developed in consultation with all disciplines and stakeholders, including adult and paediatric endocrinology, nuclear medicine, radiation physics and radiation oncology. Public and patient involvement will be included from the outset. A systematic review of the literature will be performed.
Feasibility	Over 10,000 patients are treated each year which will ensure adequate recruitment. Centres offering treatment are geographically widespread. Participating centres would require an initial set up procedure to enable absorbed doses to be calculated. This has been performed in a number of UK centres for an ongoing CRUK clinical trial with radioactive iodine treatment for thyroid cancer.
Other comments	This treatment is performed widely. This trial would therefore have international impact.
Importance	High. The guidelines are unable to provide clear guidelines for treatment protocols due to a lack of evidence. Outcomes would inform future updates.