Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

Stakeholder	Document	Page No	Line No	Comments	Developer's response
Association of Clinical Biochemistry and Laboratory Medicine	Guideline	8	General	We are concerned that this recommendation does not identify a role for TPO measurement in the investigation of suspected hypothyroidism. Various thyroid guidelines previously identified usefulness of TPOs especially for patients exhibiting an autoimmune background as the underlying cause of thyroid dysfunction. This is also relevant for page 11 section 1.5 'Managing and monitoring subclinical hypothyroidism"	Thank you for your comment. We cover TPO measurement in section 1.3 once hypothyroidism has been confirmed.
Association of Clinical Biochemistry and Laboratory Medicine	Guideline	9	5 - 8	We are concerned that this recommendation although correctly identifies a useful role for measuring TPO Abs in patients diagnosed with hypothyroidism, it does not provide any recommendation what is consider as a positive result	Thank you for your comment. The committee did not see the need to go into that level of detail in the recommendation. A positive result is one that is above the reference range for that assay.
Association of Clinical Biochemistry and Laboratory Medicine	Guideline	10	10 - 11	Section 1.4.1. Although the need to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine is mentioned, we are concerned that this recommendation does not clearly describes issues of over- or under-replacement especially in the long term and the need to carefully titrate and closely monitor compliance to avoid or prevent side effects.	Thank you for your comment. We have amended the first recommendation (1.4.1) to state "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing."
Association of Clinical Biochemistry and Laboratory Medicine	Guideline	11	General	We are concerned that this recommendation does not specifically address the issue of subclinical hypothyroidism for patients over 65 years by providing recommendations about the frequency of TFTs testing. There are some published reports advocating that patients over 65y in primary care setting, with mildly raised TSH should not be followed up because of the natural age-related decline in thyroid function that is not associated with disease; based on our own experience this adds confusion to primary care testing protocols and communication with laboratories and requires some further clarity.	Thank you for your comment. No evidence was identified for different frequency of testing based on age and the committee agreed that recommendations on testing apply to all ages. The committee agree that a different testing strategy for people aged 65 and over could cause confusion.

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Association of Clinical Biochemistry and Laboratory Medicine	Guideline	24 - 25	Recommendations for research	Given that the healthcare system is dealing with an increasingly ageing population, further high quality evidence is required especially based on real world approaches to address point 4 above.	Thank you for your comment. The research recommendations were reviewed following stakeholder comments and the committee agreed to keep the same list of questions.
Association of Clinical Biochemistry and Laboratory Medicine	Guideline	General	General	It is increasingly recognised that the public is keen to get involved in the laboratory investigations of thyroid function, by seeking and sometimes (mis)interpreting information available on the internet, which is usually not validated by appropriate professionals. As a result, clinical laboratories receive an increasing number of requests challenging current testing protocols. It would be helpful, when possible to present clear statements about the use or not of certain tests; ie use of fT3 in the investigation of suspected hypothyroidism is not recommended.	Thank you for your comment. We have made recommendations related to the tests we think are appropriate for each scenario. We have also updated some recommendations to indicate where a cascading approach for tests should be used that includes testing for FT3 (and FT4) when TSH is below the reference range. Although this is captured in the recommendations, the discussion sections of the reviews on thyroid function tests include more detail on when FT3 is and is not likely to be of use.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Algorithm on Hyperthyroidism	General	General	Overall a good summary of treatment options. In the 'Consider ATDs whilst awaiting specialist assessment box' we suggest adding 'Patients should be counselled on treatment options in the case of poor control or relapse, early in the course of disease'	Thank you for your comment. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. The NICE guideline on medicines adherence provides information on supporting adherence.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Algorithm on Hyperthyroidism	General	General	For the 'Surgery' arm, please consider adding bullet points for 'Patient choice', 'Significant Thyroid Eye Disease' and 'Adverse Drug Reactions to ATDs'	Thank you for your comment. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review K	11	25 - 29	Both total and subtotal thyroidectomy are performed as day case procedures (Evidence from the United Kingdom Registry of Endocrine and Thyroid Surgery (UKRETS) 5th Audit report,	Thank you for your comment. This text has been amended although it is not intended as a recommendation about duration of stay.

				available from www.baets.org.uk/audit/). However data from 24,469 procedures in the registry demonstrate that in the majority of cases (just under 80% of subtotal thyroidectomies and just under 60% of total thyroidectomies), patients stay one night in hospital because of the risk of haemorrhage and hypocalcaemia. Fewer than 10% of cases are performed as day cases and it has remained at this level for several years. Lastly, because of safety concerns, BAETS does not currently support daycase total thyroidectomy. Could the paragraph be rephrased to take account of this?	
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review K	11 - 12	38 - 44 and 1 - 8	This paragraph gives the impression that hemithyroidectomy may have a role in the treatment of Graves' disease, whereas hemithyroidectomy should only be employed for proven solitary toxic nodules where the risk of recurrence is zero with hemi-thyroidectomy and the incidence of hypothyroidism is lower than with radioactive iodine. Lines 43 onward of the paragraph would sound correct if the term 'hemithyroidectomy' was replaced by the term 'subtotal thyroidectomy', since hemithyroidectomy should not be used to treat Graves' disease.	Thank you for your comment. We have revised this paragraph as you suggest.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review K	12	16 - 17	In light of the above comment, this sentence might be better phrased: 'The committee agreed that total thyroidectomy is current practice for Graves' disease and toxic multinodular goitre, whereas hemithyroidectomy is employed for unilateral toxic nodules.'	Thank you for your comment. This text has been amended as you suggest.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review K (Surgical options for thyrotoxicosis)	General	General	The recommendation of Total thyroidectomy over Subtotal thyroidectomy for Graves' disease and Toxic MNG is in keeping with the views of BAETS as a specialist society representing thyroid surgeons for the reasons stated (risk of recurrence and necessity for morbid redo surgery in the event of recurrent toxicosis).	Thank you for your positive feedback.

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British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review M (Management of SubClin Toxicosis)	8	33	This is a good summary of an area with a poor evidence base. Total thyroidectomy will have a role in patients with SCT who require intervention and: (i) would prefer to avoid radioactive iodine or (ii) have a significant goitre. Could the text be modified to take account of this? The abbreviations STX and SCT are both used – should this be rationalised to one abbreviation?	Thank you for your comment. The committee did not think it was appropriate to make recommendations about which modality may be most appropriate given the lack of evidence to justify treatment of any kind. We have amended the abbreviations to be consistent.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review N	26 - 27	48 - 49 and 1 - 2	We agree that a recognised grading system is helpful but would also contend (as described above) that it would be helpful if these guidelines could recommend a minimum dataset for the reporting of USS to avoid poor quality reports, the necessity for repeats scans and diagnostic delays.	Thank you for your comment. The committee did recommend the specific features that should be included in reports.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review N (Imaging the thyroid)	General	General	BAETS commends the authors on this extensive analysis of the utility of USS in detecting thyroid malignancy and agrees that USS is the imaging modality of choice unless assessing for retrosternal extension.	Thank you for your positive feedback.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review O	12	27 - 28	This recommendation may be a challenging in practice because of the demand for and variation in availability of thyroid USS. It is also very likely to result in the over diagnosis and treatment of asymptomatic thyroid nodules, particularly low risk malignant lesions of less than 1cm. Could the clause '…following assessment in a specialist thyroid clinic, US scan should be the preliminary investigation to aid decision-making…' or similar be added? Furthermore, in some individuals, risk factors and/or clinical impression may mandate FNA in the presence of U2 thyroid USS.	Thank you for your comment. This information was used to inform the model and is not a recommendation in itself. The guideline does not recommend a specific grading system and therefore also does not recommend specific cut-offs on any one grading system.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review O	13	15	This is incorrect – a proportion of patients with benign nodules on USS or FNA will require surgery for compressive symptoms. It is also worth noting that UK and European registry data suggest that the incidental thyroid cancer rate (tumours>10mm) in such cases is 10-15%. Could this be rephrased to take account of the fact that U2 and THY2	Thank you for your comment. The modelled population was people with an enlarged but normally functioning thyroid gland being investigated for possible malignancy after a positive ultrasound (US) scan, only those with U3-U5 grade on US (U3 indeterminate, U4 suspicious for malignancy, and U5 likely malignant) would be

				nodules may require surgery and that USS has a significant false negative rate?	referred for a FNAC and it is these people specifically who are the subject of the model. For the simplicity of the model other factors such as compressive symptoms which could lead to surgery were excluded and benign nodules on US were either discharged or referred to a repeat FNAC and this forms part of the variation in the comparators. Please see evidence review P for the management of non-malignant thyroid enlargement and evidence review F for the monitoring of thyroid disease which deals with people experiencing compressive symptoms.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review O	General	General	No mention of nodule size is made in the text. Subclinical nodules of <10mm should not be sampled unless there are other high risk features e.g. lymphadenopathy (as per the American Thyroid Association (ATA) Guidelines).	Thank you for your comment. The committee recommended that a grading system should be used to justify FNA but did not make specific recommendations about which nodules should be sampled; this level of detail was deemed best left to the individual grading system chosen by any one practitioner.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review O	General	General	Could a minimum dataset for thyroid ultrasound be recommended (as mentioned in Guideline N)? BAETS members report that variation and absent information in USS reports results in delayed decision-making, may necessitate repeat scans and increase the cost of diagnosis. Could a statement be added to that effect: “All thyroid ultrasound reports should include detailed information including size of left and right lobes of thyroid, position, size and U stage of any nodules and comment on the presence or absence of pathological cervical lymph nodes”?	Thank you for your comment. The committee considered the level of detail that was appropriate to specify in their recommendations based on the evidence available and the criteria assessed. The detail you suggest is greater than they agreed was appropriate and references the U classification specifically.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review O (Ultrasound guidance for FNA)	5	9	Typo ‘the FNAFNA’	Thank you for your comment. This has been amended.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	6	Table 1	Risks/disadvantages of surgery. The vast majority of surgical procedures are undertaken with no complications. The risks of	Thank you for your comment. This table has been removed from the guideline as we were unable to

				voice change, low calcium, bleeding, and swallowing problems are low. Could this be added to give context please?	provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review P	24 - 25	44 - 45 and 1 - 3	Whilst BAETS agrees with the overall sentiment of this summary, the evidence is of very poor quality and although clinical benefit may have been shown in some studies, until there is evidence to the contrary, non-surgical treatments should only be used in the context of rigorous trials and surgery should remain the gold standard. Although the initial cost is much higher, it is a one-off, whereas the cost of multiple treatments and follow-up for non-surgically treated nodules is uncertain and may exceed this value.	Thank you for your comment. The committee's view based on the available evidence, their experience and the known costs of procedures was that the recommendations made in the guideline were appropriate.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review P	25	35 - 37	No evidence is presented on the use of radioactive iodine in the context of benign thyroid enlargement. Is this suggested in the context of hyperthyroidism and multi-nodular goitre? Can this be clarified?	Thank you for your comment. Radioactive iodine ablation was considered as an intervention for this review. Although no evidence was identified resource use is discussed and costs reported.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Evidence Review P (Management of non-malignant thyroid enlargement)	25	41 - 49	Although BAETS recognises that non-surgical treatments are available for benign thyroid enlargement, as stated the evidence base is poor. However, the review as a whole seems to give undue weight to these therapies, whilst a treatment that is associated with low morbidity (particularly with high volume surgeons), symptom resolution and that is likely to be cost-effective in the long run (surgery), is mentioned in passing. Lines 41-49 on page 25 would better reflect current practice by stating that although surgery is costly it is highly effective and until evidence improves, it should be the first line management for goitre requiring intervention.	Thank you for your comment. The text you reference is based on the evidence available in the review and is supported by committee consensus. In the absence of quality RCTs showing a substantial benefit of surgery it is not possible to make the definitive statements you recommend.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	16	1.6.11	Consider adding the following to the last bullet: "(e.g. they are pregnant or trying to become pregnant or father a child within the next 4 to 6 months, or they have active thyroid eye disease)	Thank you for your comment. The bullet point in this recommendation stating 'if radioactive iodine and antithyroid drugs are unsuitable' is intended to cover these and other scenarios. It is also worth noting the management of thyroid disease in pregnant women

					(including pre-conception) and thyroid eye disease are excluded from the scope.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	19	22	'Offer levothyroxine to adults, children and young people after a total thyroidectomy' gives the impression that it is an optional treatment rather than essential. Consider changing to 'Prescribe Levothyroxine…". Please consider adding a further bullet point: "Measure the adjusted serum calcium at the first postoperative assessment to exclude hypocalcaemia."	Thank you for your comment. The use of the word 'offer' reflects the strength of the recommendation, and recognises that patients are offered treatment which they may choose not to accept. We did not include a review on postoperative assessment, so we have not made any recommendations in this area.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	22	1.9.3	Consider adding a bullet point "size in mm"	Thank you for your comment. The omission of size in the ultrasound system was a deliberate choice by the committee as the one scoring system that heavily relied on size was the worst performing in the evidence review. That is not to say that size will not be relevant to overall clinical picture but that malignancy risk assessments should not focus on it.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	22	22	Consider adding a bullet point 'there are swallowing problems or compressive symptoms'	Thank you for your comment. The committee agreed that clinically significant compression evidenced by swallowing problems and compressive symptoms would be covered by the existing bullet points on difficulty breathing and the example of marked airway narrowing and did not think it necessary to change the recommendation.
British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	23	1.9.10	Please add 'Consider surgery for complex cysts, particularly if recurrent'	Thank you for your comment. The committee agreed that surgery would be appropriate for nodules or enlargement causing symptoms, if there has been no response with other options or if there is true compression of nearby organs (for example, tracheal narrowing). The committee made recommendations on what to do in the first instance only and did not cover all scenarios.

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British Association of Endocrine and Thyroid Surgeons (BAETS)	Guideline	23	16	Consider including 'surgery, particularly if there is marked airway narrowing, difficulty swallowing or compressive symptoms'	Thank you for your comment. The committee considered any of these options appropriate in the context of compressive symptoms and that marked airway narrowing was the predominant feature that would warrant surgery being the first consideration.
British Nuclear Medicine Society	Guideline	6	Table 1	In the section discussing the disadvantages of treatment with I-131 the following statement is provided: "Need for short-term radiation protection (limited contact with other people for a few days after treatment)" This is not correct and does not reflect current legislation the statement should read "Need for short-term radiation protection (limited contact with other people for e.g. 10 days to 3 weeks after treatment)"	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
British Nuclear Medicine Society	Guideline	8	13	In neonates with suspected congenital hypothyroidism a thyroid scintigraphy should be performed as soon as possible and certainly within 7 days to differentiate ectopic e.g. sublingual thyroid gland from dyshormonogenesis or absence of thyroid tissue. This can normally be performed using Tc-99m pertechnetate but if defects in organification are suspected additional imaging with I-123 can be helpful.	Thank you for your comment. Neonates are excluded from the scope of the guideline, so we have not made any recommendations for testing.
British Nuclear Medicine Society	Guideline	14	9 - 10	Consider technetium scanning should be a stronger recommendation to undertake "radionuclide scanning (Tc-99m pertechnetate/I-123) [Note in some cases where Tc-99m pertechnetate produces an unexpected result I-123 may be a better agent] if TRAbs are negative, if there is a palpable thyroid nodule or prior to radioiodine treatment. The British Nuclear Medicine Society is concerned about giving I-131 without a recent prior Tc-99m/I-123 scan to ensure there is uptake even when the patient is TRAB positive. In the experience of the BNMS about 7% of patients referred for treatment with "classical" Graves' disease and a positive TRAB have no or minimal uptake of tracer on their diagnostic thyroid scintigraphy performed on the day of their I-131 therapy. The	Thank you for your comment. We did not find evidence to endorse routine radionuclide scanning in all patient undergoing treatment with radioactive iodine. Evidence showed TRAB testing to be the best first test. The committee discussed that in patients with toxic nodular hyperthyroidism it is appropriate to perform radionuclide scanning in patients whose TRAB concentrations are not raised. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the

				reasons can include poor understanding of the requirements to stop anti-thyroid drugs, interfering high iodine from dietary or medical sources. Some of these the patient may be unaware of all the pre-treatment restrictions and can give an erroneous answer on the day of the treatment concerning their preparation. Also some patients have a form of thyroiditis which appears more chronic as recognised by Pariani et al J Clin Endcrinol and Metab 2018. If a diagnostic scintigraphy is not performed and the patient is one of these 7% there will be two consequences. Firstly, they will not have improved thyroid function as the thyroid would not have been irradiated. Secondly the patient will have received a significant radiation dose without benefit. This would need to be reported to the CQC as a significant radiation event. The Medical Physics Expert involved may be sanctioned and along with the ARSAC holder responsible for that administration may face prosecution. This has become more important as a recent article by Kitihara et al JAMA Int Med 2019 epub has suggested a slightly increased lifetime cancer risk in patient who have hyperthyroidism and been given I-131. Therefore, to give I-131 to a patient with no thyroidal uptake could be seen as giving the patient a risk but with no benefit. It was previously demonstrated that a significant proportion (20%) of hyperthyroid patients with no suspicion of nodules and clinical 'Graves' disease' had a diagnosis other than solely Graves' disease and would have received incorrect treatment without the result of this scan (Lacey NA, Jones A, Clarke SE Br J Radiol 2001;74:486-9). Concomitant thyroid cancer occurring in Graves' patients with increased TRAb is also a possibility. It has been reported that thyroid cancer was identified in 7% of patients undergoing surgery for Graves' disease, of which 3% were significant (not micropapillary >1 cm) and could be identified by imaging	inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.

				(Tamatea JA et al. ANZ J Surg 2014; 84:231-4). In general, thyrotoxicosis with concomitant thyroid cancer is poorly recognised, which may result in delayed diagnosis, inappropriate treatment and even poor prognosis and functional and anatomic imaging would aid to more timely diagnosis and change in management (Fu H et al. Endocr relat Cancer 2019; 26: 395-413).	
British Nuclear Medicine Society	Guideline	14	10	Add “or suspicious non active “cold nodule” on thyroid scintigraphy or unexpected focal uptake of F-18 FDG on a PET-CT scan”.	Thank you for your comment. In the situation you describe the recommendations on investigation of thyroid enlargement would be appropriate.
British Nuclear Medicine Society	Guideline	All	All	We have reviewed this guideline and believe that with a few minor alterations it provides an excellent framework for safe management of patients with benign thyroid disease.	Thank you for your comments
British Nuclear Medicine Society	Guideline	All	All	The guidelines do not cover the management of malignant thyroid disease. So, the title should reflect the content. Suggest adjusting the title- e.g. Assessment of thyroid disease and management of **benign** thyroid disease.	Thank you for your comment. The guideline context section has been amended to make it clear that the guideline does not cover managing thyroid cancer. NICE is developing a separate guideline on thyroid cancer (see https://www.nice.org.uk/guidance/indevelopment/gid-ng10150)
British Thyroid Foundation	Evidence review A	12	Item 3	I believe the overall assessment should be a higher rating.	Thank you for your comment. The quality assessment for ‘Barriers to optimal thyroid replacement’ has been amended from low to moderate.
British Thyroid Foundation	Evidence review A	15	11 - 31	Getting to the point where you are feeling well again can be a long process. There should be better support and understanding at GP level as quite often depression and repeated tests put people off further visits to the doctor. If people are busy and are repeatedly fobbed off they will not persist and will give up. Others may not be able to keep going back to the doctor as they are unable to get the time off work. Patients need to be encouraged to persist with recovery and signposted to alternative options that might benefit them, e.g.	Thank you for your comment. The recommendations include timescales for monitoring and change in symptoms which should support both professionals and patients in their expectations. The guideline also recommends starting at a dose calculated by weight for the patient which may result in quicker improvement of symptoms.

				craft vouchers to encourage time out, hobbies, mindfulness courses, adult education, food vouchers to support healthy eating, local and national support groups. Raise awareness to limit stress, look at diet and provide better dietary information, maybe healthy recipes that aid thyroid support.	We didn't include a review question on the alternative options you suggest that might benefit patients so have not made a recommendation in this area.
British Thyroid Foundation	Evidence review A	28	App D	Wider studies are needed to include patients under 30. It states that the method question of 'Are you aware of any consequences of poor control?' was subsequently changed for the patient to answer. When was it changed and were all of the people in the trial included in the revised questioning? What was the revised question and was it helpful? What level of understanding did the researcher have? The question arises was this a fair, thorough and full study?	Thank you for your comment. The paper states that the topic guide used to explore questions related to the study was revised as the study progressed and the specific questions reported are examples of what was included in the initial topic guide. No further details are provided by the study. It is common for topic guides to be revised as investigations go on in qualitative studies to ensure that information that matches the aims of the study are adequately explored. This study was quality assessed as per the NICE method processes and was judged to be of moderate quality due to limitations associated with the role of the researcher (i.e. the background of the researcher not being transparent to assess whether and how it could have influenced the study and the interpretation of findings) and data richness. The quality rating given to each study was brought to the attention of committee who reviewed its findings with caution in light of this information.
British Thyroid Foundation	Evidence review A	34	2b	'Dose adjustment' – this should be expanded. Was an explanation provided to the patient how other medication dose could change levels and take time to adjust in the body. Was this factored into findings etc.?	Thank you for your comment. The study used qualitative interviews following a topic guide to explore its aims (to explore the experience of hypothyroidism in older people and examine how this may influence their understanding of acceptance of diagnosis, treatment and monitoring). There is no evidence in the paper to suggest that the information you raise was provided and this is unlikely as information provision was not the original aim of the paper. The information summarised under 'dose adjustment' represents information emerging from the

					paper that were considered to reflect the type of information people with thyroid disease could benefit from and fell under that theme.
British Thyroid Foundation	Evidence review A	General		We request that the reference ranges be standardised and there should be increased patient awareness of them. Also that patients are given further information about the interactions with other medications and supplements. There is also the matter of supply of medications and that some brands may not be available for one or two months at a time.	Thank you for your comment. The importance of providing people with information on the possible interactions of their medication was highlighted in evidence review A and has been captured in the recommendations.
British Thyroid Foundation	Evidence review A + B	General		This states that the length that thyroxine lasts in the system is for 7-14 days, with the TSH taking up to 6 months to normalise. These studies reported at 3 months. 3 month testing is too short if supply is constantly changing. I would like more details in these sections about children with long family histories of this disease to be monitored across the larger scale.	Thank you for your comment. The information in regard to thyroxine lasting 7-14 days has been removed and the wording of recommendation 1.1.2 has been amended to reflect that symptoms may lag behind treatment changes. The committee acknowledges that TSH may take longer to return to the reference range; thus, testing every 3 months (or more frequently for children) rather than on one occasion at 3 months has been recommended (1.4.3). The committee is unable to make recommendations specifically about children with long family history as that level of elaboration is outside the remit of the guideline.
British Thyroid Foundation	Evidence review B	16	18 - 31	I don't feel there were enough studies to justify indications found/carried out/not used.	Thank you for your comment. In cases where evidence has not been sufficient the committee has used their collective experience to make consensus recommendations.
British Thyroid Foundation	Evidence review D	17	28 - 30	I am disappointed in the outcome of the trial of combination therapy with the suggestion that it was cost that was the factor for removal and I would like further research into this. References quote very old studies and American locations.	Thank you for your comment. Assuming you refer to Evidence review E, please note that the limitations of the studies that met the protocol were discussed by the committee and taken into account in decision making. The committee's decision not to recommend combination therapy routinely was based on the lack of sufficient evidence to support its effectiveness over monotherapy rather than costs alone. The committee

					acknowledges that some people may benefit from the addition of liothyronine and have therefore made a recommendation for future research to examine the clinical and cost-effectiveness of levothyroxine and liothyronine combination therapy for people with hypothyroidism whose symptoms have not responded sufficiently to levothyroxine alone, and whether DIO2 polymorphism affect the response to combination therapy with levothyroxine and liothyronine.
British Thyroid Foundation	Evidence review E	59	General	Depression is shown again as an outcome, but the studies were incomplete. Again, this emphasises the need for further research.	Thank you for your comment. The need for future research has been recognised by the committee who has made a high priority recommendation for future research in the area (Key recommendations for research 1).
British Thyroid Association	Evidence review I	6 - 7	3 - 6 & Table 1	1.1 Review question: *What is the clinical and cost effectiveness of using radioactive iodine vs antithyroid drugs vs surgery to treat thyrotoxicosis secondary to Graves' disease?* Mortality is listed as a critically important outcome for this review question but studies on hyperthyroidism mortality are not included in the review. The evidence review comprised six randomised controlled trials that focused on quality of life, treatment efficacy, and treatment-related side effects. Mortality was not addressed in these studies and was only stated as a secondary outcome in one study which recorded no deaths and was judged to be low quality by NICE (Chen 2009). Given that no randomised controlled trials have specifically addressed mortality, we are at a loss to understand why evidence from non-randomised studies was not considered in evaluating such a crucially important outcome. Five non-randomised studies have addressed treatment specific mortality in patients with hyperthyroidism (Boelaert 2013, Giesecke 2017, Hoffman 1982, Okosieme 2019, Ryodi, 2018).	Thank you for your comment. The committee considered that the evidence available at an RCT level was sufficient for decision making when supported with the additional review into the safety of radioactive iodine and the committee's own experience. The committee was aware of the conclusions of a number of the studies that you cite, even if they were not formally included as part of the evidence review as they did not meet the protocol criteria.

				Two of these studies (Boelaert 2013, Okosieme 2019) compared mortality in antithyroid drug vs radioiodine treated patients with both studies showing reduced mortality in radioiodine treated patients when hyperthyroidism was controlled but not when hyperthyroidism was uncontrolled. We believe that these studies are relevant to the choice of therapy in Graves' disease and should be included in the review. The recommendations on primary therapy (1.6.8–1.6.10) now represent a departure from current practice and it will be reassuring to stakeholders that a balanced review of the most important outcomes have been undertaken. **References** [1] Boelaert K, Maisonneuve P, Torlinska B, et al. Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. J Clin Endocrinol Metab 2013; 98: 1869-82. [2] Giesecke P, Frykman V, Wallin G, et al. All-cause and cardiovascular mortality risk after surgery versus radioiodine treatment for hyperthyroidism. Br J Surg 2017. [3] Hoffman DA, McConahey WM, Diamond EL, Kurland LT. Mortality in women treated for hyperthyroidism. Am J Epidemiol 1982; 115: 243-54. [4] Okosieme OE, Taylor PN, Evans C, *et al*. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. Lancet Diabetes Endocrinol. 2019; 7:278-287. [5] Ryödi E, Metso S, Huhtala H, et al. Cardiovascular Morbidity and Mortality After Treatment of Hyperthyroidism with Either Radioactive Iodine or Thyroidectomy. Thyroid 2018; 28: 1111-20.	

British Thyroid Association	Evidence Review I	20	2 - 3	*2.1 Review question: What are the long-term adverse events of radioactive iodine treatment for thyrotoxicosis?* In the evidence-review for radioiodine safety the committee report no clinically important harm of radioactive iodine treatment in terms of increased cancer diagnoses. However, a recent observational study of 18,805 patients, treated with radioiodine for hyperthyroidism, showed a modest positive association between radioiodine treatment and death from solid cancers (Kitahara 2019). However, this paper requires cautious interpretation for a number of reasons. First the authors adopted a new complex formula to calculate radioiodine dose at tissue level with some uncertainty in organ dose exposure. In addition, the control group comprised a general background population that was not specifically matched to radioiodine exposed individuals. Lastly, adjustments for important confounders including smoking, obesity, alcohol intake and potential treatment selection bias were not undertaken (Kitahara, 2019). These limitations are relevant given the very marginal risks observed for all solid cancers in the study (RR 1.06, 95% CI, 1.02-1.10). While further studies are clearly needed, the findings of this study will nonetheless be of some concern to clinicians and patients in the light of the committee's recommendation of radioiodine as first line therapy for hyperthyroidism. It would therefore be reassuring for the committee to address this study in the evidence review. **Reference** [1] Kitahara CM, Berrington de Gonzalez A, et al. Association of Radioactive Iodine Treatment with Cancer Mortality in	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.

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				Patients With Hyperthyroidism. JAMA Intern Med. 2019 Jul 1. doi: 10.1001/jamainternmed.2019.0981. [Epub ahead of print]	
British Thyroid Association	General	General	General	We congratulate the committee on these thoughtful and carefully considered guidelines.	Thank you for your comment and for contributing to the consultation process.
British Thyroid Foundation	General			Whilst we understand that pregnancy and thyroid disorders are beyond the scope of this guideline we feel it is essential to use this opportunity to highlight that the care of women with thyroid disorders in the pre-pregnancy and pregnancy period may need adjusting and careful monitoring. We regularly hear from women whose GPs are not familiar with the appropriate guidance. Since is likely that primary care doctors won't have the time to look at several different documents flagging up the issue in several places (e.g. in NICE and GCOG guidance) is essential.	Thank you for your comment. The guideline does not make any statements on pregnancy as thyroid disease in pregnant women (including pre-conception and postpartum advice) was excluded during the scoping of the guideline to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists.
British Thyroid Foundation	General			Personally, I would like to see more consideration and joined up thinking regarding more detailed testing for children with a family history, also more support for sufferers that stress, lifestyle and diet play a big factor as well as varied testing ranges and inconsistency of supply.	Thank you for your comment. Screening those with a family history of thyroid disease was not covered in the guideline and NICE guidelines do not usually cover screening. We looked for evidence related to family history in those suspected of thyroid disease but found no evidence of this being an indicator. Lifestyle factors were not included in the scope of the guideline.
British Thyroid Foundation	General			Finally, the proposed guidelines are consolidating practices that have been discredited over the past two decades. They fail to address large-scale patient dissatisfaction with hypothyroidism therapy and restrict the options available to patient and physician.	Thank you for your comment. These guidelines have been based on evidence of the highest quality available about the clinical and cost-effectiveness of the diagnosis and management options available to date. The committee have highlighted research recommendations in areas where more evidence would be helpful.
British Thyroid Foundation	Guideline	General	General	Patient education may be challenging in practice since I have never seen any of the helpful British Thyroid Foundation leaflets in a surgery, nor been pointed at them, and the	Thank you for your comment. Links to appropriate patient information sites may be included with the guideline when it is published on NICE's web site

				information on the NHS website seems cursory. Some patient websites promote only one form of medication (natural desiccated thyroid NDT) and include information that is highly selective, others seem a vehicle to promote their own supplements/ schemes (especially US chiropractors who style themselves 'Dr'), and we deserve more e.g. at an absolute minimum a steer to the British Thyroid Foundation website. Saying 'keep off Google' is also highly unrealistic and unhelpful. Until and unless doctors and patients have access to the same high quality information that also covers some controversies this will be a problem. Lack of information comes at a high cost: on the basis of a lack of understanding and information from doctors and internet information some patients end up self-medicating and self-testing or else get handed a lot of medication that merely addresses symptoms not cause. From seeing posts in Facebook groups some patients also give up very quickly when their treatment doesn't work straight away, when their doctor dismisses their symptoms as e.g. menopause or depression, or when they are not monitored properly and don't know to ask for a retest after a dose change or yearly. Patients also may end up paying a lot for private testing that is then ignored by their doctor even when carried out at a hospital and by accredited laboratories.	
British Thyroid Foundation	Guideline	4	5 - 19	This would also be a useful opportunity to advise women of child bearing age about the importance of good thyroid control around the pre-pregnancy and pregnancy period. Patient support groups have useful resources that offer reliable and patient friendly guidance. We understand the new Green-top guidance from the Royal College of Obstetrics and Gynaecologists (RCOG) on thyroid and pregnancy will soon be published but busy GPs may only have time to refer to one resource and therefore including the point in the NICE guidance could benefit doctors and their patients. This point	Thank you for your comment. Management of thyroid disease in pregnant women, including pre-conception and postpartum advice, was excluded from the scope of the guideline. We are aware of the forthcoming RCOG guidance, and will include a link to it from the guideline when that guidance publishes.

				could also usefully be made in the sections about hypothyroidism, hyperthyroidism and subclinical thyroid disease. At the very least this guidance could signpost the reader the RCOG Green-top guidelines.	
British Thyroid Foundation	Guideline	4	7 - 19	There is a concern that these comments may be taken to imply that everyone will feel better within a short timescale and that any symptoms they experience are unlikely to be due to hypothyroidism. This is unhelpful and distressing to patients with severe hypothyroidism who may take longer and require more dose adjustments to get back on track. It is also unhelpful if the patient seeks support from employers and family (and indeed some doctors) as they may think that hypothyroidism treatment works the same way as an antibiotic or an over the counter painkiller. In addition, they contradict the implication that symptoms are just something a patient has to put up with long-term and therefore reduce the cost of potential complications e.g. high cholesterol/ cardiac issues, recurrent infections.	Thank you for your comment. The committee has reviewed and adjusted the wording in this section in light of your comment.
British Thyroid Foundation	Guideline	4	9	One member comments that the guidelines continuously refer to the "reference ranges" but fail to state what these ranges are. In fact it is very difficult in any of the literature to find out what the reference ranges are. Some explanation of why this is lacking would be good to see.	Thank you for your comment. The reference ranges will be variable dependent on the assay used and are usually specific to the local population so it is difficult to be specific and give reference ranges that would fit uniformly
British Thyroid Foundation	Guideline	4	9	One member states that the term '*reference range'* is misleading. He believes that doctors wrongly interpret it as a diagnostic or therapeutic range and instead the term '*reference interval*' should be used, this will assist doctors and patients in understanding blood test results.	Thank you for your comment. We have kept to the term 'reference ranges' as we used it in the scope and is still used by other organisations.
British Thyroid Foundation	Guideline	4	14 - 15	This point is very, very important. The adjustment of dose within reference range was essential to my quality of life in resolving symptoms and does not seem to have made it through to the final guidance – especially adjusting dose within	Thank you for your comment. We have adjusted the wording to facilitate dose titration: Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist,

				lab range which seems discouraged by saying it is 'costly'. However, there is also a concern that these recommendations may be interpreted as doctors not needing to look at other possible causes of symptoms (e.g. iron, folate, vitamin B12 or D deficiency). I suggest adding a point that some people may have other underlying issues that require attention, for example vitamin and mineral deficiencies or other autoimmune conditions.	consider adjusting the dose of levothyroxine further to achieve optimal well-being. We did not review the evidence to make an additional recommendation on vitamin or mineral deficiencies.
British Thyroid Foundation	Guideline	4	20	It would be a good idea in this section to offer patients the opportunities to keep a record of their own thyroid function tests which may encourage them to take control of their condition and would also help at times when their dose is changed regularly or if they relocate.	Thank you for your comment. A link to the patient experience guideline has been included in the guideline which includes such advice.
British Thyroid Foundation	Guideline	4	20 - 21	We often hear from parents of children (and also the children themselves) that when they are struggling at school their teachers don't understand how the symptoms can impact on their behaviour and performance at school. Whilst schools will be aware of other long-term conditions (e.g. diabetes) thyroid disorders don't have a high profile and so the children feel they aren't given the support they need or are even 'punished' for not feeling well. An example of this are the children who miss out on treats or awards which are given for full attendance – and therefore are never available for children who have to miss school for regular blood tests/hospital appointments. We would welcome the addition of something in the guidelines that reminds doctors (where appropriate) to make relevant information available for schools.	Thank you for your comment. We have recommended that healthcare professionals consider tests for thyroid dysfunction for children and young people with abnormal growth, or unexplained change in behaviour or school performance. It is beyond the remit of this guideline to recommend how doctors communicate with schools.
British Thyroid Foundation	Guideline	5	8 - 13	I am concerned that this approach, which seems to be what happens at the moment, does not educate patients or doctors on the rationale behind the instructions i.e. maximising stomach acid which is needed to process levothyroxine, making sure tablets get to the right place, minimising the impact of foods/ drinks/ medicines/ supplements that may	Thank you for your comment. The committee believe the recommendations as written alert clinicians to the points you make.

				affect absorption. Such information can only support active compliance and accidental non-compliance e.g. taking tablets with black coffee. Any information should also include the possibility of taking levothyroxine at night to fit better around patient lifestyle, and explain that it is the weekly dose that is important – for many patients, if they forget a dose doubling up may be fine. Getting this right could reduce the costs of non-compliance (social regarding quality of life and economic contribution and also medical costs of addressing symptoms).	
British Thyroid Foundation	Guideline	5	20	We suggest the following text be added to the fourth bullet point ('the risk and impact of thyroid eye disease…'): '….and the importance of smoking cessation in reducing this risk', and include signposting to NHS smoking cessation resources. This is because all studies including RCTs have shown that smoking increases the risk of thyroid eye disease. We would also suggest that the phrase include specific reference to Graves' disease as only those with thyrotoxicosis due to Graves' disease are at risk of eye disease e.g. suggested wording 'the risk and impact of thyroid eye disease in people with Graves' disease, and the importance of smoking cessation in reducing this risk.'	Thank you for your comment. We have not included advice on smoking cessation as we did not review the evidence for this. The committee consider advising people to stop smoking is generic advice given to all people. We have amended the bullet point to read "• the risk of and impact of different treatment options on new and existing thyroid eye disease (for example, radioactive iodine may precipitate or worsen thyroid eye disease)"
British Thyroid Foundation	Guideline	7	12 - 15	I am concerned that this guideline will be extremely difficult to implement cost-effectively since no guidance is given on what symptoms may indicate thyroid disease e.g. in the patient information section. A large barrier to implementation is the insistence on 'one problem per appointment' if neither patient nor doctor has a good understanding of thyroid disease and its symptoms. This can be extremely costly to both NHS and patient. My story is not unusual and I have seen very similar ones elsewhere. I had many repeated doctor visits and treatments over a period of three years, all with problems that eventually resolved when treated for hypothyroidism. These	Thank you for your comment. Guidelines are not intended to be a text book and it is expected that healthcare professionals will be familiar with classical description of hypo- and hyper -thyroid disease. The guideline does include specific symptoms/conditions where we found evidence for an association.

				problems were dismissed as ‘menopause’, ‘getting older’ and even with signs of myxoedema evident, repeated courses of antibiotics for skin infections/ other infections, asthma going out of control, steroids for skin problems, fainting after mild exertion, calcific tendonitis, etc. etc. no-one joined the dots. When I was finally tested (due to the number of courses of antibiotics) I was told that the GP was forced to test although the testing was costly and unnecessary. My TSH was well over 100 by that time. The GP had thought that just one previous age-related health check TSH test showed I could never have thyroid disease hence the reluctance to test. On my part, I had absolutely no idea that the symptoms were connected and had got used to them being dismissed as ‘what do you expect at your age and time of life’. This approach is a) very costly and b) causes great distress. I recommend developing a questionnaire/ checklist to suggest when tests may be appropriate thus supporting both GP and patient towards an earlier diagnosis and resolution. In particular, a cluster of symptoms should never be dismissed as ‘menopause’ since this is the very time when thyroid symptoms tend to develop. There needs to be a far higher index of suspicion for thyroid disease (and other conditions) and a far lower index of suspicion that a patient is somehow making things up. I am concerned that non-specific symptoms are interpreted as ‘unimportant symptoms’ or as ‘psychological symptoms’ rather than as symptoms which need taking seriously.	The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated.
British Thyroid Foundation	Guideline	8	1 - 2	I feel it must surely be wise to keep testing thyroid function during an acute illness to know how it is responding and having an effect.	Thank you for your comment. The recommendation has been updated to read “Do not test for thyroid dysfunction during an acute illness unless you suspect the acute illness is due to thyroid dysfunction because the acute illness may affect the test results.”
British Thyroid Foundation	Guideline	8	6 - 13	I am concerned that measuring TSH only and not free T4 will be very costly if the patient has a pituitary problem since	Thank you for your comment. No evidence was identified to support routine testing of FT4. In the

				having 'ruled out' thyroid disease many fruitless investigations and further symptom medication can result. How exactly would a doctor know without testing to 'suspect' pituitary problems? There is already a great reliance on TSH to detect hypothyroidism and difficulties doctors already have with interpretation can only be made more difficult without the information required to diagnose.	absence of evidence and based on their consensus opinion the committee agreed that TSH is usually enough and that FT4 would be tested when TSH is outside of the reference range.
British Thyroid Foundation	Guideline	8	6 - 13	I am concerned that these guidelines will still leave patients without a full diagnosis. Given that autoimmune disease is a major cause of hypothyroidism why not also test thyroid antibodies (both types) given out of range TSH? This would also enable early screening of coeliac disease. Even though I have other autoimmune disease in the family, and even though the current set of recommendations say to test for thyroid antibodies, my GP has refused as 'the treatment is the same'. In addition, for subclinical hypothyroidism, this is an important indication to be used when considering whether or not to start treatment.	Thank you for your comment. This section covers the initial tests for investigating thyroid dysfunction. Antibody testing is also recommended once thyroid disease is diagnosed. In the final guideline we have added a link to the NICE guideline on coeliac disease (NG20), which recommends offering testing for coeliac disease to people with a diagnosis of autoimmune thyroid disease.
British Thyroid Foundation	Guideline	8	23	The recommendation that repeat testing should not be carried out within six weeks is sensible in most cases. However, worsening symptoms or erratically swings from hypo to hyper could be due to autoimmune flare ups. In such cases repeating tests sooner is needed for diagnosis and so consideration can be given to alternative options such as block and replace.	Thank you for your comment. The committee believe that it would be unusual for tests to swing so dramatically. The recommendations are only meant to cover the main scenarios and cannot cover every variation. It is anticipated that clinicians will make an assessment on a case by case basis.
British Thyroid Foundation	Guideline	8- 13	7- 6	Testing for suspected thyroid dysfunction should include TSH, fT3 and fT4. TSH alone is insufficient. It is important to test all three hormones initially to confirm the hypothalamic pituitary thyroid axis is intact. Many patients are severely hypothyroid as a consequence of a down-regulated axis. A record of TSH, fT3 and fT4 at initial diagnosis may prove invaluable, it would be tragic to miss this opportunity for the sake of a few pence.	Thank you for your comment. The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded

				If the patient's axis is functioning normally and TSH reflects their clinical response it is reasonable to use TSH for titration.	options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
British Thyroid Foundation	Guideline	9	3	The guideline only considers primary hypothyroidism and it may be helpful to point out that they do not cover any condition other than uncomplicated primary hypothyroidism. This should be made clear, pointing out there are multiple causes of hypothyroidism e.g. primary, central, resistance to thyroid hormone, endocrine disruption, subnormal TSH secretion (down-regulated axis) etc.	Thank you for your comment. We have made it clear in the headings and recommendations the conditions being considered. With regard to investigations this applies to any type of hypothyroidism, with regard to management we have headed the section as 'primary hypothyroidism' and added 'primary hypothyroidism' to the recommendations.
British Thyroid Foundation	Guideline	9	4 - 10	See comment 14. This recommendation will be hard to implement in practice since in my experience 'consider' means 'don't do it even if the person has other autoimmune disease and even if they have autoimmune in the family'. Either it needs to be tested or it doesn't and a guide rationale needs to be given.	Thank you for your comment. We have changed this recommendation to state "Measure TPOAbs….".
British Thyroid Foundation	Guideline	9	5 - 6	Is it possible that TPO antibodies which were initially 'normal' can increase and subsequently be significantly raised a few years after the initial testing? If so how long before a second test is warranted?	Thank you for your comment. The committee do not think so. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee also agreed that it would not be appropriate to recommend repeating tests when this is unlikely to affect management and there is no evidence to support a benefit of this approach.

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British Thyroid Foundation	Guideline	9	12	Throughout the document reference is made to '*levothyroxine*' treatment. Whilst it is reasonable that levothyroxine is the recommended first treatment option I believe that the content should not be written in such a way that levothyroxine appears to be the only option. Doctors will not have time to study the whole document, they will use relevant bits. Consider replacing '*levothyroxine*' with '*thyroid hormone supplements*'. Increasing evidence of persistent signs and symptoms during levothyroxine monotherapy and the move towards personal medicine could obsolete levothyroxine monotherapy in the near future.	Thank you for your comment. Where appropriate the recommendations have been amended to refer to 'thyroid hormone replacement'.
British Thyroid Foundation	Guideline	9	14	We hear from many patients who despite thyroid blood tests showing they were adequately replaced do not feel able to function well. Some tell us that they believe that T4/T3 combination therapy has successfully restored their quality of life and their ability to work and to contribute to family and other social commitments. We are concerned that there is a high cost to the NHS of inadequately or inappropriately treated hypothyroid patients. It can cause a significant amount of personal suffering as well.	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine). T3 Liothyronine is subject to CMA investigation and a cross reference to the CMA investigation has now been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). However, until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline. Therefore the

					guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).
British Thyroid Foundation	Guideline	9	14 - 19	I am a patient who has primary hypothyroidism, with no thyroid remaining as a result (via ultrasound). I have been on a combination of T4 and T3 for many years through my consultant. I was first diagnosed in 1986, when I was 24, after suffering with significant, undiagnosed hypothyroidism the previous 6 years. The continued symptoms of hypothyroidism only stopped once the combination treatment was introduced. There has been growing recognition that in a small group of patients a combination of T3 and T4 is helpful, although studies are poor and further research is needed to clarify why a combination is helpful, what are the mechanisms involved. Similarly, studies around the benefits of desiccated thyroid medication have been poor, and there is no research confirming any risks. I would therefore ask that the guidelines include reference to the need for more research. I note that the guidelines state '*There was no clinically important difference across the outcomes of depression and symptom scores for this comparison. No TSH suppression was evident in participants treated with natural thyroid extract or levothyroxine. There was consensus among Committee members that there was insufficient evidence to recommend natural thyroid extract, especially given its status as an unlicensed medication in the UK. The Committee also agreed that, in the absence of clear harm, there was insufficient evidence to make a strong recommendation against the use of natural thyroid extract.*' I interpret this as meaning that a doctor cannot refuse to prescribe the natural thyroid medication on grounds that it is harmful. Given that there is a	Thank you for your comment. The committee agree that further research is needed and have made a recommendation for research in this area. The committee has not made a recommendation for research related to natural thyroid extracts as these are not licensed for use in the UK. NICE cannot make a research recommendation if a product is not licensed.

				lack of research, and given its relative cost-effectiveness in comparison to T3, there is an argument that for some patients the option to try the desiccated product should be permitted. If, under review, the medical practitioner does not feel that there are sufficient differences, he or she is then justified in refusing the continue to prescribe. If, however, the medical practitioner's view is that the patient is experiencing highly evident benefits, then the above recommendation regarding insufficient evidence of harm comes into play. The patient is then in the position of having to make a choice, given the unknown risks, and the medical practitioner has an opportunity to contribute to research. To summarise, I feel that prescription of desiccated medication should be an option for some people to trial, through discussion with doctor, and outcomes monitored and recorded, in the same way that some patients respond to combination T3 and T4. I feel this point, plus that last sentence of the above recommendation, should be included in the main body of the guidelines in an explicit manner.	
British Thyroid Foundation	Guideline	9	17 - 19	We are aware that there are some patients who do not feel well on synthetic T4 or T3 and are prescribed natural thyroid extract by their NHS GP or endocrinologist. Whilst it shouldn't be offered as a first line treatment (due to cost) there is a small number of patients who fail to respond to synthetic hormone. NDT has been prescribed continuously for over a century, long enough for physicians to decide whether it has long-term adverse effects. If there are concerns about T3 / T4 ratios combined NDT / levothyroxine therapy should be recommended.	Thank you for your comment. The committee recommended against the use of natural thyroid extracts because there was no evidence of benefit over levothyroxine, they are not licensed for use in the UK and the committee was concerned about unknown adverse effects because of the high proportion of T3 to T4 in them. The guideline recommendations relate to people newly diagnosed with hypothyroidism rather than those already receiving treatment. The committee has not made recommendations on withdrawing treatment as it did not review the evidence in this area.

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British Thyroid Foundation	Guideline	10	1 - 7	I am concerned that this could lead to people with a partially functioning thyroid being over-treated (and hence thyrotoxicosis) since titrating down from over-treatment may lead to worse and more risky symptoms than titrating upwards especially perhaps if much of their weight is from fluid retention. Despite having a TSH of over 100 and an almost nowhere Free T4 at diagnosis my final dose is 28 mcg less than your predicted figure on my then-body weight would have been. My final dose is far closer (it is still lower, but 12 mcg lower) than this prediction gives for my current body weight. It's more complex than a straight 1.6mcg per kg. Perhaps a more conservative starting point would pose less risk to those with some remaining thyroid function while still giving benefit from a higher starting dose.	Thank you for your comment. The committee made the recommendation because of concern that a lot of patients have been left on a low dose of levothyroxine and feel unwell. However, they agree it may not be appropriate for all people and consequently made a weaker 'consider' recommendation to reflect that a clinician needs to decide whether this is an appropriate starting dose.
British Thyroid Foundation	Guideline	10	2 - 4	In cases where patients are diagnosed with a very high TSH we understand that the L-T4 should be initiated at a low dose and gradually titrated upwards. Should this practice point be added to the guideline?	Thank you for your comment. The committee made the recommendation because of concern that a lot of patients have been left on a low dose of levothyroxine and feel unwell. However, they agree it may not be appropriate for all people and consequently made a weaker 'consider' recommendation to reflect that a clinician needs to decide whether this is an appropriate starting dose. The recommendation has been edited to state "Consider starting levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight per day (rounded to the nearest 25 micrograms) for adults under 65 with primary hypothyroidism and no history of cardiovascular disease
British Thyroid Foundation	Guideline	10	9 - 19	I am concerned that this section may be interpreted as 'only test 6 months after starting or adjusting dose', or 3 months at best. In my own case it took 18 months to get my TSH and free t4 into the right place and symptoms to start to resolve. This was despite testing 8 weeks after dose start/ a dose change	Thank you for your comment. We have amended the first recommendation (1.4.1) to state "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms

				which is within the 6-8 weeks check of current guidelines. In the meantime symptoms continued to cause significant quality of life issues including job loss. Testing 3 or 6 months after a dose change would have caused even longer delays in finally being treated properly along with the attendant personal and NHS costs of treating symptoms. There is insufficient guidance on titration, adjustment and testing after dose changes including the use of different doses on different days to prevent over- or under- medication. There is also insufficient guidance on the possible role of fillers in levothyroxine medication (e.g. lactose) and the potential implications for patients who are switched between generics e.g. treating it as a dose change.	persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing." The recommendations are based on the appropriate advice for the majority of patients rather than all scenarios. Generally, 3 monthly testing is appropriate for most people and we recommend 3 monthly testing until there is stabilisation of thyroid function. Because of the long half-life of TSH (7 days) more frequent testing is not indicated in most people. With regard to dose titration the committee propose to start at the full replacement dose in most (1.6.mcg/kg) and to then monitor thyroid function on a 3 monthly basis which again is suitable for most people aged under 65 with no cardiovascular history. We did not find any evidence that more regular thyroid function testing would be appropriate The committee did not assess the evidence of the impact of "fillers" or different levothyroxine preparations on outcomes so cannot make specific recommendations here.
British Thyroid Foundation	Guideline	10	10	There are several references to using the TSH reference range as a diagnostic range or a therapeutic target. There is no evidence base for these statements. Many patients who have a TSH within the reference interval are hypothyroid. Some patients require a low TSH to resolve signs and symptoms of hypothyroidism. Some patients have a very narrow therapeutic range within the TSH reference interval. There is no evidence that biochemistry reflects clinical presentation in all cases. The guidance should assert the superiority of clinical response over biochemistry. Serum is the intermediate space; it does not	Thank you for your comment. We have amended the first recommendation (1.4.1) to state "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing."

				consistently reflect intracellular hormone status. We need some good science.	
British Thyroid Foundation	Guideline	10	17 - 19	Please consider adding in guidance about the importance of careful monitoring and dose possible dose adjustments during the pregnancy period.	Thank you for your comment. The guideline does not cover managing thyroid disease in pregnancy.
British Thyroid Foundation	Guideline	10	21 - 25	I would like to see full ranges tested.	Thank you for your comment. TSH and FT4 are recommended. The committee noted that FT3 measurements are not useful in managing hypothyroidism as T3 is a short acting hormone and measurements will be very different on different days.
British Thyroid Foundation	Guideline	11	3 - 13	I would like to see full ranges tested.	Thank you for your comment. TSH and FT4 are recommended. The committee noted that FT3 measurements are not useful in managing hypothyroidism as T3 is a short acting hormone and measurements will be very different on different days.
British Thyroid Foundation	Guideline	11	10 - 13	I am concerned that this will be interpreted as 'do not measure Free T4' especially when combined with other implications that a patient's symptoms are unlikely to be hypothyroidism. In addition, some local laboratories refuse requests to measure Free T4 even when the doctor requests it. Elsewhere in the guidance you recommend against measuring free T4 (see comment 13). Local CCGs may interpret these when taken together as 'never measure free T4' thus entirely missing pituitary or hypothalamus dysfunction. Finally, Free T4 is likely to give a faster response than TSH when assessing the results of a dose change: this is also why Free T4 is sometimes used to indicate patient compliance.	Thank you for your comment. No evidence was identified for FT4 testing. The committee noted that in some situations when people have symptoms there may be benefit of FT4. The committee was also concerned that in some cases monitoring FT4 during treatment may cause harm as healthcare professionals may inappropriately titrate levothyroxine to the FT4 level. The consider recommendation reflects the uncertainty.
British Thyroid Foundation	Guideline	11	14	One member comments that the term '*subclinical hypothyroidism*' is misleading and confusing. Some patients have severe signs and symptoms with a mildly elevated TSH whilst others are asymptomatic with a TSH > 10.0 mU/L. An alternative term would be '*elevated TSH*', which is easy to understand and makes no assumptions.	Thank you for your comment. The committee believe subclinical hypothyroidism is the commonly used terminology and was the term used in the scope for the guideline. Consequently, this has stayed the same.

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British Thyroid Foundation	Guideline	11	16 - 18	I would like to see the guidelines give more importance to discussion with the patient on levels of treatment when TSH and T4 are borderline. This is because in my own case I am experiencing hypothyroidism symptoms with TSH right on the lowest end of the reference range (a range I have cobbled together for myself from various sources). Yet, following my annual blood test, my GP simply left a message to say the test was satisfactory and to carry on with the same dose.	Thank you for your comment. The committee could not make recommendations to cover all scenarios. This recommendation has been edited to encompass your point and now includes reference to symptoms: “When discussing whether or not to start treatment for subclinical hypothyroidism, take into account features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous radioactive iodine treatment or thyroid surgery, or raised levels of thyroid autoantibodies.”
British Thyroid Foundation	Guideline	13	4 - 11	I would like the patient to be made more aware of how much lifestyle, diet and stress can have an effect and for it to be added here. And the guideline could pick up on the wider support for this. For example, craft sessions, food vouchers, tai chi classes are all now on offer to support chronic pain and depression through doctors’ notes and referrals but opportunities for this kind of support is not well known or discussed at appointments for patients with thyroid disease. This additional support/signposting could prevent the need for further prescriptions e.g. antidepressants.	Thank you for your comment. Lifestyle and diet were excluded from the scope of the guideline and therefore no recommendations have been made.
British Thyroid Association	Guideline	14 - 20		Section 1.6—1.7 The committee makes no specific recommendation on therapeutic targets in the management of overt hyperthyroidism. Uncorrected hyperthyroidism carries an increased risk of cardiovascular morbidity and mortality. Three cohort studies have investigated the association between long-term mortality and thyroid status in treated patients with overt hyperthyroidism. In the first study, mortality was increased per cumulative six-month period of low TSH (Lillevang-Johansen 2017) while the second study showed a positive association between serial FT4 concentrations and risk of death (Boelaert 2013). In the third study, patients with persistently low	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The specific therapeutic target in the management of overt hyperthyroidism was not an area prioritised in scoping and therefore the committee did not review the evidence in this area and are unable to make recommendations.

				TSH concentration one year after the diagnosis of Graves' disease had a higher mortality than those with normal TSH independent of therapy modality (Okosieme 2019). These studies reiterate the adverse consequences of cumulative hyperthyroidism exposure and underpin the importance of maintaining a normal thyroid status throughout the duration of treatment. While this may seem instinctively obvious it is not always achieved in practice and we suggest that rapid correction of hyperthyroidism and maintenance of a euthyroid state is recommended as a specific therapeutic goal in treating hyperthyroidism. **References** [1] Boelaert K, Maisonneuve P, Torlinska B, et al. Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. J Clin Endocrinol Metab 2013; 98: 1869-82. [2] Lillevang-Johansen M, Abrahamsen B, Jorgensen HL, et al. Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. J Clin Endocrinol Metab 2017. [3] Okosieme OE, Taylor PN, Evans C, *et al*. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. Lancet Diabetes Endocrinol. 2019 Apr;7(4):278-287	
British Thyroid Foundation	Guideline	15	10	It is reasonable to offer Graves' patients a choice between RAI and surgery. A minority of patients report life-changing consequences of RAI, and feel that they never recover a normal life. Recommending RAI as first line treatment conflicts with the recommendation for research number 4 '*Long-term effectiveness and safety of radioactive iodine therapy*'. NDT and RAI have a similar evidence base; NDT therapy can be	Thank you for your comment. This choice is included as part of our recommendations. The recommendations aim to advise on the most appropriate treatment options for different patients. Where there is more than one option this has been made clear in the recommendation.

				stopped; RAI is definitive and has known cases of adverse outcome. A more balanced and rational approach to the two therapies is required. We do not understand why a small group of patients do so badly after RAI treatment, but it is reasonable to keep all options open. From a physics point of view, it seems irrational to use a systemic therapy to treat a single diseased organ. Whilst most iodine accumulates in the thyroid radioactive T3 molecules attach to receptors and DNA response elements, a few atoms away from the DNA. Most cells can regenerate, except brain cells. We might expect cognitive impairment in patients receiving large doses of RAI. More caution should be exercised when recommending RAI treatment, until its consequences are understood, and safer RAI protocols are available. For these reasons I feel patients should be offered an informed choice between RAI or surgery.	The research recommendations are aimed to supplement these. The committee believe it is important to find out which subgroup of people with Graves' disease do well on antithyroid drugs because in their experience approximately 50% of people who start antithyroid drugs end up having RAI or surgery as drugs only provide temporary relief. This group may get side effects with the drugs and they do not have a realistic prospect of curing thyrotoxicosis. Equally the committee believed it important to monitor the long term effects of radioactive iodine and have made a recommendation for research in this area.
British Thyroid Association	Guideline	15	10 - 21	Section 1.6.8-1.6.9. The guideline recommends that patients with Graves' disease should be offered radioactive iodine as first line therapy except where there are concerns about compression or malignancy; or in patients who are pregnant, trying to become pregnant or father a child; patients with active thyroid eye disease; or patients with mild uncomplicated disease (1.6.8-1.6.9). However, there is no specific mention of patient preference in these recommendations. Although a generic disclaimer acknowledging patient autonomy is stated in evidence-review I (page 3), we suggest that patient preference is also included in the list of exceptions for recommendation 1.6.8-1.6.9. Patient choice is particularly relevant to Graves' disease treatment considering the differences in treatment options. Individuals who place a high value on avoiding lifelong thyroxine therapy may prefer antithyroid drugs. Although the	Thank you for your comment. The recommendations give the most appropriate treatment options to offer or consider for patients. Where there is a choice this is noted in the recommendation. The recommendations also advise what to offer when a treatment option is not appropriate. It is hoped that the discussion on risks and benefits with the person will establish which treatment they choose. The study was published after the cut-off for our search and was therefore not included in the guideline.

				recommendation in its current form would suggest that such a choice is inferior to radioiodine, the reality is more nuanced. An observational study of over 4000 well-characterised patients with Graves' disease showed that survival was associated with early and effective correction of hyperthyroidism regardless of therapy modality (Okosieme 2019). Thus, individuals who opt for antithyroid drugs should be reassured that their preference is valid and that optimal outcomes can be realised with effective hyperthyroidism control regardless of choice of therapy. **References** [1] Okosieme OE, Taylor PN, Evans C, *et al*. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. Lancet Diabetes Endocrinol. 2019 Apr;7(4):278-287.	
British Thyroid Foundation	Guideline	18	13 - 14	Should the guideline also state that where patients develop liver dysfunction they should also stop ATDs immediately and not restart them? i.e. not just have this advice in respect of agranulocytosis.	Thank you for your comment. The guideline recommends that liver function should be checked before starting treatment. Monitoring liver function was not included as a recommendation. The committee agreed that if liver dysfunction develops following the start of treatment it will be clinically obvious and assumed that the treating physician will take appropriate action including the discontinuation of antithyroid drugs if required.
British Thyroid Foundation	Guideline	19	26 - 28	Clarity of information is essential in this issue as we hear from patients who struggle to get to see a doctor post thyroidectomy and do not seem to have been made aware of the importance of TFTs or that L-T4 may need initiating. Verbal and written importance should be given to patients before the operation so they are well prepared.	Thank you for your comment. This has been amended to recommend measuring TSH and FT4 at 2 and 6 months post-surgery, then TSH annually. If TSH is below the reference range FT4 (if not already measured) and FT3 should also be measured.
British Thyroid Foundation	Guideline	20	4	We note there is no mention of the benefit of testing TRAb levels as a possible indicator as to when to stop antithyroid drugs. Yet one member advises us that this appears to be a debated issue in the care of her teenage child.	Thank you for your comment. No evidence was identified for retesting TRAb levels and the committee felt unable to recommend that this be done routinely.

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British Thyroid Foundation	Guideline	25	6	This section (Long-term effectiveness and safety of radioactive iodine therapy) should include the development of regimes to minimise the side effects (eg optimal combination with short term antithyroid drugs) including radiation thyroiditis, post-I-131 hypothyroidism, weight gain and thyroid eye disease.	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
British Thyroid Association	Guideline	25	20 - 22	*Other recommendations for research* *7 Levothyroxine for subclinical hypothyroidism in people under 65* *What is the clinical and cost effectiveness of T4 for people under 65 with symptomatic subclinical hypothyroidism?* The research recommendation on subclinical hypothyroidism is mentioned under “other recommendations for research”. However, we believe that this should merit a key research recommendation. Subclinical hypothyroidism affects over half a million people in the UK and is more prevalent than subclinical hyperthyroidism which the committee categorises as a key research priority. Only one large prospective RCT of Levothyroxine has been conducted in patients with subclinical hypothyroidism and this study was limited to the elderly (Stott, 2017). Meta-analysis of observational studies suggest that the greatest benefit would be in the under 65 age group (Razvi 2012). The committee’s recommendations on levothyroxine for subclinical hypothyroidism in people under 65 years represents a balanced position (section 1.5.2) consistent with the guidelines of professional endocrine associations (Jonklaas 2014). A recent BMJ Clinical Practice guideline however strongly recommends against treating subclinical hypothyroidism in adults >30 years except in severely symptomatic patients, women trying to become pregnant, or patients with TSH >20	Thank you for your comment. The committee agreed that this was an important area for further research. However, on advice from NIHR, the presence of a number of pre-existing studies in the area (even if insufficient to base strong recommendations), means that it was not prioritised as one of the limited key research recommendations for the guideline.

				mU/L (Bekkering 2019). In response to this a joint statement by the British Thyroid Association and the Society for Endocrinology have highlighted that a 20 mU/L threshold for treatment may be too stringent and is not supported by the current evidence from RCTs and would ultimately deny treatment to individuals with intrinsic thyroid disease. These ongoing controversies underpin the pressing need for high-quality trials in this area and we suggest that this is reflected in the key research recommendations. **References** [1] Stott DJ, Rodondi N, Kearney PM, Ford I, et al; TRUST Study Group. Thyroid Hormone Therapy for Older Adults with Subclinical Hypothyroidism. N Engl J Med. 2017; 376: 2534-2544. [2] Razvi S, Weaver JU, Butler TJ, Pearce SH. Levothyroxine treatment of subclinical hypothyroidism, fatal and nonfatal cardiovascular events, and mortality. Arch Intern Med. 2012; 172:811-7. [3] Jonklaas J, Bianco AC, Bauer AJ, et al. American Thyroid Association Task Force on Thyroid Hormone Replacement. Guidelines for the treatment of hypothyroidism: prepared by the American Thyroid Association task force on thyroid hormone replacement. Thyroid. 2014; 24:1670-751. [4] Bekkering GE, Agoritsas T, Lytvyn L, et al. Thyroid hormones treatment for subclinical hypothyroidism: a clinical practice guideline. BMJ. 2019;365: l2006. [5] https://www.endocrinology.org/press/press-releases/society-for-endocrinology-british-thyroid-association-issue-statement-against-new-treatment-recommendations-for-subclinical-hypothyroidism/	

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British Thyroid Foundation	Guideline	26	18 - 22	It is also important that parents are given appropriate information to pass on to schools since there is often a poor understanding of how thyroid disorders (especially when newly diagnosed or poorly managed) can impact on a child or young person's behaviour or performance at school. This may be particularly important around exam time.	Thank you for your comment. We anticipate that parents will be given appropriate information about their child's condition and can liaise with the school. It is beyond the remit of this guideline to recommend how information should be given to schools.
British Thyroid Foundation	Guideline	30	18 - 19	We welcome the recommendation for more research in this area to help inform future guidance. The research into combined levothyroxine / liothyronine therapy isn't strong. Half the studies substitute L-T3 for L-T4 in a 1:4 or 1:5 ratio based on their relative serum potency. Of course, the ratio patients swallow is not reflected in the blood, due to different absorption rates and elimination half-lives. Researchers should have an elementary understanding of pharmacokinetics! All the studies fail to select appropriate cohorts – patients who fail to do well on levothyroxine. None of the studies attempted to determine the L-T3 dose patients required. The researchers decree that the patients must suffer from primary hypothyroidism (and no other form of hypothyroidism) and this must be corrected by small amounts of L-T3, contrary to clinical experience. Demanding patients respond according to unproven theory is bad science.	Thank you for your comment, the committee agree that further research is important.
British Thyroid Foundation	Guideline	30	25 - 28	In cases of people who may have gone undiagnosed for some time and who may have a very high TSH we understand that they should be initiated on a low dose initially and titrated upwards cautiously. Should this point be included in the guideline?	Thank you for your comment. The recommendation is intended to cover the majority of people and not every scenario. It is anticipated that clinicians will use their judgment on a case by case basis as to whether the recommendation is appropriate for each patient.
Coeliac UK	Guideline	General	General	The NICE guideline for recognition, assessment and management of coeliac disease, NG20 includes a relevant recommendation (1.1.1) to offer serological testing to people with autoimmune thyroid disease, at diagnosis. The rationale for this recommendation is the higher prevalence of coeliac	Thank you for your comment. We have amended the guideline to cross-refer to the recommendations in NG20 on testing for coeliac disease in people with diagnosed autoimmune thyroid disease as you suggest.A

				disease in people with autoimmune thyroid disease (1.5 – 3.8%) [1] compared to 1% in the general population [2]. This recommendation is not reflected in the draft guideline for thyroid disease. The guideline should be updated to reflect the recommendation in NG20 to ensure that diagnosis of coeliac disease is not missed. Coeliac disease affects 1 in 100 people [2] but in the UK only 30% are diagnosed [3]. In line with NG20, healthcare professionals and patients should be aware that investigations for coeliac disease are only accurate if a gluten-containing diet is eaten during the diagnostic process [1]. It is essential that consistent messaging around diagnosis of coeliac disease is provided across NICE guidelines. [1] National Institute of Health and Care Excellence, Clinical Guideline NG20, Coeliac Disease Recognition, Assessment and Management, September 2015 [2] Bingley, P.J., Norcross, A.J., Lock, R.J., Ness, A.R. and Jones, R.W., 2004. Undiagnosed coeliac disease at age seven: population based prospective birth cohort study. BMJ, [online] 328(7435), pp.322–323. [3] West, J., Otete, H., Sultan, A.A. and Crooks, C.J., 2019. Changes in Testing for and Incidence of Celiac Disease in the United Kingdom. Epidemiology, [online] 30(4), pp.e23–e24.	
Diabetes UK	Guideline	7	18	We agree with the recommendation to routinely test for thyroid dysfunction for people living with Type 1 diabetes and suggest that this section recommends that this is done annually, as per recommendations in section 1.15.40 of NG17 on *Type 1 diabetes in adults: diagnosis and management.* https://www.nice.org.uk/guidance/ng17/chapter/1-Recommendations	Thank you for your comment. As routine testing for thyroid dysfunction in people with type 1 diabetes is already covered by NG17 we would not repeat this recommendation in this guideline. This section of the guideline is to test for thyroid dysfunction when people present with suspected thyroid disease and is not related to routine testing.
Diabetes UK	Guideline	8	3 - 4	While we agree that people living with Type 2 diabetes do not necessarily need to be routinely tested for thyroid dysfunction,	Thank you for your comment and for providing this reference. The information highlighted in this article is

				we suggest that these recommendations should highlight the connection between thyroid dysfunction and raised blood glucose level for people living with both Type 1 and Type 2 diabetes. Rebecca J Ward, Adrian H Heald, Seyi Ogunmekan, Anthony A Fryer and Christopher J Duff; *Should we be screening for thyroid dysfunction in patients with type 2 diabetes mellitus?*; British Journal of General Practice 2018; 68 (667): 94-95. DOI: https://doi.org/10.3399/bjgp18X694793	not sufficient to support testing of people with type 2 diabetes, in agreement with what you state. Evidence from cross-sectional studies meeting our protocol inclusion criteria showed that type 2 diabetes is not associated with thyroid dysfunction and the committee concluded that thyroid function tests should not be performed solely because a person has this condition. Nevertheless, the link between type 1 diabetes and thyroid dysfunction is highlighted in the recommendation to offer tests for thyroid dysfunction in adults, children and young people with this condition (1.2.2), but since the recommendations provide advice on what to do rather than stating the evidence, the connection between thyroid dysfunction and diabetes cannot be highlighted further.
ENT UK	Algorithm on Hyperthyroidism (Supporting Documentation - Hyperthyroidism in adults: management and monitoring)	General	General	Please review the radioiodine and surgery boxes – it would be clearer if the exclusions noted in the radioiodine box could be added to the surgery box ie add Thyroid Eye Disease, Pregnancy, Malignancy. Patient Choice should also be included in the surgery box as some patients do not wish radioiodine.	Thank you for your comment. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been included in the recommendation on providing information to people with thyrotoxicosis.
ENT UK	Evidence Review K	11 12	38 - 44 1 - 8	It should be clarified that hemithyroidectomy is an option for solitary toxic nodule but NOT for Graves disease	Thank you for your comment. Your statement is reflected in the recommendations themselves.
ENT UK	Evidence Review O	12	27 - 31	There will be patients where there is an increased risk of malignancy and where FNAC is required despite U2 ultrasound findings as stated in the BTA 2014 guidelines. It should be made clear that there may be occasions when it is appropriate it undertake for a U2 nodule	Thank you for your comment. This information was used to inform the model and is not a recommendation. The guideline does not recommend a specific grading system and therefore also does not recommend specific cut-offs on any one grading system.
ENT UK	Evidence Review O	General	General	It is very important that thyroid ultrasounds include a full relevant dataset. Our members report that this is often not the case leading to repeat ultrasounds needing to be performed delaying decision making and adding to cost of diagnosis. This	Thank you for your comment. The committee considered the level of detail that was appropriate to specify in their recommendations based on the evidence available and the criteria assessed. The detail you suggest is greater

				has also been shown in a number of local audits presents at national meetings. We would therefore request that there is a statement that all thyroid ultrasound reports should include a full relevant dataset with information to include size of left and right lobes of thyroid, position, size and 'U' category of any nodules and comment on the presence or absence of pathological cervical lymph nodes.	than they agreed was appropriate and references the U classification specifically.
ENT UK	Supporting Documentation - Hyperthyroidism in adults: management and monitoring	General	General	Whilst this shows a flow chart of treatment options it could be clearer including information on what medication to start, and precautions required with antithyroid drugs.	Thank you for your comment. The visual summary only focuses on the key points from the recommendations. More information related to the use of antithyroid drugs can be found in the recommendations and evidence review.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	15	10 1.6.8	We have serious concerns and disagree that radioiodine treatment should be offered as the first line treatment in Graves' thyrotoxicosis. This is not currently standard practice in the UK. The points from our discussions in this area are as follows; "Thyrotoxicosis must be controlled pre RAI -thus ATD's are needed, Increased burden to Nuclear Medicine Service, GP's likely to refer to NM if RAI is documented as first line, Risk of patients with thyroiditis being ablated, Population predominantly women of child bearing age with young children therefore RAI not suitable, Cancer risk ambiguous: "no clinically important increased risk of cancer from RAI, RAI can exacerbate TED". Specifically the guidance does not emphasise that ATD treatment is associated with significant long-term remission for approx. 50% of GD patients. RAI treatment results in permanent hypothyroidism in the majority (at GSTT 80%) of patients treated with 6000 mBq. Patients with severe thyrotoxicosis due to Graves' disease cannot safely be given primary RAI. They must have medical treatment to reduce the risk of crisis with RAI, therefore RAI is not primary treatment. All patients should be offered ATD as there is a chance of remission. The guidance does not define	Thank you for your comment. The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore, the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options. The committee believe approximately 50% of people who start antithyroid drugs end up having RAI or surgery as drugs only provide temporary relief. This group may get side effects with the drugs and they do not have a realistic prospect of curing thyrotoxicosis.

				'mild, uncomplicated GD', and there are no consistent predictors of remissions or a reliable model. It is our view (and we believe the representative view) that ATDs are first line treatment for GD. There are considerable risks and consequences to recommending RAI as first line and we encourage the committee to re-consider with a more balanced recommendation. Many new patients with GD are women of child-bearing age. To recommend a first-line treatment that is unsuitable or unwanted by many patients will de-value the guidance.	The committee also recommend antithyroid drugs while patients wait to be seen by a specialist, and has added a recommendation to offer antithyroid drugs to stabilise hyperthyroidism for people waiting for treatment with radioactive iodine and surgery
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	18	13 1.6.24	Stop when patient develops agranulocytosis. The guidance must be clearer here. The evidence that agranulocytosis will develop with PTU once having occurred with carbimazole is not clear. Many experienced clinicians have used alternative thionamide successfully, usually as a bridge to thyroid surgery in this circumstance and I think the guidance is duty bound to provide an alternative suggestion. This could be, manage with KI or Lugols and consider thyroidectomy. It is unreasonable to make a statement and offer no alternative.	Thank you for your comment. Most guidelines recommend that antithyroid drugs should not be restarted after agranulocytosis has developed. Whilst this may have been successfully employed in some specialist settings the committee felt it would be unsafe to recommend restarting in a non-specialist setting. Similarly, the options of thyroidectomy or lugols iodine are specialist management and the guideline did not cover this. We have added a clause to the end of the recommendation about considering referral to a specialist for further management.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	37		"How the recommendations might affect practice". The description is extremely limited and does not acknowledge the practical barriers to administration (majority of patients being female, of child bearing age and/or may have carer responsibilities) or the implications to nuclear medicine services.	Thank you for your comment. This section of the guideline is meant to describe overall resource impacts and not the level of granularity that you highlight. Further information can be found in the committee's discussion in the evidence review chapters.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	4	12	'Even when thyroid function tests are in the normal range…' This is an ambiguous statement that will potentially lead to patients seeking thyroid treatment without evidence of disease. It would best to clarify, titrating thyroid replacement to ensure maximum well-being and normalised biochemistry is appropriate for individuals with treated hypothyroidism	Thank you for your comment. We have reworded this to state "Even when there are no symptoms, treatment may be recommended to reduce the risk of long-term complications." The purpose of the recommendation is to inform people who have been diagnosed with thyroid

					disease that even if they feel well treatment may be advisable.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	49	10	Treatment with radioactive iodine requires HCP to follow the IR(MER)17 regulations – there is a link at the bottom of page 49 below line 21 . Comment: Regulation 12 (2) of this IRMER17 requires the practitioner (ARSAC licence holder) to ensure that all therapeutic exposures are individually planned and verified … Accepting there is no evidence for the choice of treatment using radioiodine by either dose (Gy)by dosimetry(radiotherapy planning) or the use of fixed activities (MBq) and that fixed activities (out -patient <800MBq) is accepted practice in the UK, there is still a legal requirement to verify the radiation dose to the thyroid is optimal and the non-target volumes and tissues are as low as reasonable practicable and as intended. Taking that fixed activities are acceptable pre- treatment imaging of the thyroid with 99mTc-pertechnetate provide acceptable evidence of uptake of ^{131}I-iodide and is acceptable to comply with the regulatory requirement to verify the radiation dose targets the thyroid as expected. If there is no pre-treatment imaging with an appropriate radiopharmaceutical there is no evidence that the treatment radiopharmaceutical targets the thyroid.	Thank you for your comment. Each recommendation including radioactive iodine also includes a footnote advising healthcare professionals to follow the regulations on medical exposure to ionisation radiation.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	6	Table 1	ATD column "Small chance of not needing thyroid medicines in the long term" and "small risk of birth defects if CBZ is taken in pregnancy" The wording implies incorrectly that this "chance" and "risks" are numerically comparable. The respective percentages should be clearly documented.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	9	5	The terms lack accuracy. TRAb, not TRAbs; TPOAb not TPOAbs.	Thank you for your comment. The committee believe using TRABs and TPOAbs would be more accurate.

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Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	9	14	The line about liothyronine will be subject to variable interpretation. More clear guidance is required. We have concerns that the word routine, means that many patients and clinicians will consider the situation non-routine. Why not be clear- Levothyroxine is the first line treatment for patients with hypothyroidism in the UK. Use of liothyronine is controversial, expensive and potentially harmful. Clinical trials of T4/T3 have produced inconsistent findings with respect to benefit. The NICE panel recommends levothyroxine alone. In exceptional individual cases the patient preference may be to try T3 in addition. This can be considered but without obligation for the NHS to prescribe the T3 whilst costs are high, and the evidence case for benefit limited.	Thank you for your comment. The committee have used the phrase do not offer routinely, liothyronine to reflect that most people will not be considered for liothyronine. The committee agreed that it is plausible in some people who are not responding to levothyroxine that liothyronine may be beneficial either alone or in combination and that its use is controversial, expensive and potentially harmful. They agreed in the absence of evidence and because of the high list price of liothyronine it could not be recommended as first-line treatment but that it should also not be completely excluded. The recommendation is written to reflect this.
Guy's & St Thomas' NHS Foundation Trust/King's College Hospital	Guideline	General	General	No mention of assay issues leading to misleading thyroid test results. 2. Inconsistent use of full stops at the end of statements throughout the document. Needs consistency in this regard. 3. The Guidance may benefit from a brief introduction clarifying the nature of the HPT axis, and the role of autoimmunity in thyroid disorders, emphasising disorders or thyroid function, and development of thyroid nodular enlargement. Explicit definition of primary and secondary hypothyroidism is required. Clarification that pregnancy outside the scope at the beginning. No mention of symptom control, or management of severe life threatening thyrotoxicosis. No mention of management of atrial fibrillation in thyrotoxicosis or drug induced thyroid disorders.	Thank you for your comment. We agree that interpretation of thyroid test results may be difficult depending on the assay used but we did not review the evidence and were unable to make recommendations. We have edited the document to remove any inconsistencies. Recommendation 1.6.6 on considering antithyroid drugs along with supporting treatment for adults with hyperthyroidism covers symptom control while people are waiting for the assessment and discussion on their definitive treatment. Management of co-existing conditions is beyond the breadth of topics that could be considered within the scope of this guideline. Atrial fibrillation and drug-

					induced thyroid disorders were excluded from the scope of the guideline.
Hyperparathyroid UK Action4Change	Evidence Review A	5	16 - 18	We are concerned that whilst recommending both patient groups; British Thyroid Foundation and Thyroid UK here, many of your recommendations contradict theirs.	Thank you for your comment. This guideline makes recommendations in specific areas of thyroid disease using best available clinical and cost effectiveness evidence. The guideline however is not a text book and we understand the value of patient organisations in providing information and support to people with thyroid disorders.
Hyperparathyroid UK Action4Change	Evidence Review A	7	2	Table 2: Summary of studies included in the review. This table lists 3 studies used for evidence. The first was 27 patients, the second was Health professionals from general practice and community pharmacies comprising 9 GPs, 4 pharmacists, 2 practice nurses and 1 nurse practitioner, and the third was 18 patients aged 80 and over with a diagnosis of primary hypothyroidism. So your studies were based on the experience of 45 patients in total? That is quite astonishing. Why didn't you use the information from a study compiled by Thyroid UK with thousands of responses from people aged 18-60+? The full survey results are available as Appendix E on their website; Thyroid UK, Hypothyroid Patient Experience Survey 2015: http://thyroiduk.org.uk/tuk/TUK_PDFs/patient-experience-survey/Appendix%20E%20-%20Full%20Survey%20Results.pdf	Thank you for your comment and evidence you provide. According to our review protocol, qualitative interview and focus group studies were prioritised for inclusion. Since these were available we did not look at quantitative/survey data from questionnaires/surveys as it had been pre-specified (Appendix A: Review protocol). As a result we could not use this information.
Hyperparathyroid UK Action4Change	Evidence review B	16	12	Table 11: UK costs of thyroid tests; We were surprised to see the cost of FT3 is only £3.12 considering the number of doctors who refuse to test it using cost as a reason. We assume their reason would be the cost of prescribing it for those with a low FT3, but surely it is better for the patient to know the result?	Thank you for your comment. The costs presented are average costs from five NHS hospitals and not exact costs. The guideline outlines the cascade approach in testing which highlights the need for testing in a synchronised strategy.

				We feel certain for the cost to the patient of £3.12, many would prefer to pay for it than not have it tested.	The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is, if TSH is above the reference range measuring FT4 in the same sample and if TSH is below the reference range measuring FT3 in the same sample. The committee agreed that this approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
Hyperparathyroid UK Action4Change	Evidence Review B	19	11 - 12	We would recommend adding primary hyperparathyroidism before or after auto immune disease as there is also a high association to thyroid disease.	Thank you for your comment. There are a range of autoimmune conditions that could be listed as examples here and the committee did not consider it appropriate to single out specific examples.
Hyperparathyroid UK Action4Change	Evidence Review B	5	15	Table 1: PICO characteristics of review question. We would recommend you add primary hyperparathyroidism to co-existing conditions. The new guideline was published 23 05 19: https://www.nice.org.uk/guidance/NG132	Thank you for your suggestion. The committee has deliberated extensively on potential co-existing conditions and is confident that the co-existing conditions listed in the protocol reflect the most significant ones that should be examined for recommendation making. This does not imply that there are no other co-existing conditions which may be associated with thyroid disease but that these were the specific markers where recommendations for or against testing could be most useful.
Hyperparathyroid UK Action4Change	Evidence Review C	5	18 - 22	*Your statement: However there are notable exceptions when serum TSH concentration alone 19 may not accurately reflect thyroid hormone production. This is most frequently encountered 20 when the homeostatic mechanism has been impaired by long standing primary thyroid 21 disease or the pituitary-thyroid axis has not reached equilibrium following changes to thyroid 22 therapy'; is indeed experienced by several of our members who have had hypothyroidism in*	Thank you for your comment. This section serves as a chapter introduction. The aim of the recommendations is to provide guidance to clinicians on the best clinical practice for the management of thyroid disease in the majority of people they are likely to encounter and cannot cover every possible scenario such as impaired homeostatic mechanisms. Clinical evidence regarding the benefits of liothyronine alone or in combination with levothyroxine was reviewed (Evidence review E) and it

				excess of 20 years, who have benefitted from addition of T3. It would be helpful to reference this in the guideline.	was not sufficient to recommend its routine use. However, the committee acknowledges that the addition liothyronine may be beneficial for some people and has made a recommendation for future research on the clinical and cost effectiveness of levothyroxine and liothyronine combination therapy compared to levothyroxine alone for people whose symptoms have not responded sufficiently to levothyroxine alone (Key recommendations for research 1).
Hyperparathyroid UK Action4Change	Evidence Review C	5	26 - 30	If this statement is true; *Most UK labs would advocate the 27 measurement of free thyroid hormones rather than total thyroid hormone (thyroid hormone 28 that is not bound to thyroid carrier proteins) as the best marker for biologically active 29 hormone. This avoids situations where variation in thyroid hormone binding proteins rather 30 than thyroid function per se is responsible for abnormal test results';* how can you get this message across to primary care so that patients don't have to fight for it?	Thank you for your comment. The recommendations made by the committee specify where measurement of FT4 and FT3 would be clinically appropriate in addition to TSH. We hope these help raise awareness in primary care and facilitate the diagnosis of thyroid dysfunction
Hyperparathyroid UK Action4Change	Evidence Review C	5	35	*'Many laboratories offer FT3 testing but this is not universally, available'* Yet we are all the same, so why should it be a postcode lottery? Can you not recommend this is made universal?	Thank you for your comment. The circumstances under which FT3 testing would be required for diagnosis have been specified in the recommendations. We hope these will raise awareness and improve diagnosis. The availability of FT3 testing in individual laboratories is outside the remit of the guideline.
Hyperparathyroid UK Action4Change	Evidence Review C	6	3 - 6	*'addition of FT4 and FT3 to the TFT represents a 4 considerable financial burden to the UK health economy'* We are concerned that not testing them represents a greater financial burden to the UK health economy as well as the Department of Work and Pensions for people with untreated hypothyroidism not being able to work.	The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below

					the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease. In addition, as reported in the Manual for developing NICE Guidelines (https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview), "productivity costs and costs borne by people using services and carers that are not reimbursed by the NHS or social services should not usually be included in any analyses". This is for different reasons, for example, time off work is implicitly incorporated in QALY. In addition, if we included productivity costs in our analyses, we would favour those interventions aimed at the working population and would discriminate against the elderly, children, unemployed people, and people with disabilities.
Hyperparathyroid UK Action4Change	Evidence Review C	7	24	*'The committee considered mortality and quality of life to be critical outcomes'.* We could not agree more that quality of life is a critical outcome, but your recommendation not to treat people unless their TSH is greater than 10 obliterates this statement (referring to page 11, lines 20-22)	Thank you for your comment. Assuming you refer to recommendation 1.5.3, please note that this refers to the treatment of adults with subclinical hypothyroidism and the committee is confident this reflects best practice for this particular group of people.
Hyperparathyroid UK Action4Change	Evidence Review C	7	24	I have tried dose changes myself to see if I can manage on a lower dose of levothyroxine. I dropped from 125mg to 112mg but quickly started struggling at work with complex problem solving. I could watch daytime TV on 112mg once I retire, but multi-generation family history research issues might not be possible. It is essential patients are treated as individuals by their doctors rather than a one dose suits all statistic. Treating people only according to their TSH level only does not take care of the quality of life you consider to be critical here.	Thank you for your comment. Please note that the aim of the current recommendations is not to introduce a one-size-fits-all approach to treatment but to provide guidance on the management of thyroid disease according to what constitutes best clinical practice. The committee recognises that the individuality of patients should always be taken into account in clinical practice and this guideline is not to replace clinical judgment in the management of patients on a case-by-case basis according to their individual characteristics and needs.
Hyperparathyroid UK Action4Change	Evidence Review D	5	6 - 15	We believe this should be referenced in the recommendations guideline: '*The commonest cause of hypothyroidism is*	Thank you for your suggestion. Please note that this section serves as an introduction to this chapter and its

				autoimmune thyroid disease, which is associated 7 with the presence of circulating thyroid antibodies. Therefore, tests for thyroid antibodies, 8 including TPO-Ab and TG-Ab, are useful to confirm autoimmunity as the cause in a patient 9 with hypothyroidism. Furthermore, in a patient with subclinical hypothyroidism, the presence 10 of thyroid antibodies (in particular, TPO-Ab) is associated with an increased risk of 11 progression to overt hypothyroidism. Despite the potential value of testing thyroid antibodies 12 in hypothyroidism, there is uncertainty in terms of which antibodies should be tested during 13 investigation for hypothyroidism, when should the test be carried out and should the test be 14 repeated. Currently, there is no national standard on the topic, resulting in a wide variation in 15 the clinical practice'	inclusion in the recommendations has not been considered necessary.
Hyperparathyroid UK Action4Change	Evidence Review E			Looking at Table 6 UK costs of hypothyroidism treatments, I would be happy to trade my combination of synthetic T3 and T4 for Natural Thyroid Extract, which contains T1 and T 2 as well. I was on this originally, but my GP later refused to prescribe it as it was an unlicensed medicine. Now they want to take away my T3/T4 mix that I was offered instead of the Natural thyroid Extract. I know I could buy the latter online myself, but I would rather have it prescribed/supplied by the NHS so that it is hopefully of a consistent quality.	Thank you for your comment. The guideline states that liothyronine should not be routinely prescribed as no clinically important difference was identified for health-related quality of life, between T4 and T4/T3. There was a clinically important harm of combined levothyroxine and liothyronine for quality of life-role physical functioning and TSH suppression. There was a clinically important benefit of combined levothyroxine and liothyronine for quality of life-social functioning and quality of life-role-emotional. Overall, the committee agreed that the evidence was generally suggestive of combined therapy having no important effect on quality of life and the small and contradictory benefits and harms in subdomains of quality of life were more likely to reflect the low quality of the underlying evidence. Discretion is available to healthcare professionals for individual patients.

					The committee agreed that the potential long-term adverse events of natural thyroid extract are not known, noting that it is currently unlicensed in the UK. They therefore agreed that it should not be offered as treatment.
Hyperparathyroid UK Action4Change	Evidence Review E	15	10	Table 6 It is obvious that liothyronine costs are extortionate but we also know they are available so cheaply outside the UK. It is imperative that the NHS source supplies outside of the UK to bring down the costs, in order to stop denying people treatment.	Thank you for your comment. Training and information on the possible ways to purchase medications are beyond the remit and scope of this guideline. This NICE guideline is written from the UK NHS and PSS perspective, and therefore only takes account of UK list prices and does not account for prices outside the UK.
Hyperparathyroid UK Action4Change	Evidence Review E	16	29 - 30	*Mortality and quality of life were agreed by the Committee to be the critical outcomes for this review. We feel you should keep this sentence in mind before publishing this review. We agree with it but don't feel it reading through your recommendation.*	Thank you for your comment. The committee kept both these outcomes in mind when making the recommendations for managing primary hypothyroidism. We found no evidence relating to mortality and the evidence relating to quality of life outcomes did not reach thresholds for significance.
Hyperparathyroid UK Action4Change	Guideline	11	16 - 18	Your recommendation here of considering treatment for raised levels of thyroid antibodies reinforces our comments on page 9 line 5 to change consider to measure.	Thank you for your comment. The following recommendation has been added to the subclinical hypothyroidism section to state: "Consider measuring TPOAb for adults with TSH levels above the reference range, but do not repeat TPOAb testing.). As with antibody testing for people with confirmed hypothyroidism. The committee agreed that while testing may be useful it may not affect the management for the person. In the absence of evidence, the committee agreed that a 'consider' recommendation would be the most appropriate option.
Hyperparathyroid UK Action4Change	Guideline	11	20 - 22	This effectively rules out people above range and below 10 mIU/litre which not only will condemn people to poor life quality but also puts them at risk of long-term complications for which you recommended treatment on page 4 lines 12-13; '*Even in*	Thank you for your comment. The committee agreed there was no evidence of benefit for treating patients with a TSH of lower than 10. They made a weaker 'consider' recommendation for people under 65 based

				the absence of symptoms, treatment may have benefits in 13 terms of reducing the risk of long-term complications' on Page 4 lines 14-15, you have written: '*Even when thyroid function tests are within the reference range, changes to treatment may improve symptoms for some people'.* Surely it is plain to see that this guideline gives conflicting recommendations? Treat people within range but don't treat some of them outside the range?	on TSH or symptoms. They agreed not to make a recommendation for people over 65 because of the potential for harm with treatment in this age group.
Hyperparathyroid UK Action4Change	Guideline	11	20 - 22	Consider levothyroxine for adults with subclinical hypothyroidism who have a TSH of 10 mIU/litre or higher on 2 separate occasions 3 months apart. Are you suggesting not treating anybody with a TSH below 10? Optimal levels are between 1 and 2 whilst the population reference range is between 0.4 and 4 mIU/litre. The following information from endocrineweb.com; *'0.4 mU/L to 4.0 mU/L is considered the reference range (there may be a slight variation depending on the laboratory), and people who have a normally functioning thyroid gland usually fall within this range. If TSH measures > 4.0 mU/L, a second test (T4) is performed to verify the results. TSH > 4.0/mU/L with a low T4 level indicates hypothyroidism*'. Thinking about quality of life and the risks of untreated hypothyroidism, please can you explain your recommendation?	Thank you for your comment. The committee recommend treatment for people with a TSH of less than 10 if they are under 65. They agreed not to make a recommendation for people over 65 with a TSH of less than 10 as there is no evidence of benefit and the potential for harm with treatment.
Hyperparathyroid UK Action4Change	Guideline	11	20 - 22	We are concerned that the decision not to treat people until TSH reaches 10 mIU/litre or higher may be a means to reduce the number of people entitled to free prescriptions?	Thank you for your comment. The committee recommend treatment for people with a TSH of less than 10 if they are under 65. They agreed not to make a recommendation for people over 65 with a TSH of less than 10 as there is no evidence of benefit and the potential for harm with treatment.
Hyperparathyroid UK Action4Change	Guideline	11	20 - 22	Given that women are ten times more likely than men to have thyroid problems (from thyroiduk.org.uk), any attempt to extend the cut off point for treatment to greater than 10 mIU/litre or	Thank you for your comment. The committee agreed there is no evidence to support a different treatment strategy for men and women: both have identical ranges for TSH.

				higher can be considered sex discrimination, as it is mostly women who will be adversely affected by this change.	
Hyperparathyroid UK Action4Change	Guideline	11	20 - 22	Not prescribing levothyroxine for new patients until TSH reaches 10 mIU/litre or higher, is likely going to contribute to ruin of the UK economy in my view. Tired exhausted people are going to be falling asleep at work, and possibly actually being unable to get out of bed and get themselves to work, and be going back and forth to their GP because they feel shattered and don't know why. Not only a detrimental effect on their quality of life but how much more is that going to cost in GP's time, and treatment for depression let alone in missed work days?	Thank you for your comment. The committee recommend treatment for people with a TSH of less than 10 if they are under 65. They agreed not to make a recommendation for people over 65 with a TSH of less than 10 as there is no evidence of benefit and the potential for harm with treatment.
Hyperparathyroid UK Action4Change	Guideline	12	1	It is not appropriate to rule people out by age, offering 6 months trial of levothyroxine to under 65's.Please read this article on attitudes to age in Britain: https://www.gov.uk/government/publications/measuring-attitudes-to-age-in-britain-wp90 Please also refer to your guideline which starts with *'This guideline covers promoting mental wellbeing in people aged over 65'*: https://www.nice.org.uk/guidance/ph16 Please read the NHS constitution which states: *1. The NHS provides a comprehensive service, available to all* *It is available to all irrespective of gender, race, disability, age, sexual orientation, religion, belief, gender reassignment, pregnancy and maternity or marital or civil partnership status. The service is designed to improve, prevent, diagnose and treat both physical and mental health problems with equal regard. It has a duty to each and every individual that it serves and must respect their human rights. :* https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england	Thank you for your comment. The committee recommend treatment for people with a TSH of less than 10 if they are under 65. They agreed not to make a recommendation for people over 65 with a TSH of less than 10 as there is no evidence of benefit and the potential for harm with treatment.

				Please read this information (Factsheet 44) from Age UK:: https://www.ageuk.org.uk/globalassets/age-uk/documents/factsheets/fs44_nhs_services_fcs.pdf?dtrk=true	
Hyperparathyroid UK Action4Change	Guideline	12	6 - 9	*'If symptoms do not improve and persist when serum TSH is within reference range, consider stopping levothyroxine and monitor'* How will this help people relieve their symptoms and improve their quality of life?	Thank you for your comment. The committee agreed that if levothyroxine has not worked after this period then it is possible that the symptoms are due to causes other than hypothyroidism and there would be no benefit in continuing levothyroxine.
Hyperparathyroid UK Action4Change	Guideline	13	4 - 6	Why would levothyroxine treatment have stopped?	Thank you for your comment. Recommendation 1.5.3 refers to a trial of levothyroxine for 6 months. Following this trial, a decision may be taken to stop treatment.
Hyperparathyroid UK Action4Change	Guideline	13	7	Refers to raised auto antibodies levels. How would you know? When would they have been tested? Not under these guidelines	Thank you for your comment. The recommendation for antibody testing in people with hypothyroidism has also been added here for people with subclinical hypothyroidism: Consider measuring TPOAb for adults with TSH levels above the reference range, but do not repeat TPOAb testing.
Hyperparathyroid UK Action4Change	Guideline	14	27 - 30	'*the lack of sufficient verbal information provided by health professionals leads patients to online and potentially inaccurate resources in order to gain an understanding of their thyroid condition and its management'.* You have recommended Thyroid UK as a good source of information in Evidence Review A pages 16-18. Maybe you should include that recommendation here also, although we would assume it was one of the first online sources patients look at for information, we appreciate there is conflicting information from patients groups but if all doctors and endocrinologists were encouraged to sing from the same hymn sheet and keep up to date, patients would feel they could trust their doctors are giving the right information. When doctors give conflicting information, of course patients feel a need to do their own research.	Thank you for your comment. We agree that information-sharing is very important and have included a recommendation that written and verbal information should be provided. Links to appropriate patient information sites may be included with the guideline when it is published on NICE's web site.

Hyperparathyroid UK Action4Change	Guideline	15	5 - 8	Should say Discuss benefits and all risks. Risk of cancer should be discussed and included in table 1 as should hyperparathyroidism.	Thank you. This table was deleted following the stakeholder consultation process.
Hyperparathyroid UK Action4Change	Guideline	17	7	*Discussing radioactive iodine treatment.* We recommend the committee are aware of and include the following risk in the guideline (including Table 1)from an original investigation published 1st July 2019:'*Association of Radioactive Iodine Treatment With Cancer Mortality in Patients With Hyperthyroidism': In this cohort study of 18 805 patients with hyperthyroidism treated with radioactive iodine, a statistically significant positive dose-response relationship for risk of death was observed for all solid cancers (6% increase in risk per 100-mGy dose to the stomach), breast cancer (12% increase in risk per 100-mGy dose to the breast), and all solid cancers excluding breast (5% increase in risk per 100-mGy dose to the stomach). Conclusion and relevance*: *In RAI-treated patients with hyperthyroidism, greater organ-absorbed doses appeared to be modestly positively associated with risk of death from solid cancer, including breast cancer. Additional studies are needed of the risks and advantages of all major treatment options available to patients with hyperthyroidism'.* Here is the link to the study: **https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2737319**	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Hyperparathyroid UK Action4Change	Guideline	21	8 - 9	*'Consider measuring TSH once a year for adults with untreated subclinical 8 hyperthyroidism. If the TSH level is outside the reference range, consider 9 measuring FT4 and FT3 in the same sample'* Why would they be untreated and only tested once a year as you have stated on page 4 lines12-13*; 'Even in the absence of symptoms, treatment may have benefits in terms of reducing the risk of long-term complications.*	The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to

					measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
Hyperparathyroid UK Action4Change	Guideline	24	14 - 18	If procurement of liothyronine was better managed to bring costs down in line with other EU countries; 25p per tablet as opposed to £9 per tablet here, how would it affect your recommendation? http://thyroiduk.org/tuk/campaigns/T3-Campaign/Improving%20T3%20Prescription%20in%20the%20UK%20for%20Submission%20to%20NHS%20%20England%20(1).pdf	Thank you for your comment. The guideline is based on current UK list prices rather than future prices. Liothyronine is subject to CMA investigation but until the new prices are transparent and can be consistently available across the NHS and when the period for which the specified price is available is guaranteed they cannot be considered in the guideline. A cross reference to the CMA investigation has been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). The NICE surveillance process (more information in the Guidelines Manual) will pick up on any price change and consider if the guideline needs updating.
Hyperparathyroid UK Action4Change	Guideline	24	14 - 18	We all know T3 has become ludicrously expensive of late, but it's not the patients' fault that Concordia International has the NHS over a barrel on the price. It's coming at the problem from the wrong end to try and take patients off a combination of drugs that suits them. The NHS should be tackling the greedy family that runs Concordia instead, or finding an alternative supplier at a reasonable price. How many more GP visits will there be due to patients having their medication dosage/effects disrupted by taking away their T3? A total false economy.	Thank you for your comment. The role of the guideline and guideline committee is to make the best possible recommendations based on the available cost-effectiveness evidence. If the price of T3 changes considerably, the guideline may be updated as part of the routine NICE surveillance process of guidelines (more information in the Guidelines Manual).
Hyperparathyroid UK Action4Change	Guideline	29	17 - 23	We understand not regularly testing anti TPO antibodies but the presence of these antibodies is the diagnostic criterion for Hashimotos autoimmune thyroiditis, and Hashimoto patients have a 5-7% (this may be higher) risk of thyroid lymphoma. If you have Hashimotos you would want to know about it.	Thank you for your comment. The committee agree there is some benefit to testing anti-TPO antibodies and recommended it in the context of confirmed hypothyroidism.

				This study of 2811 subjects discusses Hashimotos thyroiditis pathology and risk of thyroid cancer: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4080848/	
Hyperparathyroid UK Action4Change	Guideline	30	5 - 19	We are glad to see this paragraph ends with '*and made a recommendation for research to help inform future guidance' after 'some of the trials did show some small benefits in specific quality of life domains and anecdotal evidence from some committee members suggested beneficial effects of combination treatment with levothyroxine and liothyronine in small subgroups of patients'. Members in our organisation who take a combination of T4 and T3 have said they would dread losing the T3 because it would have quite a devastating effect on their quality of life. One common theme was that it would make the difference between being employed or not, as well as living rather than existing. We would recommend that the NHS considers employing less endocrinologists to save costs rather than denying their patients treatment that maintains a decent quality of life. An estimated saving of £70,000 per annum per endocrinologist would buy 67,961 packets of 28 x 100mg of levothyroxine.*	Thank you for your comment and positive feedback. NICE guidelines do not routinely make recommendations on staffing levels. Should further evidence show a definitive benefit of T3 and/or there is a substantial price decrease of T3, the recommendations in the guideline may be updated as part of the NICE surveillance programme (more information in the Guidelines Manual).
Hyperparathyroid UK Action4Change	Guideline	4	10 - 11	*'General information; 'People may feel well even when their thyroid function tests are outside the reference range'.* Why would they have had thyroid function tests if they feel well? It is hard enough to get an appointment with a doctor when you feel unwell, let alone when you feel well.	Thank you for your comment. These bullet points are for clinicians to provide information to people with thyroid disease of what they might experience.
Hyperparathyroid UK Action4Change	Guideline	47	16 - 17	Your figures stating hypothyroidism affects only 2% of the UK population are in line with The Association of clinical biochemistry, The British Thyroid Association and the British Thyroid Foundation, but Thyroid UK state that according to the president of the International hormone Society (the third largest hormone society in the world), thyroid deficiency affects 20-	Thank you for your comment. This context section is not part of the recommendations and provides background information.

				30% of a standard population. That is some difference. How certain are you that your figures are correct?	
Hyperparathyroid UK Action4Change	Guideline	48	9 - 12	*'Data on the long-term consequences of subclinical thyroid dysfunction largely come from people over 65. They indicate increased cardiovascular morbidity and mortality, an increased risk of osteoporosis and potential links to dementia'.* I think there is a need for data from people under 65. I am 52, have been hypothyroid 24 years. Knowing the risks to cardiovascular and bone health and dementia, should you not include recommendations for prevention of these risks such as magnesium supplements and advise monitoring?	Thank you for your comment. The guidelines include research recommendations on the benefits of treatment of people under the age of 65 who have subclinical hypothyroidism.
Hyperparathyroid UK Action4Change	Guideline	6	1 - 2	Radioactive Iodine; no mention of increased risks of secondary cancers following radioactive iodine treatment. Dangers of RAI: Most common side effect is hypothyroidism. Swapping one disease for another	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Hyperparathyroid UK Action4Change	Guideline	6	2	*Table 1 The possible benefits/advantages and risks/disadvantages of the 2 treatment options for thyrotoxicosis with hyperthyroidism (overactive thyroid):* Risks/disadvantages of radioactive iodine should include primary hyperparathyroidism. This is an extract from the following case study; '*Our patient demonstrates that, while rare, hyperparathyroidism may occur following a short latency period after RAI. We recommend that serum calcium levels be included in routine yearly surveillance of these patients, particularly in those with a history of additional radiation exposure.* https://www.hindawi.com/journals/cripe/2014/163848/ This conclusion is from the American journal of surgery; '*Patients who undergo RAI treatment are at risk of developing HPT, and this risk appears to increase in elderly patients.*	Thank you for your comment, the issue of a potential association between radioactive iodine use and cancer is explored in detail in the evidence review on radioactive iodine safety. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.

				Serum calcium surveillance is recommended for patients who have undergone RAI treatment': https://www.sciencedirect.com/science/article/abs/pii/S0002961007004497 *Review of medical records in 600 consecutive cases of primary hyperparathyroidism revealed 10 patients with a documented history of iodine 131 (131I) treatment. In seven cases 131I had been given because of Graves' disease and in three cases for ablation of thyroid remnants after tumor operations. All but one of the patients were women. Their age at the time of 131I treatment ranged from 21 to 72 years, and the interval to detection of hypercalcemia was between 3 and 27 years. It is noteworthy that all patients treated for Graves' disease had absorbed radiation doses large enough to cause permanent hypothyroidism, and half of them showed complete absence of the thyroid gland at subsequent operation for hyperparathyroidism. Furthermore, parathyroid adenomas had developed at the sites of thyroid remnants in cases with 131I ablation after tumor operations. Our findings support other observations indicating that not only external radiation but also radiation from 131I is a risk factor for development of hyperparathyroidism, and it is emphasized that age at the time of radiation treatment may be of decisive importance in this context*. https://www.surgjournal.com/article/0039-6060(89)90302-4/abstract:	
Hyperparathyroid UK Action4Change	Guideline	7	20	In our opinion This should read *'offer'* rather than consider test, although we are happy to see recognition of testing young people with depression or unexplained anxiety	Thank you for your comment. The committee do not think it will be helpful to test everyone with depression and unexplained anxiety as there are a number of possible causes for these. The GP will need to make a judgment call on whom to test for thyroid dysfunction.
Hyperparathyroid UK Action4Change	Guideline	8	7	Recommends only to initially test TSH. Don't agree that T4 and T3 should only be tested as described. Peoples levels are not	Thank you for your comment.

				all the same, individual's ranges vary. I also consider that autoantibodies should be tested to aid diagnosis and determine risks and when borderline subclinical hypothyroidism.	The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
Hyperparathyroid UK Action4Change	Guideline	9	5	We would recommend changing "consider" to read Measure TPO antibodies. We understand not to repeat but the majority of our members have never had them tested with TSH levels above the range.	Thank you for your comment. No evidence was found for this review. The committee agreed that while testing may be useful it may not affect the management for the person. In the absence of evidence, the committee agreed that a 'consider' recommendation would be the most appropriate option.
Hyperparathyroid UK Action4Change	Guideline	9	14 - 16	A combination of T3 & T4 is offered in Europe and America. To say there is no evidence of a benefit with a combination of T4 & T3 is not true at all. It would be better to be honest and say this recommendation is based purely on cost rather than that there is no evidence. This is taken from Thyroid UK who you recommend as a good source of information in Evidence Review A, page 5, lines 16-18: 'We are aware that liothyronine (T3) is very difficult to get on the NHS now. NHS England held a consultation in 2017 - *"Items which should not be routinely prescribed in primary care: a consultation on guidance for CCGs"* because of the huge increase in the cost of T3. Their decision was that patients already on T3 should be referred to an endocrinologist	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to a combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).

				for a review and that any new patients should be referred to an endocrinologist to ask for a trial of T3'	
Hyperparathyroid UK Action4Change	Guideline	9	14 - 16	I have been taking a combination of liothyronine and levothyroxine for 7 years. I would dread having liothyronine taken from me because my life has been more manageable since it was prescribed. You recommend The British Thyroid Association in Appendix A. Have your committee actually considered the advice they recommend as it contradicts your recommendations. http://www.btf-thyroid.org/information/liothyronine/397-liothyronine-dossier-2018 Thyroid patients are being harmed by failures in prescribing of drug, liothyronine, says new report A widespread failure of local NHS bodies to consistently follow national guidelines on the prescribing of a thyroid drug is causing harm to patients, says a significant new report published today. The report shows that liothyronine, a drug used in the treatment of underactive thyroid (hypothyroidism), is not being routinely provided across the country to the people who need it. The evidence gathered shows that vulnerable people have ended up with depression, diabetes, heart problems, weight gain, high cholesterol and exhaustion from having this drug either taken away or not prescribed in the first place. The case studies also show people being unable to work and trying to find ways of funding the drug privately. This is all despite NHS England approved guidance from last year stating that liothyronine should be provided to those who really need it.	Thank you for your comment. The committee makes the recommendations for NICE guidelines using the available evidence and consensus of the committee. Evidence was not found to support the use of liothyronine. The high list price also made it highly unlikely to make it cost-effective should the evidence exist. With this in mind the guideline recommends that liothyronine should not be routinely prescribed. This allows for healthcare professionals to use their discretion on using liothyronine for individual patients. The guideline recommendations relate to people newly diagnosed with hypothyroidism rather than those already receiving treatment. The committee has not made recommendations on withdrawing treatment as it did not review the evidence in this area.

				The report, which was requested by the Department of Health, has been produced by a consortium of thyroid patient organisations, with guidance from the British Thyroid Association – the UK's body for thyroid specialists. The organisations received over 400 patients' stories that showed how local NHS Clinical Commissioning Groups are not following the national NHS England approved guidance. Patients who have had liothyronine withdrawn said *"Like thousands of other UK patients, I cannot have a prescription for T3 from my GP or my endocrinologist. I am left in a frightening place."* *"Life without liothyronine for me is no life at all."* *"I feel completely abandoned by the National Health Service."*	
Hyperparathyroid UK Action4Change	Guideline	9	14 - 16	If there is not enough evidence to support that liothyronine offers benefits over levothyroxine alone, why do you think 11,467 people signed a petition set up by Thyroid UK requesting official research? Why do people get private prescriptions and buy from abroad if there is no benefit? There is plenty of evidence but the cost is the NHS stumbling block.	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Hence the committee's recommendations for further research in this area.
Hyperparathyroid UK Action4Change	Guideline	9	14 - 16	Whilst we appreciate not to routinely offer liothyronine, it should be made clear this is based on cost rather than '*not enough evidence that it offers benefits over levothyroxine monotherapy'*. Clearly this is a cost saving exercise, putting quality of life second to cost saving. There is evidence within our organisation as well as a recorded 49% of people felt	Thank you for your comment. The rationale does indicate that the recommendation is based on a lack of evidence and the list price.

				improvement; Liothyronine Dossier 2018 from British Thyroid Foundation. Liothyronine should be offered to those who feel poor improvement on monotherapy or who show poor ability to convert T4 to T3.	
Hyperparathyroid UK Action4Change	Guideline	9	17 - 19	It is extremely difficult not to be tempted to buy NDT online when there are so many patient groups with people sharing their experiences and benefits of taking NDT. We know those of you with a healthy thyroid have T1, T2, T3 and T4 as well as calcitonin which is denied to those of us only offered T4 replacement. It seems very cruel and a lifelong condemnation to poor quality of life.	Thank you for your comment. The committee recommended against the use of natural thyroid extracts because there was no evidence of benefit over levothyroxine, they are not licensed for use in the UK and the committee was concerned about unknown adverse effects because of the high proportion of T3 to T4 in them.
Hyperparathyroid UK Action4Change	Guideline	General		Most GP's will only test TSH and nothing else. This does not give a full picture. There are many on the Thyroid UK forums who are not tested properly and even some who are have great difficulty getting replacement treatment. Why don't they try and treat their patients? By doing nothing under such circumstances they are causing harm to their patients.	Thank you for your comment. We have recommended when testing TSH if it is above the reference range, then free thyroxine (FT4) should also be measure in the same sample. And if the TSH is below the reference range, FT4 and free tri-iodothyronine (FT3) should be measured in the same sample. These recommendations apply to all NHS settings.
Hyperparathyroid UK Action4Change	Guideline	General		There are inconsistencies throughout the guideline that must be checked and corrected before publication. It is very worrying that age discrimination is obvious in the guideline and also that treatments are recommended against, quite obviously due to cost yet excuses have been made and evidence ignored relating to the benefits, to sidestep the issue of cost. Surely honesty is the decent approach. To admit cost is the main decider against liothyronine and to recommend that the NHS pull together with thyroid and endocrine associations to facilitate purchasing T3 from cheaper sources would be a win-win situation for both the NHS and patients. Let us all stop banging our heads against the wall and just rectify this situation without the need for deceit, which is completely transparent. A reminder of Evidence Review E lines 29-30	Thank you for your comment, NICE recommendations are required to take cost effectiveness into account. However, the evidence identified in this guideline, from multiple randomised controlled trials, did not demonstrate a definitive clinical benefit of combination T3 + T4 over T4 alone. The committee agreed that it is possible the combination may have a benefit in some subgroups but that there is not definitive evidence to make this statement currently not to warrant recommending the combination at its current price.

				under the heading; The outcomes that matter most: '*Mortality and quality of life were agreed by the Committee to be the critical outcomes for this review'*	
Hyperparathyroid UK Action4Change	Guideline	General		I would like to know if the laypersons on the committee were asked if they would be happy to forgo their thyroxine treatment until their TSH exceeded 10 mIU/litre or higher? I would also like to know if they were selected because they only take levothyroxine and not liothyronine, or if they take both, would they happily forgo their liothyronine. I would also like to know if the committee read the NICE guideline on liothyronine.	Thank you for your comment. Lay members are recruited according to their ability to contribute to the work of the committee and are expected to interpret the evidence using their personal experience as well as their wider experience and knowledge of a condition. The personal medical condition and medication of any committee member is a confidential matter. We are not aware of NICE guidance on liothyronine.
Hyperparathyroid UK Action4Change	Guideline	General		We would like to bring to your attention for future updates to this guideline an article about a proposed new drug for hypothyroidism; '*poly-zinc-liothyronine (PZL) worked well in laboratory studies. Safety tests in animals and clinical trials in humans must still be conducted, and funding must be obtained to support that work. If all goes well, though, PZL could be offered to patients in only a few years'* http://deiodinase.org/wp-content/uploads/2018/10/2018-10-Thyroid.pdf	Thank you for this information. New treatments are considered for inclusion for all guidelines when the guideline is reviewed, and the scope of the update is agreed. There is also a NICE surveillance process which identifies when information and evidence is published (more information in the Guidelines Manual)
Hyperparathyroid UK Action4Change	Guideline	General		We share the same concerns about some of your recommendations that The Society for Endocrinology and The British Thyroid Association expressed in this statement in May 2019: https://www.endocrinology.org/press/press-releases/society-for-endocrinology-british-thyroid-association-issue-statement-against-new-treatment-recommendations-for-subclinical-hypothyroidism/	Thank you for your comment. The recommendations to which you refer relate to a BMJ guideline and not the NICE guideline. The NICE guideline recommendations for subclinical hypothyroidism will appear on NICE's web site when the guideline is published with a URL prefixed as https://www.nice.org.uk/guidance
Hyperparathyroid UK Action4Change	Guideline	General		'*Evidence showed no clinically important benefits of maintaining TSH levels in the lower rather than the higher end of the normal reference range'; this comment has been questioned by many people in our organisation, all who have been told people will feel better when optimal levels between 1*	Thank you for your comment. The comment you highlight reflects the identified evidence which showed no difference between groups who aimed for a TSH in the lower end of the reference range. The committee agreed that this meant that the starting point should be

				and 2 are achieved. It almost appears that you have considered adolescents, people over 80 and nobody in between those ages although you class adults as people over 16. Surely you would not treat a 16 year old, a 35 year old and an 80 year old equally when it comes to hypothyroidism?	aiming for a TSH within the reference range but do include recommendations elsewhere to reflect that some people may feel symptomatic benefits from adjustments to medication even when their TSH is within the reference range.
Hyperparathyroid UK Action4Change	Guideline	General		There appears to have been little consideration of the complications of hypothyroidism during pregnancy, with pregnancy only mentioned briefly 4 times throughout. You mention a small risk of birth defects if taking carbimazole during pregnancy, but the following is taken from NHS UK and surely must be included in this guideline? *If an underactive thyroid isn't treated during pregnancy, there's a risk of problems occurring. These include:* *pre-eclampsia – which can cause high blood pressure and fluid retention in the mother and growth problems in the baby* *anaemia in the mother* *an underactive thyroid in the baby* *birth defects* *bleeding after birth* *problems with the baby's physical and mental development* *premature birth or a low birthweight* *stillbirth or miscarriage* *These problems can usually be avoided with treatment under the guidance of a specialist in hormone disorders (an endocrinologist). Therefore, tell your GP if you have an underactive thyroid and you're pregnant or trying to get pregnant.* Similarly in the same link above cardiovascular disease is listed as a complication of untreated hypothyroidism, yet the 4 mentions of cardiovascular disease in your recommendations	Thank you for your comment. The guideline does not cover managing thyroid disease in pregnancy. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendations on providing information to people with thyroid disease.

				are directly linked to hyperthyroidism. '*If you have an untreated underactive thyroid, your risk of developing cardiovascular disease is increased. This is because having low levels of thyroxine can lead to increased levels of cholesterol in your blood. High cholesterol can cause fatty deposits to build up in your arteries, restricting the flow of blood.*	
Hyperparathyroid UK Action4Change	Guideline	General		We are concerned that these Guidelines reflect a money saving exercise rather than improving testing, diagnosis and treatment. They do not reflect changes to improve quality of life.	Thank you for your comment. The guideline is based on the available evidence and committee consensus and the committee believe it includes the best recommendations to improve a person's quality of life. The committee also believe the following recommendations will be (for at least some centres where there may be variability) a change in practice for the better and hope this will improve the overall quality of life in people with thyroid disease: the recommendation for cascading tests (i.e. TSH and FT4 and/or FT3 when TSH is outside the reference range); radioactive iodine as a first-line definitive treatment for people with thyrotoxicosis; adjustment of thyroid hormone replacement therapy within the reference range; confirming the aetiology of hyperthyroidism and the treatment of symptomatic subclinical hypothyroidism in people under 65 years of age.
Hyperparathyroid UK Action4Change	Guideline	General		Nothing is mentioned in diagnosis about examining throat or neck for swelling or nodules, or when to refer to an endocrinologist. In fact there is only one mention of endocrinologist on page 45, line 12 under cystic nodules; '*investigation by a radiologist (or endocrinologist).'*	Thank you for your comment. These recommendations are not a comprehensive list of all steps involved in diagnosis but focus on key questions prioritised during scoping with stakeholders and informed by committee discussions. NICE guidelines can only focus on a limited number of areas in order to conduct the most rigorous evidence searching and analysis.

ITT (Improve Thyroid Treatment Campaign)				**References** **Published research papers** 1.The Swinging Pendulum in Treatment for Hypothyroidism: From (and Toward?) Combination Therapy Elizabeth A. McAniinch and Antonio Bianco July 2019 https://www.frontiersin.org/articles/10.3389/fendo.2019.00446/full 2. Time for a reassessment of the treatment of hypothyroidism. John E M Midgley et al 2019 https://bmcendocrdisord.biomedcentral.com/articles/10.1186/s12902-019-0365-4 3. The Impact of thyroid hormone dysfunction on Ischemic heart disease. M Von Hafe et al https://doi.org/10.1530/EC-19-0096 (May 2019) **Published Clinical Studies** 1. The long-term follow-up of patients with thionamide-treated Graves' hyperthyroidism. Bandai S et al. Endocr J, published March 2019 https://www.ncbi.nlm.nih.gov/pubmed/30918165 2. Symptomatic Relief is Related to Serum Free Triiodothyronine Concentrations during Follow-up in Levothyroxine-Treated Patients with Differentiated Thyroid	Thank you for your comment. We have checked each of these references. None meet the inclusion criteria of our protocols. Some of the papers are published after the cut-off for evidence for inclusion in the guideline. However, to ensure we have not missed any important papers we have reviewed these, and they also do not meet the inclusion criteria of our protocols.

				Cancer. Larisch R, MidgeleyJEM, Dietrich JW, Hoermann R 2018https://www.ncbi.nlm.nih.gov/pubmed/29396968 3. Assessment of the Relationship between Genetic Determinants of Thyroid Function and Atrial Fibrillation: A Mendelian Randomization Study Ellervik C eta l JAMA Cardiol https://doi.org/10.1001/jamacardio.2018.4635 4. Long-term monitoring of Graves' disease in children and adolescents: a single-centre experience Tunc S et al Turk J Med Sci 2019 Apr 18;49(2):464-471 https://doi.org/10.3906/sag-1804-177 *5.* Hyperthyroidism influences renal function. Sonmez E et al. Endocrine 2019 Jul:65(1):144-148 https://doi.org/10.1007/s12020-019-01903-2 **Article with references:** 1. Against TSH-T4 Reference Range Thyroidology: The Case for Clinical Thyroidology. Henry Lindner https://pdfs.semanticscholar.org/b233/ce7559d04eeb00f46abd06ed42d94263219b.pdf **Document by Andrew Toft 2017** AD Toft: Thyroid hormone replacement – a counterblast to guidelines 2017 https://www.rcpe.ac.uk/sites/default/files/jrcpe_47_4_toft.pdf	

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

ITT (Improve Thyroid Treatment Campaign)	Economic review	General	General	One of the two considerations for not recommending liothyronine for treatment is the cost. The analysis is misleading because of the artificially inflated cost of liothyronine in the UK. Furthermore, the economic analysis should reflect the latest price of liothyronine and not the historical cost. 1. The cost of liothyronine is only prohibitively expensive in the UK. It is much cheaper elsewhere; for example in Greece, Turkey and Mexico the cost is between £3 and £10 x 100 25ug tablets. The CMA provisionally found the manufacturer had inflated the price of liothyronine and profiteered at the expense of the NHS. This investigation is still ongoing. ITT is of the view that no NICE recommendation should be made based on cost until the CMA has concluded its investigation. A mechanism to review the cost must be put in place when the CMA has concluded its investigation. 2. In 2018, two more suppliers Teva and Morningside were also licensed to supply Liothyronine, at an almost identical prohibitive price. 3. The cost quoted in the NICE guideline for Liothyronine in the UK is out of date. The cost has reduced to £204.39 (per BNF June 2019) for a packet of 28 tablets and is therefore £2664.36 per annum, or £7.29 per day for 20ug Liothyronine, and not £3,365 as quoted. This cost equates to the tax from a working salary of approximately £25,000, which is considerably below the average UK salary. In ITT's opinion the cost of a treatment for a chronic illness should consider the opportunity cost of losing taxation revenue if treatment does not work.	Thank you for your comment. We have now updated all drug costs in the guideline to 2019 prices; the costs have not changed enough to affect the conclusions. This NICE guideline is written from the perspective of the UK NHS and PSS, and therefore takes account of current UK prices available across the NHS. Liothyronine is subject to CMA investigation and a cross reference to the CMA investigation has now been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). However, until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine). We will flag the CMA investigation and cost of liothyronine to the NICE surveillance team and the guideline can be reviewed if there is a significant change in list price.

				4. From a German pharmacy with a UK prescription, a pack of 50 x 20mcg Thybon Henning currently cost €21.85 including VAT plus €17 for shipping. 100x 20mcg cost €53 including VAT plus €17 shipping. 5. Thybon Henning imported as special into UK by a pharmacist is currently £50 for 50 x 20mcg on NHS. GPs and endocrinologists need to be made aware of the EU licence. 6. A recent report has been published by Oxera Consulting LLP - independent economists, commissioned by the BGMA [British Generic Manufacturers Association) – into the mechanism of the UK generic pharmaceutical sector. The report assesses the effectiveness of the UK model versus other large, mature European markets. Additionally, it describes the mechanisms of the Department of Health and Social Care (DHSC) Drug Tariff (DT) and compares DT prices with manufacturers' actual selling prices, which the report concluded were "around half of the reimbursement price paid by the NHS". The report can be found at the BGMA webpage. The report's findings would indicate that manufacturer selling prices for Liothyronine Tablets, may have been reduced (by the competition now in the market) by round 60%, with prices at / or below £100 per pack. Due to the cost of Liothyronine in the UK being artificially high, this has led to many patients having liothyronine removed or refused. ITT believes that NICE must report the cost accurately to avoid liothyronine being removed from NHS provision due to cost.	
ITT (Improve Thyroid Treatment Campaign)	Economic Review	General	General	In ITT's view there is insufficient consideration of potential negative workforce impacts. The patient survey conducted by	Thank you for your comment. As reported in the Manual for developing NICE Guidelines

				ITT demonstrates that thyroid disorders can significantly impact on the quality of life of patients and their economic well-being. A key impact has been in terms of workforce makeup and numbers overall. The ITT survey indicates that 80% hypothyroid respondents have taken time off work and/or changed their roles/hours at some point because of their thyroid disorder, and 82% of hyperthyroid respondents had taken time off work and/or changed their roles/hours. Some patients have told ITT they have had to give up work entirely. Hypothyroid patient absence: • 37% have been absent from work • 20% have never been absent • 20% changed their job to one with less hours/stress • 23% gave up work Of the respondents who said they were absent due to Hypothyroidism: • 52% were absent from 2-4 Weeks • 29% were absent between 4 Weeks and 6 Months • 7% were absent between 6 Months and 1 Year • 11% were absent for more than 1 Year Hyperthyroid patient absence: • 54% have been absent from work • 18% have never been absent • 12% changed their job to one with less hours/stress • 16% gave up work Of the respondents who said they were absent due to Hyperthyroidism: • 51% are off from 2-4 Weeks • 35% are off between 4 Weeks and 6 Months	(https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview) “productivity costs and costs borne by people using services and carers that are not reimbursed by the NHS or social services should not usually be included in any analyses”. This is for different reasons, for example time off work is implicitly incorporated in QALY. Also, if we included productivity costs in our analyses, we would favour those interventions aimed at the working population and discriminate against the elderly, children, unemployed people and people with disabilities.

				• 14% are off between 6 Months and 1 Year ITT recommends that the economic analysis is updated to reflect the impact of treatment on patient ability to work.	
ITT (Improve Thyroid Treatment Campaign)	Evidence Review E	15	Table 6	ITT notes the economic analysis for NDT is based on an Amazon search. Amazon does not sell NDT and the item referred to is unknown to ITT. Typically a patient will not take 6 tablets a day; 2.5 tablets (grains) of NDT are equivalent to 100 mcg levothyroxine (T4). NDT has been available on the NHS for many decades and ITT is disappointed that NICE has not used the information available from NHS sources to properly cost the treatment. Members of ITT confirm they can obtain NDT from a range of suppliers at a range of prices from 1000 tablets for approximately £70, to 100 tablets for £80. ITT recommends that NICE reperform the evidence gathering on NDT pricing because it is not robust.	Thank you for your comment. This is an unlicensed medication in the UK and there is no standard pricing available to the NHS for unlicensed medicines. Therefore, it was decided that the costs of NDT should not be reported.
ITT (Improve Thyroid Treatment Campaign)	Evidence Review E	17	29 - 35	1.7.1.3 "*The committee were aware that the use of combination therapy is a critical issue in hypothyroidism. Based on the evidence available and the high costs of liothyronine the committee could not recommend its use. However, the committee agreed that it is plausible in some people who are not responding to levothyroxine that combination therapy may be beneficial. Without RCT evidence to support this hypothesis, the committee agreed it was not appropriate to recommend the use of liothyronine even in this subpopulation however they made a high priority research recommendation for trials conducted in this subpopulation to allow for firmer guidance in the future*." ITT strongly disagrees with the recommendation that there is little or no value to liothyronine. Neither BTA specialist consultant advice, existing NHS guidelines nor patient feedback has been considered. This recommendation will	Thank you for your comment. The committee did not state that there was little or no value to liothyronine. The committee was aware of the various additional consensus viewpoints you reference on this topic. We acknowledge that different expert groups may arrive at different conclusions however, having considered evidence of clinical effectiveness (which has included quality of life) as well as costs along with their clinical expertise, the committee is confident that the recommendations made reflect best practice.

				result in patients being deprescribed Liothyronine or NDT without consideration of patient clinical well-being or quality of life. Patients can only be recommended for treatment on liothyronine or NDT by an endocrinologist, and will have previously been treated and not made euthyroid by levothyroxine, therefore their need for an alternative treatment has already been proven. The NICE recommendation will result in patients being without a treatment that has worked previously, pending the results of expensive and difficult to construct RCTs. In the opinion of ITT this is not an acceptable patient treatment strategy. ITT recommends that the guideline be changed to recognise that a small cohort of patients does not become well on levothyroxine and, while there is no RCT to support combination therapy, alternative treatment is to be continued until that evidence can be obtained.	
ITT (Improve Thyroid Treatment Campaign)	Evidence Review E	General	General	ITT has a number of comments on the evidence quality and availability. 1. The draft recommendations still privilege RCT evidence and fail to consider evidence arising from both UK and international patient observational studies and leading endocrinologist non-RCT research. It is widely acknowledged in the endocrine field that RCT on thyroid patients is difficult and potentially dangerous. Given there is unlikely to be an RCT in the near future, prioritising RCT evidence over other studies by NICE prejudices the quality of life and well-being of those with thyroid disease. 2. Given that the paucity of RCT evidence was known at the outset of the consultation, it is disappointing that NICE has relied on the experience of its committee	Thank you for your comment. 1. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. The same principles applied throughout whereby the committee considered that lower quality evidence was more likely to be unreliable and therefore may not assist in making recommendations. 2. In areas where no clinical evidence was identified, the committee members used their collective experience to

				members rather than other valid data and scientific sources. 3. It is also disappointing that, with the lack of evidence known, NICE did not engage with patient groups and stakeholders to input their experience of working with and supporting patients from the outset of the drafting process. 4. ITT is disappointed that the liothyronine Dossier supported by many key UK thyroid patient groups working with the British Thyroid Association (BTA) has not been included in the evidence and was not incorporated into the committee recommendations. Following assurance from the NICE thyroid project team that links that can be included in this response, the link to the Dossier is here: bit.ly/LiothyronineDossier2018 5. ITT is concerned that it is still very difficult to understand which studies have been included in the various analyses conducted. The lack of clarity about what evidence was included and relied upon means that a vital part of the NICE analysis is not transparent and thus not amenable to review. 6. The limited consultation time given the significant length of the documentation (the main report plus all appendices) and the great complexity of the analyses run, made it impossible for ITT to do a full search for additional literature. However, at the end of our response form, ITT does list a number of relevant papers which do not appear to have been considered by the NICE committee. We also include one recent document from July 2019.	make consensus recommendations. The committee noted that in some areas not making a recommendation would leave a gap and, in such cases, expert guidance was better than none at all. 3. The committee considered that performing a systematic review of all lower quality studies and engaging with patient groups to input their experience would have taken a huge amount of resource and would not have further assisted in decision making. The committee included 3 lay members to help with decision making. 4. The dossier that you link to is not the category of evidence that is routinely considered for inclusion within NICE guideline evidence reviews. 5. Details of the included studies can be found in the included studies table and Appendix D. Findings from individual studies or meta-analysis findings are then presented in table format within the standardised NICE evidence review template. The exact studies that were included in each analysis can be seen in the forest plots in appendix E. 6. NICE has a standard response time for all guidelines and publishes the dates at the start of guideline development to give stakeholders as much notice as possible. We realise that some guidelines are larger than others and can generate a lot more thought. We find that overall, we get a comprehensive all stakeholder replies we get a good critique of the guideline. We have checked the list of references you supplied and commented on these where they occur in the list of comments. 7. We realise that a guideline can become out of date as soon as it publishes. We try to mitigate against this by

				7. ITT is not convinced that the included literature is up-to-date: No studies published after the start of January 2019 have been included in the analysis which means that by the time this guideline is published (potentially end of 2019) the literature review will be nearly a year out of date. ITT has identified 136 new papers not covered by the review. ITT also highlights the lack of reference to the clinically tested SPINA-Thyr which is a patented algorithm. It is our opinion that this is a robust clinically tested tool that is free and readily available to assess patient thyroid function and its use could be widely used to assist clinicians.	rerunning all searches near the end of development of the first draft of the guideline. Re-runs of the literature search were conducted 7th January 2019 and no further studies meeting the protocol inclusion criteria were identified. The NICE surveillance process (more information in the Guidelines Manual) will identify when new information or evidence becomes available. 8. SPINA-Thyr is an algorithm for the analysis of various tests, many of which are recommended in the guideline. The guideline did not cover the interpretation of thyroid function tests
ITT (Improve Thyroid Treatment Campaign)	General	General	General	In ITT's opinion, NICE prioritises RCT evidence and does not give sufficient weight to other relevant evidence, including evidence from patients with thyroid disorders. ITT does not think it appropriate for the guideline committee members to disregard all the evidence and input from patient support groups and charities who represent thousands of patients living with thyroid disorders. The paucity of RCT evidence on the treatment of thyroid disorders was well known at the outset of the project, and therefore NICE should have sought patient group input at an early stage.	Thank you for your comment. NICE guidelines prioritise evidence from randomised controlled trials for interventions, as these are viewed as the most rigorous design and are least susceptible to bias. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. The committee represents all the main specialties that are involved in the diagnosis and management of thyroid disease who work with a range of patients on a day-to-day basis. Also, NICE guideline committees always include people with experience of the condition and three people with experience of thyroid disease were lay members of this committee.
ITT (Improve Thyroid Treatment Campaign)	Guideline	10	17 - 19	*1.4.3 For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised within the reference range, and then once a year.*	Thank you for your comment.

				ITT is supportive of regular reviews of a patient. TSH is a pituitary hormone and not a thyroid hormone. TSH, while indicative of thyroid function, will not always provide sufficient information on the thyroid function of all patients. It is ITT's view that the aim of treatment is to alleviate patient symptoms and not just to bring levels within reference ranges. ITT is disappointed that the guideline does not recognise this as an aim of treatment. A majority of patients have told us that they do want to be treated for their symptoms, and that they find they feel better and have a better quality of life if their TSH is lower in the range, rather than just 'in range'. A majority of patients also tell us that they would like their FT4 to be tested. At a cost of approximately 92 pence for a test, most patients felt this was important information for them to understand or manage their condition. ITT is disappointed that the draft guideline is silent on patient involvement in joint decision-making on treatment. Hypothyroidism is a chronic illness and can significantly impact on the well-being and quality of life of patients. Many patients have provided feedback to ITT that hypothyroidism and a prolonged time before receiving diagnosis and treatment have a significant adverse impact on their well-being and quality of life. A significant number of respondents told us in our survey that they have had to take time off work, or leave work. The ITT survey asked respondents to tell us if they agreed that treatment should have the aim of maintaining TSH within reference range. When asked whether or not they agreed with TSH as the indicator, most respondents clearly believed that TSH was not the only indicator, and other factors must be	Measuring FT4 as well as TSH is covered in recommendation 1.4.6 at the end of the follow up and monitoring section for hypothyroidism recommends "Consider measuring FT4 as well as TSH for adults, children and young people who continue to have symptoms of hypothyroidism after starting levothyroxine". The committee noted that FT3 measurements are not useful in managing hypothyroidism as T3 is a short acting hormone and measurements will be very different on different days. Reference ranges for thyroid function tests will be assay dependent and will be set based on the local population covered by the laboratory.

				considered including symptoms and the levels of FT4 and FT3. Many respondents requested the reference range be defined. Many respondents felt that patient symptoms must be considered, and an annual test should not prioritise tests results over symptoms when the patient remains symptomatic. A majority of respondents also felt strongly that thyroid hormones should be tested in addition to TSH. ITT recommends the final guidance reflects that the treatment aim is to alleviate patient symptoms within the reference range. NICE should make it clear to clinicians that this may require patients to be towards the lower end of the TSH reference range. The final guideline should also recommend that, where a patient is not hypothyroid symptom free, further testing and more frequent testing may be needed and that this should include full thyroid hormone testing. *"Only if relevance is given to symptoms, it's so easy for these to be overlooked by doctors with closed minds who will only look at the reference ranges."* *"Yes, but other thyroid blood tests are necessary too. TSH alone is not sufficient for adequate monitoring."* *"Patients do need checking more frequently, but going by TSH alone is pointless. T3 and T4 levels should also be checked routinely."* *"TSH should not be the sole measure of thyroid function. It's not even a thyroid hormone."*	

				"Until the reference range reflects actual good health this is irrelevant." *"The TSH reference range is too high. Patient symptoms should be taken into consideration rather than relying on TSH levels."* *"The number of blood tests is fine but the aim of treatment is not. Once per year is fine once symptoms are resolved."* *"It is useless in assessing thyroid health. Brilliant in assessing your pituitary gland though!"* *"After diagnosis the only tests that should be done are FT3 and FT4. TSH is useless"* *"It is a matter of how the patient feels, not figures and guidelines."*	
ITT (Improve Thyroid Treatment Campaign)	Guideline	10	17 - 19	*1.4.3 For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised within the reference range, and then once a year.* This guideline will be difficult to manage in practice because it is silent on how patients who remain symptomatic despite levels in range will be treated. ITT recommends that the final guideline provides clinicians with a patient treatment pathway on how to treat patients if they remain symptomatic e.g. a referral to secondary care where a patient remains symptomatic or when euthyroid status is not achieved. ITT is concerned at the number of respondents to the survey who have been denied referral for a review or their treatment or alternative treatment despite remaining symptomatic. 77% of women and 61% of men who	Thank you for your comment. Recommendation 1.4.6 at the end of the follow up and monitoring section for hypothyroidism recommends further testing if symptoms persist: "Consider measuring FT4 as well as TSH for adults, children and young people who continue to have symptoms of hypothyroidism after starting levothyroxine"

				responded to the question in our survey had been denied a review of T3/NDT treatment options.	
ITT (Improve Thyroid Treatment Campaign)	Guideline	12	3 – 5	*Page 12 Line 3-5 a TSH above the reference range but lower than 10 mIU/litre on 2 separate occasions 3 months apart, and symptoms of hypothyroidism*. ITT is disappointed that the draft guideline is silent on patient involvement in joint decision-making on treatment. Hypothyroidism is a chronic illness and can significantly impact on their well-being, quality of life and on their ability to be economically active in the workplace. A majority of survey respondents have provided feedback to ITT that hypothyroidism has had significant impact on their well-being and quality of life. A majority of patients report needing time off work, with 80% reporting they required time off work or had changed jobs or reduced hours because of thyroid illness, and 18% of those needing more than 6 months off work. A majority of patients surveyed want treatment to alleviate their symptoms. ITT recommends that the final guideline be amended to include joint decision-making and to encourage patient involvement in treatment decisions.	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The guideline has included a link to the NICE patient experience guideline, which includes recommendations on shared decision-making.
ITT (Improve Thyroid Treatment Campaign)	Guideline	12	3 - 5	*TSH above the reference range but lower than 10 mIU/litre on 2 separate occasions 3 months apart, and symptoms of hypothyroidism*. ITT welcomes clearer guidance on when to treat subclinical hypothyroidism where a patient has an elevated TSH and symptoms of hypothyroidism. There is a wide range of symptoms associated with hypothyroidism and ITT recommends that the final guideline includes a comprehensive list to support diagnosis. 97% of patients who responded to the survey or provided comments to ITT felt such a list would improve the guideline and their treatment outcomes.	Thank you for your comment. The committee considered it was not possible to develop a definitive list of symptoms that may be associated with thyroid disease. The guideline makes specific reference to testing where an association was found between some conditions or symptoms and thyroid disease.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
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ITT (Improve Thyroid Treatment Campaign)	Guideline	12	6 - 7	*1.5.3 If symptoms do not improve after starting levothyroxine, re-measure TSH and if the level remains raised, adjust the dose*. 1. ITT recommends that this section be cross-referenced to 1.4.2 to assist with the time period over which monitoring takes place. 2. ITT recommends that clinicians be advised to prescribe a named brand of levothyroxine, as many patients report to ITT that they find different brands of levothyroxine are not interchangeable. As reported in JCEM (*The Journal of Clinical Endocrinology & Metabolism)* article 98 June 2013. 3. Many patients report to ITT their difficulty with some brands of hormone replacement. ITT recommends guidance on trying an alternative brand when patients remain symptomatic e.g. Teva brand contains mannitol and this has upset many hundreds of ITT patients. Other patients report difficulty with brands that contain lactose. This is evidenced by many yellow card reports. If symptoms do not improve, ITT recommends full thyroid function tests (TFTs) are performed to pick up those patients with low T3/T4 levels indicating possible central hypothyroidism or conversion difficulties.	Thank you for your comment. The committee agreed recommendation 1.4.2 was specific to hypothyroidism. The evidence for different brands was not reviewed so has no recommendations have been made regarding this. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
ITT (Improve Thyroid Treatment Campaign)	Guideline	12	7 - 9	*1.5.3 (if symptoms persist when serum TSH is in reference range, consider stopping levothyroxine and follow recommendation 1.5.6 on monitoring)* ITT has a number of recommendations on this draft guideline. 1. ITT notes there is no mention here of patient involvement in this guideline. Many patients express	Thank you for your comment. Shared decision making is part of NICE guidelines and it has been mentioned within the guideline. These recommendations are based on the available evidence and committee consensus.

				concern that their symptoms can be very debilitating and they want these to be taken into consideration when treatment is being discussed. ITT recommends the guideline is clear that the treatment is a joint decision with the patient. 2. ITT recommends other investigations are undertaken before levothyroxine is stopped because these may be masking any improvement in thyroid function. Many patients have reported to ITT that they frequently need supplementing to improve their levels of Vitamin D, folate, Vitamin B12, ferritin and magnesium. ITT recommends that a link in the NICE guidance to these tests is included in the final guidance and these are assessed before treatment is ceased. 3. ITT has been told by members that they react differently to different brands of levothyroxine and ITT recommends that, if a patient reports feeling unwell on a brand of levothyroxine or remaining symptomatic, an alternative named brand is tried before treatment is ceased. 4. In relatively rare circumstances where a patient reacts very badly to a particular brand of Levothyroxine, ITT recommends that treatment should immediately be replaced with an alternative brand and, if strong intolerance is repeated, cease prescription and consider other courses of action. 5. ITT member feedback is that many patients have never been advised to take medication on an empty stomach away from caffeine and certain supplements and medication. 6. Before cessation of treatment, ITT patient feedback is that the guidance includes a recommendation that a full thyroid panel test is needed before stopping	The evidence for vitamin and mineral supplements was not reviewed and no recommendations have been made relating to this. The evidence for different brands of levothyroxine was not reviewed and no recommendations have been made relating to this. Recommendation 1.1.4 (previously 1.1.3) advises clinicians on how to provide information on how and when to take levothyroxine The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.

				levothyroxine add (TSH, FT4 and FT3 and antibodies). This will ensure there are no underlying issues with the thyroid that are not identified by testing the pituitary TSH.	
ITT (Improve Thyroid Treatment Campaign)	Guideline	15	1 - 3	1.6.6 *Consider antithyroid drugs along with supportive treatment for adults with hyperthyroidism while awaiting specialist assessment and further treatment*. Current NICE guidelines state this, however ITT member feedback from a majority of patients reiterates that, although this is good advice, it does not always happen in practice. Many patients tell ITT that they were not offered any treatment while waiting for a specialist appointment; waiting times can vary considerably, leaving some patients very unwell. Respondents to the survey expressed a need for urgency in the referrals process and suggest that the correct and relevant tests be completed prior to the prescription of any antithyroid drug. ITT recommends that the treatment pathway is clarified in this section. 48% of respondents to the survey strongly agreed and 29% somewhat agreed with the draft recommendation. *"People need the advice of specialists as soon as possible. The implications of not having the right treatment urgently are potentially very serious."* *"Some patients are having to wait an unacceptably long time to see a specialist. Do GPs have the relevant expert knowledge and experience to be treating people prior to them seeing a specialist. Perhaps the better answer might be to increase the number of specialists."*	Thank you for your comment. The committee hope that clinicians will read and adhere to the recommendations. We did not review the evidence for referral pathways so have not made recommendations in this area.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
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ITT (Improve Thyroid Treatment Campaign)	Guideline	15	10 -19	*1.6.8 Offer radioactive iodine as first-line treatment for adults with Graves disease, unless antithyroid drugs are likely to achieve remission (see 11 recommendation 1.6.9), or it is unsuitable (for example, there are concerns about compression, malignancy is suspected, they are pregnant or trying to become pregnant or father a child within the next 4 to 6 months, or they have active thyroid eye disease). 1.6.9 Offer a choice of antithyroid drugs or radioactive iodine as first-line treatment for adults with Graves' disease if antithyroid drugs are likely to achieve remission (for example, mild and uncomplicated graves' disease.* ITT welcomes a range of treatment options for hyperthyroid patients. However, ITT questions how an endocrinologist can know in an early appointment if a newly presented case of Graves disease is unsuitable for Antithyroid drugs without trying them first. ITT recommends the final guidance provides a more supporting rationale on why a treatment option may be more suitable. Some patients tell ITT that they felt rushed into radioactive iodine treatment (RAI) without enough information to make such an important decision. Many patients did not know what the impact of hypothyroidism could be on their well-being, and did not think they have been adequately supported with treatment choices. ITT encourages full disclosure of information, transparent and joint decision-making with the patient. Endocrinologists should explain any decision for the use of RAI without first trying antithyroid drugs.	Thank you for your comment. The committee agreed that for a lot of patients, radioactive iodine is the most effective option. They believe approximately 50% of people who start antithyroid drugs end up having RAI or surgery as drugs only provide temporary relief. This group may get side effects with the drugs and they do not have a realistic prospect of curing thyrotoxicosis. As well as the recommendation highlighting discussing the possible benefits and risks of each treatment option the committee has also made a cross reference to the recommendations on shared decision making in the patient experience guideline to emphasise the importance of discussion. .

				Overall a majority of survey respondents agreed with the treatment options but expressed a preference to first try antithyroid drugs and a concern that RAI was tried too often and soon. Of the survey respondents 18% strongly agreed with the recommendation, 30% somewhat agreed, 23% neither agreed nor disagreed, 16% disagreed and 13% strongly disagreed. Many respondents also felt that the auto-immune disorder should be addressed and efforts should be made to understand this more and include it in the guideline. *"Having had all of these treatments I agree they should all be considered depending on outcome of each treatment."* *"More must be done to offer medicine route before RAI or TT."* *"I would prefer they make it more clear that RAI and surgery should not be first-line treatment options. They should be secondary and last resort options wherever possible."* *"I feel that RAI is sometimes the default option and as this is a permanent option, anti thyroid drugs should be exhausted before pushed towards RAI"* *"How about investigating the underlying cause of hyperthyroidism, rather than just treating the symptoms."* *"RAI is being pushed to people without any real attempt to get Graves into remission. First focus should be to treat with aim to achieve remission."* *"The patient should be offered the free choice of any option, supported by comprehensive data to aid their decision-making.*	

				For instance they should be able to choose anti-thyroid drugs if that is their preference, not only if radioactive iodine or surgery is unsuitable." *"RAI should not be offered as the first line of treatment. A patient must be given time on anti thyroid drugs to see if they respond well before being offered RAI. The potential complications of RAI must be explained before it is offered."* *"You need to treat the root cause, which is an immune system that is attacking an otherwise healthy organ."*	
ITT (Improve Thyroid Treatment Campaign)	Guideline	16	6 - 8	1.6.12 *Consider radioactive iodine or surgery for adults with Graves' disease who have had antithyroid drugs but have persistent or relapsed hyperthyroidism* In feedback to ITT, patients ask that they are confirmed to be in remission before medication is discontinued. Patient feedback requests that TRAb levels are tested to make sure active disease is not prevalent, and therefore risk of relapse is avoided. 83% of respondents to the survey felt that antibodies should be retested. Comments suggest that patients prefer continuation with antithyroid drugs over RAI or surgery.	Thank you for your comment. No evidence was identified for retesting TRAb levels and the committee felt unable to recommend that this be done routinely.
ITT (Improve Thyroid Treatment Campaign)	Guideline	20	2 - 6	*1.7.9 For adults, children and young people who are taking antithyroid drugs for hyperthyroidism, consider measuring: TSH, FT4 and FT3 every 6 weeks until TSH is within the reference 4 range, then TSH every 3 months until antithyroid drugs are stopped.* Hyperthyroid patients generally agreed with the recommendation. The majority of survey respondents felt that test frequency must be proactive and quick and considered on an individual patient basis. 52% of respondents either strongly agreed or agreed with the recommendation, 14% neither	Thank you for your comment. The committee agreed that for most patients testing 3-monthly once TSH is in the reference range is appropriate. We also recommend testing TSH and FT4 if there are ongoing symptoms. In both these scenarios the recommendations have changed to state if TSH is below the reference range measure FT4 (if not already measured) and FT3 in the same sample.

				agreed nor disagreed, 16% agreed and 18% strongly agreed. Many comments indicate that patients request regular blood tests more frequently than 3-monthly (6 – 8 weekly) if they experience hypothyroid symptoms. This is to help them avoid being overmedicated and their well-being being affected. ITT recommend the final guidance clarifies that where a patient is experiencing symptoms more frequent testing may be required. *"All of these tests should be done routinely ... this is a very severe disease."* *"When not tested every 6 weeks your levels can quickly go way out of range and you get poorly. It then takes you longer to get your symptoms back under control."* *"If the patient feels unwell or out of sorts, those markers need to be retested."* *"I agree though there should be somewhat regular testing for patients with cases of persistent hyperthyroidism so relapses don't go undetected for prolonged periods."* *"If patient is feeling well, why keep testing every 3 months? Leave this for 6 months."* *"Testing sooner than every 6 weeks is often needed."* *"it depends on the patient's symptoms."* *"Antibodies and Free T4 and Free T3 are necessary for both hyper as well as hypo."*	The committee assumes that a person with significant symptoms will seek medical advice and may be tested more frequently if needed.

				"I do not believe TSH to be an accurate measure of how patients feel. T4 and T3 should be optimal in range also." *"Every 4 weeks as levels can change drastically also FT3, FT4 and TSH, not just TSH."* *"Patient symptoms and FT4 & FT3 must be the driver, not TSH coming into range."* *"Full testing is necessary to provide a complete picture of wellness for the patient. NICE experience is not patient experience."* *"T3 needs to be tested most definitely & patients' symptoms must be taken into consideration."*	
ITT (Improve Thyroid Treatment Campaign)	Guideline	41	14 - 15	*1.7.1 – 1.7.12 on monitoring full blood count and liver function tests and these tests have a treatment burden for people with hyperthyroidism.* ITT patient feedback is that these tests give peace of mind to the patient, and are not a burden. ITT questions where the evidence of burden has come from and asks this to be confirmed before inclusion in the guideline.	Thank you for your comment. This is based on committee experience and consensus. All tests involve some degree of burden to both the person being tested and the system conducting and following up the test.
ITT (Improve Thyroid Treatment Campaign)	Guideline	8	7	*Consider measuring only thyroid-stimulating hormone (TSH) for adults when secondary thyroid dysfunction (pituitary disease) is not suspected* ITT does not support the testing of TSH alone when thyroid disorders are suspected or confirmed. Many thyroid patients tell ITT that it is was only when their T4 and T3 levels were tested, and their medication was changed accordingly, did they become well. They report that it is inconvenient and disruptive to them to try to return repeatedly to their GP for further blood	Thank you for your comment. The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below

				tests. Many patients report lengthy delays in accessing their GP and nurses to obtain the blood tests. ITT recommends that the guideline be changed to test thyroid hormones at the same time as TSH where thyroid disorders are suspected, in order to deliver a better patient outcome. A freedom of information request confirmed the price for a T4 and T3 test is 92 pence. ITT suggest that this is not a high cost and will be covered by reduced GP consultations and a quicker, more accurate diagnosis.	the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
ITT (Improve Thyroid Treatment Campaign)	Guideline	9	5	1.3.1 testing of antibodies. ITT welcomes the initial testing of antibodies to determine if the thyroid disorder is autoimmune in nature. Many of our members tell us that continued monitoring of antibodies when they remain symptomatic does help them manage and understand their condition. Many patients do follow diets to manage the autoimmune response, and the tests allow them to determine if actions they are taking have helped to improve their health and well-being. ITT recommends that the final guideline includes guidance to clinicians that, where a patient remains symptomatic and there is clear evidence of antibodies, retesting may be helpful and a patient should be supported to understand the triggers of auto-immune thyroid disorder. ITT's independent survey a majority of respondents disagreed with the recommendation not to continue to test antibodies. 61% disagreed with the NICE recommendation. A large majority felt that it is best to repeat antibody tests to understand the full extent of the auto-immune reaction and impact on symptoms. Respondents also felt the need for treatment to establish a cause and for advice to be available.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee also agreed that it would not be appropriate to recommend repeating tests when this is unlikely to affect management and there is no evidence to support a benefit of this approach.

				"Shows complete disregard for potential slowing of disease and disinterest in possible research into causes and therefore improvement in treatment." *"Monitoring the lowering of antibodies can improve a patient's overall health and prevent further autoimmune problems, thus saving the NHS money in the long run."* *"It should be mandatory to measure at least once, preferably at diagnosis. Otherwise 'consider' = 'don't bother'."*	
ITT (Improve Thyroid Treatment Campaign)	Guideline	9	12	1.3.3 Offer levothyroxine as first-line treatment for adults, children and young people with primary hypothyroidism. ITT agrees that levothyroxine should be the first treatment offered to patients for hypothyroidism. 42% of respondents to the survey similarly agreed that levothyroxine should be the first line treatment. *"You always need a start point for treatment and it makes sense to start with the simplest treatment, other options come in further down the line."* *"I think it should be tried initially but if the patient is still unwell other medication should be available."* However 49% disagreed with the recommendation. The clear steer from the verbatim comments was that other options should be made available. A majority of respondents felt that there should be patient preference and involvement in their treatment, treatment based on the individual, and that full thyroid testing is required to establish the best course of treatment.	Thank you for your comment. The committee knew that some people still feel unwell with levothyroxine monotherapy and discussed other treatment in this group. In the absence of evidence, they made a recommendation for research to help inform future guidance in this important area.

				"I am on levothyroxine only and still don't feel well. The treatment has to be personalised to benefit the individual, as any other medication should be." *"What happens if your body does not convert T4 to T3?"* ITT recommends that the final guideline makes it clear that there are other treatment options available to patients.	
ITT (Improve Thyroid Treatment Campaign)	Guideline	9	12	ITT recommends that the final guideline makes it clear that, while levothyroxine is the first treatment of choice, there are alternative treatment options available to patients. This would be in line with the British Thyroid Association guidance, which recognises some patients do benefit from the use of liothyronine. Many patients tell ITT they remain unwell on levothyroxine, and were not made aware of alternative treatments or have been refused referrals and consideration for alternative treatments. In the survey ITT asked respondents if they had been refused treatment or a referral when still symptomatic with a view to an alternative treatment. 77% of women respondents had been refused and 61% of the men had been refused.	Thank you for your comment. The committee knew that some people still feel unwell with levothyroxine monotherapy and discussed other treatment in this group. Because of the absence of evidence and the high list price of liothyronine it could not be recommended either alone or in combination. They have made a recommendation for research to help inform future guidance in this important area.
ITT (Improve Thyroid Treatment Campaign)	Guideline	9	14	ITT supports patient access to liothyronine where a specialist recommends it for treatment. This is supported by the majority of our members. A majority (73%) of respondents to our survey disagreed with the committee recommendation, and they supported access to liothyronine. A majority of respondents to the survey also agreed that the NICE draft guideline should make it clear when liothyronine should be used for treatment. There was concern by most respondents that the cost of treatment with liothyronine was the reason for the recommendation, and that patient experience of treatment was ignored. 15% of	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare

				respondents agreed that liothyronine should not be routinely prescribed, but in the verbatim comments many strongly agreed that liothyronine should be an option for a patient if required. 89% of respondents agreed that there should be clarification in the NICE guideline on when liothyronine could be prescribed. Respondents felt that, without the addition of a clear pathway on how and when to prescribe liothyronine, it would be assumed by clinicians that there is no appropriate circumstance for prescribing it. Many respondents felt that both patient and clinician would benefit from this. Some respondents also felt that NICE would word their final guidance in a way that would further restrict access to liothyronine. *"Money. Nothing more to expand on. Are they worried people will recover/feel better?"* *"It may be OK to not routinely offer liothyronine, AS LONG AS it remains an option where other treatments fail."* *"As long as 'not routinely offered' is not taken to mean 'never offered, even when indicated as a possibility'"* *"I am being denied medicine, which completely stops all symptoms, based on cost alone! The doctors just point blank refuse to even consider it."* *"There's not enough evidence because sufficient clinical trials have not been done - that does not mean it's not effective."*	professionals for individual patients (including those already taking liothyronine). A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).

				"Current guidance is working against the best interests of patients by creating a virtual blanket ban." *"Without more specifics, it is very easy for doctors to refuse without good reason."* *"Allow patients and doctors decide together."* *"If NICE clarifies when they think it appropriate to prescribe T3 then they will be stopping doctors from using their experience and common sense. After all, each hypothyroid patient is an individual with individual symptoms."* *"Depends how it is worded, it may exclude more people from a trial."* ITT is disappointed that the committee members have not considered the recommendations in the liothyronine dossier prepared and supported by many UK thyroid patient support groups, with the British Thyroid Association, and have not reflected its content in the draft guideline. This dossier was published in November 2018 and submitted to NICE in November 2018, and again in April 2019. ITT recommends that the dossier recommendations by the UK patient groups and British Thyroid Association be incorporated into the guideline. ITT also recommends that the guidance is changed to make it clear that, while not routinely offered, liothyronine can be used as a treatment. ITT is of the view that it would assist both doctors and patients if clear indication was given in the NICE guideline as to when, and in what circumstances, it would be appropriate to prescribe liothyronine.	

				ITT recommends that the guideline should state clearly when Liothyronine should be prescribed, in order to provide clarification for endocrinologists. Guidance is available from the NHS in the document "Updated RMOC (Regional Medicines Optimisation Committee) Guidance – Prescribing of Liothyronine". A link to this document is provided below. https://www.sps.nhs.uk/articles/updated-rmoc-guidance-prescribing-of-liothyronine/?fbclid=IwAR0cYs8lH7XvFrvD8Y-NTYTb9kxis2TF4D1dvfiR8JOp5o5nt41OQpBmWxs Concerns about the NICE project economic analysis based on an artificially high cost of liothyronine are addressed in a separate comment.	
ITT (Improve Thyroid Treatment Campaign)	Guideline	General	General	To assist its response, Improve Thyroid Treatment Campaign (ITT) conducted an independent patient survey on the draft NICE guideline using an industry recognised survey tool, Google Forms. The responses to the questions are included in this document. The survey was designed to capture the views of thyroid patients following the release of the NICE draft guideline on "Thyroid disease: assessment and management". The survey was shared widely across all types of thyroid patient groups and not solely with ITT members. The survey was anonymous and no individual comments can be ascribed to respondents. ITT also included a copy of the draft guideline and provided the reasons for the committee's recommendations to ensure respondents had full access to the project documents and decision rationale as they were required to make informed responses. Because of the short time available, the survey was only open between 21 June and 30 June 2019. ITT includes pertinent comments from the survey in this response to NICE. In total there were 42,181 answers provided across the entire survey that had to be	Thank you for your interest in the guideline and for this information from your survey. We acknowledge that the guideline does not cover many areas of interest to people with thyroid disease. The intention in developing the guideline is not to produce a text book that will cover all areas but to provide guidance on the areas prioritised during the scoping process. The guideline is limited by the scope set at the beginning of development and by the evidence available at the time of development and we agree that research is required to answer many questions important to patients. We hope that the inclusion of research recommendations will provide an impetus to funding of research.

				analysed (the sum of all mandatory questions + free-text responses) on the NICE guideline were received and 2022 respondents completed the survey. 93.22% of respondents were female and 6.28% were male. The % split of respondents by category was 81.4% hypothyroidism and 7.8% hyperthyroidism, and 10.8% responded to questions on both disorders. Of the hypothyroid respondents 54% state they were treated with levothyroxine, 21% with a combination of treatments, 16% with NDT, 6% with liothyronine only and 3% were not on any medication. Of the hyperthyroid respondents 30% were treated with antithyroid drugs, 20% with RAI, 13% with a partial/total thyroidectomy, 10% were in remission following ATD, and the remaining respondents were either awaiting treatment/sub-hyperthyroid or displayed high antibodies but had a normal thyroid function. A full copy of the ITT survey is available to the NICE project and committee members. Following assurance from the NICE thyroid project team that we are allowed to add links to this response form, the link to the ITT survey is here: ITT Survey on NICE draft guideline: https://tinyurl.com/yysg5ojs The ITT Survey Executive Summary: https://tinyurl.com/yyr5sxgc ITT asked survey respondents: “Having read the full draft guideline, please indicate your view of the following NICE draft guideline statement: ‘*This guideline covers assessing and managing thyroid disease. It aims to improve quality of life by*	

				making recommendations on diagnosis, treatment, long-term care and support'." Overall a majority of respondents did not think the draft NICE guideline delivered an improvement to diagnosis, treatment, care and support. 45% strongly disagreed that the NICE draft guideline improved diagnosis, treatment and support. The comments received indicate that a large majority of those who strongly disagreed felt that patient perspective and symptoms are disregarded throughout the guideline and therefore quality of life is not a focus. Many individuals felt that the cost of treatment as opposed to patient well-being influences some decisions. Many expressed a view of being disappointed that after 18 months there is little change to the current clinical knowledge summaries. *"So little seems to be changing. There is an emphasis on the TSH being the only test, little mention of symptoms and quality of life."* *"I don't believe that they are taking patient experience into account"* *"I don't think the guidelines are sufficient and as usual - price factors"* *"Dismissive and patronising guideline. Why do they think there are so many dissatisfied thyroid patients?"* 22% disagreed. Respondents felt that the draft guideline lacks a patient representation throughout and that additional content	

				is needed e.g. patient referrals process, symptoms list and when it is appropriate to prescribe alternative treatment options. There was emphasis placed on the requirement for recommended studies and research to take place quickly and a general sentiment of disappointment this has not been done previously. *"They appear to offer a quick fix, but nothing on cause or cure."* *"Because the guidelines do not recommend when the GP should refer patients to endocrine expert or try other solutions."* *"It appears that not enough studies have taken place or questions asked of genuine sufferers. I have been horrified at the disregard to people's lives."* 13% neither agreed nor disagreed with the statement. However the verbatim comments indicate uncertainty that it will promote improvement in treatment. *"I feel the guidance relies too much on achieving correct TSH and fails to address looking at the whole person and their symptoms."* *"I'm not sure it does prove quality of care."* 13% agreed with the statement. The comments point to acknowledgement of the guideline content being acceptable but somewhat basic. Many felt that further detail and clarification is needed in parts and more consideration given to patient feedback and experience.	

				"They are trying to get a balance, unfortunately the guidelines fall short of actually succeeding in their aim. More treatment options and on-going testing is needed." *"Need more input from actual thyroid patients, as they will be able to cover the problems we have had to face during diagnosis and treatment."* 7% strongly agreed with the statement and there were very few verbatim comments.	
ITT (Improve Thyroid Treatment Campaign)	Guideline	General	General	ITT considers the time provided for responding to the guideline inadequate to allow for proper scrutiny of all the documents given their length (some 1339 pages of material), as well as the complexity of both the research analyses conducted and of the issues involved. This is especially true when the stakeholder group is not a formal organisation but is voluntary and comprises patients who work full-time and/or have other commitments, in addition to health issues as a result of their condition. A consultation period should be flexible to accommodate lengthy and/or complex documents and should not be a standardised one-size-fits-all regardless, especially when the outcome will have a major impact on the quality of life of those with thyroid conditions for many years to come. ITT considers it vital that patient experience is factored into the NICE decision-making process in a meaningful way. This is negated by the limited time allowed by NICE for stakeholder organisations to respond as fully as they would wish to. As a patient representative organisation, ITT considers that the lack of adequate time to provide a more in-depth response	Thank you for your comment. NICE has a standard consultation time for all guidelines and publishes the dates at the start of guideline development to give stakeholders as much notice as possible. We realise that some guidelines are larger than others and can require a lot more thought..

				calls into question whether NICE is acting in the best interests of the patients, their families, employers and the wider public, who will all be affected, either directly or indirectly, by its guideline. ITT considers that a longer consultation period should be allowed where there are lengthy documents to consider, where there is complexity in the analyses of data and in the issues affecting patients, and where the outcomes will have far-reaching long-term implications for many patients. ITT therefore recommends that there should be a further period of consultation to allow stakeholders time to review in detail the material provided before the guideline is finalised.	
ITT (Improve Thyroid Treatment Campaign)	Guideline	General	General	ITT is of the view, as is a majority of its members, that the draft guideline does not consider the patient voice, which is contrary to the commitment from both NICE and the NHS to provide person-centred care and to prioritise the patient voice. A theme in the responses to the survey was that the patient should be consulted and included in the approach to their treatment. ITT strongly recommends that patient input should be reflected in the final guideline.	Thank you for your comment. The committee consisted of both clinical and lay members, and their views are considered with equal weight during discussions and when developing recommendations. The committee agree that patient choice is central to care for people with thyroid disease, and for this reason included the section on patient information at the beginning of the guideline. As much focus as possible on choice has been included throughout the guideline.
ITT (Improve Thyroid Treatment Campaign)	Guideline	General	General	ITT notes that the guideline is silent on hormone replacement dose levels after initiation of treatment. ITT welcomes a treatment approach which allows clinicians to prescribe based on their clinical experience and which is personalised for patients. ITT recommends that NICE include guidance that treatment may require changes to the medication dose; and this is to be determined based on patient symptoms, blood test results and clinical need, and is not directed by local CCG or Health Board policy.	Thank you for your comment. We have amended our first recommendation on monitoring and follow up of primary hypothyroidism to state “Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal well-being.”

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

ITT (Improve Thyroid Treatment Campaign)	Guideline	General	General	Thyroid disorder impacts approximately 10 times as many women as men (British Thyroid Association). The results of the ITT survey were that 79% of respondents had a combination of absence and/or job changes as a direct result of thyroid disorder. The gender split of the responses shows that both men and women had been absent from work or had job changes because of their thyroid disorder. However, the survey showed that hypothyroid women were more likely to give up work or change their job because of their thyroid disorder. This is a significant disruption to working lives and careers of women, and to the payments they make to society in tax and other contributions. One of the questions in the survey was “Have you taken time off work as a result of either awaiting diagnosis or because of ongoing symptoms of Hypothyroidism despite treatment?” 80% of hypothyroid respondents have been absent, given up work or reduced their work hours, or changed job to reduce stress because of their disorder. More women gave up work (23%) than men (17%) and more women reduced their hours or changed to a lower stress role (20% women compared to 16% men). ITT suggests that there is an indirect gender bias in the failure to consider patients’ ability to work, and that gender does need to be considered in any economic analysis and approach to treatment guidelines. Given that there are 2.6 million thyroid patients in the UK of whom approximately 90% are women, this represents 2.34 million women. If the ITT survey is representative and 43% have reduced hours, changed roles or given up work because	Thank you for your comment and this information. As reported in the Manual for developing NICE Guidelines (https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview), “productivity costs and costs borne by people using services and carers that are not reimbursed by the NHS or social services should not usually be included in any analyses”. This is for different reasons, for example time off work is implicitly incorporated in QALY. Also, if we included productivity costs in our analyses we would favour those interventions aimed at the working population. We would discriminate against the elderly, children, unemployed people and people with disabilities.

				of their thyroid disorder, that is approximately 1 million women who have had their economic well-being impacted by their thyroid disorder. ITT recommends that the NICE economic review is amended to include the economic impact to patients. ITT understands from NHS data that there are no statistics collated on thyroid patient health. ITT therefore also encourages NICE to include in its recommendations research on the health and well-being of thyroid patients.	
ITT (Improve Thyroid Treatment Campaign)	Guidline	9	15	ITT does support the use of Natural Desiccated Thyroid (NDT) in treatment where levothyroxine and combined treatment with liothyronine have not worked for a patient. ITT supports patient choice of treatment according to their individual needs. NDT, or Desiccated Thyroid Extract (DTE), was the successful treatment of choice for many decades prior to the development of levothyroxine. There are large scale patient observational studies demonstrating the successful use of NDT over long periods of treatment. It is untrue that NDT is of unknown quality. NDT goes through the same process that levothyroxine goes through and is tested to ensure that the correct amount of T4 and T3 is in each tablet. United States Pharmacopeia (USP) is the official public standards–setting authority for all prescription and over–the–counter medicines and other healthcare products manufactured or sold in the United States where most NDT is sourced. NDT has never been approved by the Food and Drug Administration (FDA), because it was already on the market when the FDA gained the authority to regulate drugs. However, the FDA allows its sale. Synthetic forms of thyroid hormone, such as levothyroxine (Synthroid), are newer and have therefore gone through the standard approval process.	Thank you for your comment. The committee recommended against the use of natural thyroid extracts because there was no evidence of benefit over levothyroxine, they are not licensed for use in the UK and the committee was concerned about unknown adverse effects because of the high proportion of T3 to T4 in them. With regard to the Hoang study you reference, this study was included in our evidence review. This was a small study with 70 participants and showed no benefit of NDT for the outcomes it reported that the committee specified in their protocol (thyroid symptoms and depression). The study did not report on other critical outcomes like quality of life. While the preference of people with thyroid disease is of course important and taken into account, expressing a preference for a treatment is not sufficient evidence to warrant recommendations to use an unlicensed product.

				UK tolerance for Levothyroxine is 90% to 105% of the stated dose (upper limit fairly recently reduced from 110%). The manufacturing specifications for NDT e.g. Thyroid USP require that each gram contains levothyroxine (T4) 34.2 to 41.8 mcg and Liothyronine (T3) 8.1-9.9mcg. This produces a T3-T4 ratio of 4.22:1 to meet the stringent standards a US pharmacopeia monograph with a permissible variance of +/- 10% Some manufacturers claim +/1-2% which is more stringent than for UK levothyroxine. Levothyroxine has been withdrawn because of manufacturing consistency issues more often than NDT/DTE. There is one randomised, double-blind, crossover study comparing the effectiveness of DTE with levothyroxine (Hoang TD, Olsen CH, Mai VQ et al. Desiccated thyroid extract compared with levothyroxine in the treatment of hypothyroidism: a randomized, double-blind, crossover study. J Clin Endocrinol Metab 2013; 98(5):1982-1990). The results of this study showed nearly half (48.6%) of the study patients expressed preference for DTE over L-T4. 75% of respondents disagreed with the recommendation on NDT/DTE in the draft guideline. A majority felt that there was patient and survey evidence for the effectiveness of NDT, but that NICE was disregarding it. Some commented that there is more evidence for the effectiveness of long-term treatment of patients with NDT than for those taking levothyroxine. Of those patients who agreed with the NICE recommendation, 13% respondents tended to agree that more evidence was required, but that it should remain an option for some patients who feel better when using NDT.	

				"There is plenty of evidence. Look for it. Countless people live healthy, active lives on NDT, there is no evidence of adverse effects at the correct dose." *"There is much evidence in other countries of the efficacy of thyroid extract. NICE ignore that and appear to want to either keep patients ill, or save money."* *"More evidence that NDT works better than Levo"* *"There is a great deal of anecdotal evidence that NDT etc. works for many patients. In the absence of scientific evidence, patient evidence should be respected and acted upon, and of course that scientific evidence should be urgently sought."* *"As far as I am aware NDT was all that was available before Levothyroxine was developed by pharmaceutical companies and people seemed to do very well on it."* *"If levo isn't working then for some people NDT seems to work better than adding T3. I would 100% not want to be forced on to it but it should be an option."* ITT recommends the final guideline is changed to reflect the views of patients that NDT can be prescribed where there is a clear patient preference and where they respond to the treatment. ITT also supports further research into the use of NDT as a treatment option.	
Midlands Thyroid Support Group	Committee Membership List	General	General	We consider the small size of the committee an inadequate representation of the advice currently available, e.g. only one pharmacist was part of the committee and no thyroid patients were represented.	Thank you for your comment. The committee constituency was discussed at a stakeholder workshop and consulted on during development of the scope for this guideline. The guideline committee was recruited using policies and procedures detailed in the guideline

					manual and the appointment of successful candidates was based on a number of factors including their expertise in thyroid disease. The candidates who best met the pre-specified criteria were recruited. We are confident that the committee represented all main specialities involved in the diagnosis and management of thyroid disease. NICE guideline committees always include people with experience of the condition and three people with experience of thyroid disease were lay members of this committee.
Midlands Thyroid Support Group	Evidence Review B	General	General	In our opinion the entire guideline is not adequately evidence based, it is formed from a minority of low-grade studies/randomised control trials. For example, in Evidence Review B, Indications for Testing, from the thousands of available studies, only 8 were detailed in relation to who should be tested, we are shocked at the number of studies that have been disregarded.	Thank you for your comment. Evidence reviews have been carried out in accordance with the NICE guideline method processes. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. Given the nature of the question of Review B, the committee felt it was appropriate to look at cross-sectional and cohort studies. The studies included are those that have met the protocol criteria that were pre-specified to prevent bias and ensure that only studies of the highest quality available that would provide relevant information are included in the evidence reviews. The committee has reviewed findings from those studies in light of their limitations and have furthermore employed their clinical expertise while making recommendations.
Midlands Thyroid Support Group	Guidance	9	12 – 16	The treatment options discussed on page 9 do not reflect current national guidelines from NHS England, NHS Clinical	Thank you for your comment. NICE recommendations are made independently of other organisations.

				Commissioners or the British Thyroid Association. Neither do they reflect the latest and final guidance "Prescribing of Liothyronine" published by the Regional Medicines Optimisation Committee in June 2019	A footnote has been added to the rationale and impact section for recommendation 13.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).
Midlands Thyroid Support Group	Guideline	1	4	This heading could be missed by a medical professional who is looking for help with diagnosis of thyroid disorders. We consider the title should include the word "diagnosis" and therefore read: "Thyroid Disease: Diagnosis, Assessment and Management".	Thank you for your comment. We have amended the guideline context section to make it clear that the guideline covers investigation of suspected thyroid disease.
Midlands Thyroid Support Group	Guideline	10	2 - 4	Statement 1.3.6 is unclear. If we have assumed the meaning of this statement correctly, we feel it would be better if it was reworded as "Start levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight for adults under 65 with primary hypothyroidism and no history of cardiovascular disease".	Thank you for your comment. The recommendation has been edited to state "Consider starting levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight per day (rounded to the nearest 25 micrograms) for adults under 65 with primary hypothyroidism and no history of cardiovascular disease
Midlands Thyroid Support Group	Guideline	10	10 - 15	We strongly disagree with statements 1.4.1 and 1.4.2. Firstly, symptoms happen for a reason and if symptoms are persistent, it is indicative of a shortage of active hormone (triiodothyronine or FT3). Secondly, Thyroid Stimulating Hormone (TSH) is a good diagnostic tool but it does not provide all the information needed. Once a patient is on medication, the TSH will drop, regardless of how much active hormone (triiodothyronine or FT3) is available for use at a cellular level. If there is not enough active hormone, symptoms will persist. TSH testing does not confirm how much active hormone is available. Due to genetic mutation many patients have reduced ability to convert the inactive hormone into the active one, and this will quickly be identified in blood tests that confirm how much triiodothyronine (FT3) is present.	Thank you for your comment. The committee agreed that FT3 doesn't help determine if treatment should change as it is a short acting hormone so will be very different on different days. Symptoms give a better indication. Recommendation 1.4.1 has been edited to reflect this and states "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing." Liothyronine is not routinely recommended and is therefore not included in these recommendations.

				Statement 1.4.1 should therefore read “Aim to alleviate symptoms whilst maintaining TSH and triiodothyronine (FT3) levels close to or within the reference range when treating primary hypothyroidism with levothyroxine”. Statement 1.4.2 should therefore read “Be aware that the TSH level can take up to 6 months to normalise for people who had a very high TSH level and/or a very low triiodothyronine (FT3) level before starting treatment or a prolonged period of untreated hypothyroidism. Take this into account when adjusting the dose of levothyroxine or liothyronine”.	
Midlands Thyroid Support Group	Guideline	10	17 - 25	We also strongly disagree with statements 1.4.3 and 1.4.4. If symptoms are persistent, it is indicative of a shortage of active hormone (triiodothyronine or FT3). Secondly, Thyroid Stimulating Hormone (TSH) is a good diagnostic tool but it does not provide all the information needed. Once a patient is on medication, the TSH will drop, regardless of how much active hormone (triiodothyronine or FT3) is available for use at a cellular level. If there is not enough active hormone, symptoms will persist. TSH testing does not confirm how much active hormone is available. Many patients have reduced ability to convert the inactive hormone into the active one, and this will quickly be identified in blood tests that confirm how much triiodothyronine (FT3) is present. Keeping the TSH level in range if there is still not enough active hormone available for the body to function will result in the patient remaining ill. This practice has been happening for far too long, testified by many patients remaining ill despite treatment. There are now well over 100,000 people complaining about their treatment and the failings of the TSH test, on UK thyroid forums.	Thank you for your comment. The evidence on patients being unable to convert T4 to T3 remains controversial. T3 is a short acting hormone and measurements of FT3 will be very variable on different days and at different times. There are currently no good tests available to measure the tissue level of active thyroid hormone. The guideline evidence review did not identify that measurements including reverse T3 and SHBG are useful in this setting.

				Statement 1.4.3 should therefore read “For adults who are taking levothyroxine and/or liothyronine for primary hypothyroidism, consider measuring TSH, thyroxine (FT4) and triiodothyronine (FT3) every 3 months until symptoms have been significantly reduced or completely eradicated, and/or all three levels have stabilised within or close to the reference range, and then once a year. Statement 1.4.4 should therefore read “For children aged 2 years and over and young people taking levothyroxine and/or liothyronine for primary hypothyroidism, consider measuring TSH, thyroxine (FT4) and triiodothyronine (FT3): - every 6 to 12 weeks until symptoms have been significantly reduced or completely eradicated, and/or all three levels have stabilised within or close to the reference range, then - every 4 to 6 months until after puberty, then once a year”.	
Midlands Thyroid Support Group	Guideline	11	3 – 13	We also strongly disagree with statements 1.4.5 and 1.4.6. Persisting symptoms are indicative of a shortage of active hormone (triiodothyronine or FT3). Thyroid Stimulating Hormone (TSH) is a good diagnostic tool but it does not provide all the information needed. Once a patient is on medication, the TSH will drop, regardless of how much active hormone (triiodothyronine or FT3) is available for use at a cellular level. If there is not enough active hormone, symptoms will persist. TSH testing does not confirm how much active hormone is available. Many patients have reduced ability to convert the inactive hormone into the active one, and this will quickly be identified in blood tests that confirm how much triiodothyronine (FT3) is present. Keeping the TSH level in range if there is still not enough active hormone available for the body to function will result in the patient remaining ill. This practice has been happening for far too long, testified by many patients remaining ill despite treatment. There are now well	Thank you for your comment. The ability of patients being unable to convert T4 to T3 remains controversial. T3 is a short acting hormone and measurements of FT3 will be very variable on different days and at different times. There are currently no good tests available to measure the tissue level of active thyroid hormone. The guideline evidence review did not identify that measurements including reverse T3 and SHBG are useful in this setting.

				over 100,000 people complaining about their treatment and the failings of the TSH test, on UK thyroid forums. Statement 1.4.5 should therefore read “For children aged between 28 days and 2 years who are taking levothyroxine and/or liothyronine for primary hypothyroidism, consider measuring TSH, thyroxine (FT4) and triiodothyronine (FT3): - every 4 to 8 weeks until symptoms have been significantly reduced or completely eradicated, and/or all three levels have stabilised within or close to the reference range, then - every 2 to 3 months during the first year of life, and - every 3 to 4 months during the second year of life”. Statement 1.4.6 should therefore read “Consider measuring TSH, thyroxine (FT4) and triiodothyronine (FT3) for adults, children and young people who continue to have symptoms of hypothyroidism after starting levothyroxine and/or liothyronine”.	
Midlands Thyroid Support Group	Guideline	11	16 - 18	In statement 1.5.1 symptoms are being ignored. If symptoms are present, then there is a problem and treatment should begin. Delaying supportive/preventative treatment will result in an increase of symptoms and a higher risk of associated illnesses and conditions developing, such as Diabetes, gallstones, fertility problems, weight gain and fatty liver disease.	Thank you for your comment. This recommendation has been edited to encompass your point and now includes reference to symptoms: “When discussing whether or not to start treatment for subclinical hypothyroidism, take into account features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous thyroid surgery or raised levels of thyroid autoantibodies.”
Midlands Thyroid Support Group	Guideline	11	20 - 23	Statement 1.5.2 also ignores symptoms. Thyroid Stimulating Hormone (TSH) testing alone is not an adequate method of testing and is certainly not a good long-term diagnosis tool, we would also point out that there is no evidence that there is a starting point for treatment based on TSH level alone. Each person is different and the level that is right for them is unique to them. It is also worrying that the possibility of primary thyroid disease could be the cause and is not being further	Thank you for your comment. Recommendations in section 1.4 of the guideline provide clarification on what should be done for children and adults in whom symptoms persist.

				investigated at this stage. We also dispute the reference range for TSH as it has never been based on fair and unbiased research. The research was significantly flawed as non-healthy patients were used alongside healthy patients to set the reference range and therefore the conclusions are unreliable. The TSH reference range in the UK is amongst the widest in the world. It discourages correct diagnosis on two grounds; firstly, because the range is too wide and secondly, because it does not give the whole picture. Many of our members and patients worldwide do not regain their health until their TSH is below 2.5 mIU/litre.	
Midlands Thyroid Support Group	Guideline	12	1 – 5	In our opinion statement 1.5.3 on page 12 is nonsensical, we consider the age of the patient is irrelevant. The differences between statements 1.5.2 (on page 11) and 1.5.3 imply that if you are over the age of 65, and you have symptoms, then symptoms are ignored, but if you are under the age of 65, symptoms are taken into account. Symptoms should never be ignored. We already disagree with statement 1.5.2 and we feel that if it were changed to include our recommendations, it would apply to any adult of any age. Therefore, lines 1 - 5 on page 12 should be removed and lines 6 - 9 should be tagged on to the end of statement 1.5.2.	Thank you for your comment. The committee recommend treatment for people with a TSH of less than 10 if they are under 65. They agreed not to make a recommendation for people over 65 with a TSH of less than 10 as there is no evidence of benefit and the potential for harm with treatment.
Midlands Thyroid Support Group	Guideline	12	6 - 9	We do not agree with this guidance, as we have mentioned previously that testing Thyroid Stimulating Hormone (TSH) levels in isolation does not give enough information. Therefore, if symptoms persist, triiodothyronine (FT3) and thyroxine (FT4) levels also need to be tested to gain more information. If FT4 is towards the top of range with no symptom improvement, but FT3 is low in range, it is likely to indicate that conversion from inactive to active hormone is impaired. Experience from members and patients worldwide shows that approximately 15% of adults are unable to eradicate symptoms with levothyroxine alone. Approximately	Thank you for your comment. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.

				1.5% of these patients have also managed to go on to identify one or more genetic faults that are known to impede or even block conversion of the inactive hormone to the active hormone.	
Midlands Thyroid Support Group	Guideline	12	11 – 26	Statements 1.5.4 and 1.5.5 again focus on testing Thyroid Stimulating Hormone (TSH) in isolation, as a means of monitoring. We must re-emphasise the pointlessness of testing TSH alone. Triiodothyronine (FT3) and thyroxine (FT4) levels need to be tested to gain more information and understand the full picture. The patient may have conversion problems. It seems unethical to us, to restrict increased or alternative treatments purely based on clinical results alone. It is immoral to let patients suffer as a result of inaction and/or incorrect treatment as symptoms are not only dreadful, but debilitating, resulting in patient suffering. Section 1.5.4 disregards reference ranges for TSH, FT4 and FT3, there seems little point in having these reference ranges if they are going to be ignored resulting in patient suffering.	The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Midlands Thyroid Support Group	Guideline	13	4 - 6	We feel that there are omissions in statement 1.5.6 pertaining to our previous arguments surrounding symptoms, Thyroid Stimulating Hormone (TSH) and triiodothyronine (FT3) testing. This statement should read “For adults with untreated subclinical hypothyroidism or adults who have stopped levothyroxine or liothyronine treatment for subclinical hypothyroidism, and who are symptom free, consider measuring TSH, FT3 and FT4:”	Thank you for your comment. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Midlands Thyroid Support Group	Guideline	13	13 – 25	Statements 1.5.7, 1.5.8 and 1.5.9 include no reference to the testing of triiodothyronine (FT3), and there is no reference to symptoms. There is still too much focus on Thyroid Stimulating Hormone (TSH). We also must remind the committee that there is no evidence that there is a recognised and correct point in terms of the TSH range, where treatment should begin. Each child, young person or adult is unique.	Thank you for your comment. These recommendations relate to children who are not receiving treatment or have had treatment stopped and therefore they are unlikely to have symptoms. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to

				The most important hormone to test is triiodothyronine (FT3), and the objective should be to relieve symptoms.	diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Midlands Thyroid Support Group	Guideline	14	7 - 9	We disagree with statement 1.6.1 in that measuring TSH receptor antibodies (TRAbs) alone will not necessarily correctly confirm Graves' Disease. It is important to test for Thyroglobulin Antibodies (TgAbs) and Thyroid Peroxidase Antibodies (TPOAbs) as well. Testing for Thyroid Stimulating Immunoglobulin (TSIAbs) should also be considered. TPOAbs are tested positive in approximately 95% of patients with Hashimoto's Disease, but they are also found in between 50% and 80% of patients with Graves' Disease and we are aware of cases where patients have been diagnosed as having Graves' Disease and are treated for it, when in fact, they were actually suffering from Hashimoto's Thyroiditis, which can cause a short but debilitating period of hyperthyroidism in its early stages.	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Midlands Thyroid Support Group	Guideline	14	17	We feel that technetium scanning should be considered if testing for thyroid antibodies (TRAbs, TgAbs, TPOAbs and TSIAbs) prove negative, i.e. testing for all thyroid antibodies should be carried out first.	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Midlands Thyroid Support Group	Guideline	15	1 - 3	We disagree with statement 1.6.6. Because of the risks involved with using antithyroid drugs, and the fact that there is a chance that they are inappropriate, we feel that only a specialist should consider commencing their use. However, if it is the right treatment approach, in order to start treatment sooner, perhaps the doctor and the specialist could consult on	Thank you for your comment. The committee believe it is appropriate for the GP to start treatment and anticipate that GPs will talk to a specialist before initiating treatment on a case by case basis if they are unsure of what to do.

				the matter first to agree on the way forward, whilst the patient is waiting for their specialist assessment.	
Midlands Thyroid Support Group	Guideline	15	10 - 21	We strongly disagree with statements 1.6.8, 1.6.9 and 1.6.10. We have knowledge of cases where patients were not given a choice between radioactive iodine and antithyroid drugs, and as a result, they were left with a totally non-functioning thyroid gland, many debilitating side-effects and permanent hypothyroidism. In some of these cases, patients were knowledgeable and would have preferred to try antithyroid drugs in order to retain a functioning thyroid gland, but they were not given an option. We feel that in most cases, if patients fully understood the risks involved, e.g. that they could become hypothyroid for the rest of their life, they would also prefer to try to save their thyroid gland, before writing it off completely. It makes sense to at least attempt treatment with antithyroid drugs before considering treatment with radioactive iodine, even if there is a strong chance that the antithyroid drugs will not work. The consequences of radioactive iodine treatment could be life-changing in a very negative way, and therefore, patients need to have a say in how they are treated. They have to live with the consequences of the treatment - not the doctor - not the specialist. Recent research has also found links between radioactive iodine treatment and solid cancer mortality in hyperthyroidism (see comments 46 – 48 below), and this is yet another important reason why patients must be given a choice between RAI and antithyroid drugs. This is absolutely not a decision for the doctor or the specialist to make, as they will not have to live with the consequences of the treatment, and whilst they might not wish to admit it, they could even find themselves too easily influenced by cost, putting the patient's needs last. Of course, if antithyroid drugs do not work, then there may be no choice but to consider radioactive iodine or surgery.	Thank you for your comment. The committee agreed that is it important to offer choice in any decision about treatment and have included this as part of our guidance. They hope that this will improve equity of information and choice across the NHS. This study you mention was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.

Midlands Thyroid Support Group	Guideline	16	10 - 15	In light of recent research linking radioactive iodine with solid cancer mortality in hyperthyroidism, we would suggest that statement 1.6.13 needs review. Kitahara CM, Berrington de Gonzalez A, Bouville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism [published online July 1, 2019]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.0981	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Midlands Thyroid Support Group	Guideline	16	19 - 21	In light of recent research linking radioactive iodine with solid cancer mortality in hyperthyroidism, we would suggest that statement 1.6.15 needs review. Kitahara CM, Berrington de Gonzalez A, Bonville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism [published online July 1, 2019]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.0981	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared

					with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Midlands Thyroid Support Group	Guideline	17	5 – 13	In light of recent research linking radioactive iodine with solid cancer mortality in hyperthyroidism, we would suggest that statements 1.6.17 and 1.6.18 need review. Kitahara CM, Berrington de Gonzalez A, Bouville A, et al. Association of radioactive iodine treatment with cancer mortality in patients with hyperthyroidism [published online July 1, 2019]. *JAMA Intern Med*. doi:10.1001/jamainternmed.2019.0981	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

Midlands Thyroid Support Group	Guideline	19	1 - 3	There is too much reliance on keeping Thyroid Stimulating Hormone (TSH) within the reference range and there is no reference to symptoms. Upon becoming hyperthyroid, the body's cells become accustomed to higher levels of triiodothyronine (FT3), so it is important to keep these levels relatively high to eradicate symptoms for most patients. It is often impossible therefore to maintain FT3 levels at the top of range whilst keeping TSH levels within range. If symptoms persist, there is something wrong and the FT3 levels are not right for that patient.	Thank you for your comment. The guideline recommends that initially TSH, FT3 and FT4 are monitored. Once the patient becomes hypothyroid we recommend that the guidance on monitoring hypothyroidism is followed. This guidance suggests that TSH and FT4 should be measured if symptoms are ongoing.
Midlands Thyroid Support Group	Guideline	19	6	Statement 1.7.2 refers to following recommendations in statement 1.3.6, we have asked for clarification on 1.3.6.	Thank you, we have responded to that comment.
Midlands Thyroid Support Group	Guideline	19	7	Statement 1.7.2 refers to following recommendations in statements 1.4.1 to 1.4.6. In various comments, we have expressed disagreement with these statements.	Thank you, we have responded to those comments in turn
Midlands Thyroid Support Group	Guideline	19	9 - 15	We disagree with statements 1.7.3 and 1.7.4. Thyroid Stimulating Hormone (TSH) testing alone is inadequate. Other patients with hypothyroidism (i.e. those who were not hyperthyroid to start with) are often not diagnosed as being hypothyroid because the TSH test does not give all the required information. Why should it be any different for patients who become hypothyroid as a consequence of radioactive iodine treatment? Testing triiodothyronine (FT3) levels is far more useful and accurate.	Thank you for our comment. Recommendation 1.7.3 has been amended to recommend measuring TSH and measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range.
Midlands Thyroid Support Group	Guideline	19	22 - 25	Statement 1.7.7 refers to following recommendations in statements 1.3.6 and 1.4.1 to 1.4.6. In various comments, we have expressed disagreement and/or a need for clarification with these statements.	Thank you, we have responded to those comments in turn
Midlands Thyroid Support Group	Guideline	19	26 - 28	Again, there is over-emphasis on Thyroid Stimulating Hormone (TSH) testing. Triiodothyronine (FT3) and Thyroxine (FT4) should also be tested, especially if symptoms persist or have worsened.	Thank you for your comment. This has been amended to recommend measuring TSH and FT4 at 2 and 6 months post-surgery, then TSH annually. If TSH is below the reference range FT4 (if not already measured) and FT3 should also be measured.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

Midlands Thyroid Support Group	Guideline	20 – 21	2 – 19 & 1 - 13	On pages 20 and 21, under the headings of “Monitoring of antithyroid drugs” and “Managing and monitoring subclinical hyperthyroidism”, we feel that there is still far too much emphasis on Thyroid Stimulating Hormone (TSH) testing, and not enough consideration given to symptoms or levels or triiodothyronine (FT3).	Thank you for your comment. The recommendations on monitoring after antithyroid drugs have been amended to recommend testing with cascading. By cascading we mean measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range. For treating subclinical hyperthyroidism seeking specialist advice is advised. It is anticipated the treating clinician will decide the most appropriate strategy. For untreated subclinical hypothyroidism FT4 and FT3 are already recommended for adults when TSH is outside the reference range and for all children when TSH is tested.
Midlands Thyroid Support Group	Guideline	22	18 - 19	We disagree with statement 1.9.7. If there are no symptoms, and there appears to be normal thyroid function, then there is indeed no need to offer treatment to adults with non-malignant thyroid enlargement. However, even if there appears to be normal thyroid function but there are mild symptoms, treatment should be considered, as having symptoms at all is indicative of a problem and ignoring them could lead to a worsening of symptoms because the problem is not being resolved.	Thank you for your comment. In the absence of evidence, the committee agreed that mild symptoms alone were not enough to warrant treatment unless a person has difficulty in breathing of there are clinical concerns.
Midlands Thyroid Support Group	Guideline	24	14 – 18	Under key recommendations for research we consider that in addition to studies into Levothyroxine and Liothyronine combination therapy, more studies are also required into Liothyronine only therapy for patients with the D102 gene polymorphism.	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
Midlands Thyroid Support Group	Guideline	28 – 29	General	Under the heading “Why the committee made the recommendations” and throughout all the documents, there is repeated over-reliance on the Thyroid Stimulating Hormone (TSH) test. We understand that many people are not being diagnosed with secondary or central hypothyroidism, when it is	Thank you for your comment. The TSH test is an important part of thyroid disease investigation and management. However additional testing, signs and symptoms are also important. The committee has considered all available evidence in order to make the

				present because of the reliance on Thyroid Stimulating Hormone (TSH) testing in isolation. Dr Robert Utiger was a pioneering doctor in the field of endocrinology and the creator of the TSH test as well as helping develop other thyroid tests also. Dr Utiger, with all of his background knowledge, said that he hoped that doctors will still practice medicine and treat the patient - not the TSH levels. He believed that the best way to evaluate whether a patient's metabolism was causing their symptoms or not, was to measure body temperature and heart rate and to offer a therapeutic trial of T3. He did not want his test to be used as a substitute for all other possible tests and to be considered more important than symptoms. To get a full picture of what is actually happening, TSH needs to be taken into account, but it also needs to be taken in context. TSH only reveals part of the full picture. Even if Free Thyroxine (FT4) testing is performed too, this still does not provide information about Triiodothyronine (FT3) levels, and this is the active hormone that is actually needed at a cellular level. If there is not enough active hormone present, hypothyroid symptoms will be present, and there is a strong possibility that thyroid disease is present too. Reverse Triiodothyronine levels (RT3) and various thyroid antibody levels reveal a lot about what is going on too. If further testing reveals more questions than answers, there are many more tests that can be done to give an even larger picture, such as testing for important vitamin and/or mineral deficiencies and keeping a diary of diet, basal body temperature and heart rate. Symptoms are probably the most important clues of all though. If symptoms are present, there is a situation that needs to be addressed.	most appropriate recommendations possible. Some of these recommendations reflect the fact that people may feel unwell despite their TSH being within the reference range and specifically recommend consideration of changes to treatment in these situations.

				When a patient visits their doctor for diagnosis, they are not presented with a list of symptoms. We understand that most symptoms are vague, but there are so many symptoms that are caused by thyroid conditions that it is not so much about what symptoms a patient has – it is more about how many symptoms a patient has. To have most of the symptoms on a symptoms list, no matter how vague they are, strongly indicates a thyroid condition or problem is present. This does not necessarily mean that there is thyroid disease, but it does mean that the patient is genuinely ill, perhaps through a deficiency of Vitamin D or Vitamin B12. That is why it is so important to treat the patient based on symptoms foremost, and to not rely on TSH alone. We can only estimate, but we believe that it is possible that the TSH test fails to recognise and correctly diagnose up to 85% of all thyroid patients.	
Midlands Thyroid Support Group	Guideline	31	1 - 2	We find it hard to understand why the committee was unable to find evidence to support the use of iodine and selenium supplements. There are numerous papers published on the subject of supplements and it has been found that selenium deficiency decreases the production of thyroid hormones, as it decreases the function of selenoproteins, in particular, in the iodothyronine deiodinases (DIOs), which are a family of enzymes that remove specific iodine atoms, and are responsible for the conversion of Thyroxine (T4) to Triiodothyronine (T3). We can provide evidence.	Thank you for your comment. There was no evidence that met the protocol criteria for these evidence reviews. While there may be some published research into these treatments which will have its merits, it is not of the nature required to make definitive recommendations on treatment in a NICE guideline in this context.
Midlands Thyroid Support Group	Guideline	31	11 - 17	Under the heading “Why the committee made the recommendations”, we are also concerned about the reference to the increased cost involved by having to increase medication to achieve a TSH level in the lower half of range. It is felt that this is a short-sighted approach, as Levothyroxine	Thank you for your comment. Thank you for your comment. This NICE guideline is written from the perspective of the UK NHS and PSS, and therefore takes account of current UK prices available across the NHS. Liothyronine is subject to CMA investigation and a

				(T4) is very cheap and therefore, an increased dose of Levothyroxine is justifiable if it alleviates or eradicates symptoms completely, helping to fully restore the patient's full health, compared to the costs involved in trying to investigate and treat remaining symptoms instead thus incurring patient suffering in the meantime. We believe that this applies to the use of Liothyronine (T3) too, although in the case of T3 it is currently unjustifiably very expensive in the UK at this time. It is not expensive in other countries and if it were being sourced at a fair price, it could be more cost-effective in the long-term. The pricing issue needs to be resolved, and not used as an excuse for denying T3 to patients, who would definitely benefit from its use.	cross reference to the CMA investigation has now been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). However, until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline. The guideline states that liothyronine should not be routinely prescribed as no clinically important difference was identified for health-related quality of life, between T4 and T4/T3. There was a clinically important harm of combined levothyroxine and liothyronine for quality of life-role physical functioning and TSH suppression. There was a clinically important benefit of combined levothyroxine and liothyronine for quality of life-social functioning and quality of life-role-emotional. Overall, the committee agreed that the evidence was generally suggestive of combined therapy having no important effect on quality of life and the small and contradictory benefits and harms in subdomains of quality of life were more likely to reflect the low quality of the underlying evidence. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).
Midlands Thyroid Support Group	Guideline	37	13 - 17	Under the heading "How the recommendations might affect practice", we are concerned about the strong possibility that radioactive iodine will end up becoming the preferred treatment and possibly even the only option open to patients based on cost, and not what is best for them. There are many	Thank you for your comment. On the basis of full breadth of the clinical and cost effectiveness evidence the committee agreed it was appropriate to make recommendations that meant radioactive iodine would be offered over the other first line definitive treatment

				associated risks with radioactive iodine treatment and, as mentioned in other comments, the patient has to live with the long-term consequences of any treatment, they should therefore be offered as many options as possible.	options (long term ATDs or surgery) to more people than is currently the case. However, they listed a number of situations in which either of the alternatives may be preferable. and emphasised the importance of discussing this treatment with the patient in recommendation 1.6.7. If a person refuses radioactive iodine then other options can be considered.
Midlands Thyroid Support Group	Guideline	4	General	In Evidence Review A, Information for people with thyroid disease, on page 5, lines 14 – 19, sources of further health information for patients are discussed and named, e.g. The British Thyroid Foundation and Thyroid UK but these are not mentioned in the guidance and we consider they should be included in section 1.1 so that health professionals are able to refer patients to sources of further information about their conditions.	Thank you for your comment. Links to appropriate patient information sites are included with the guideline when it is published on NICE's web site
Midlands Thyroid Support Group	Guideline	4	7	This line should read "Thyroid disease usually responds well to correct treatment. For people who do not improve other options should be considered".	Thank you for your comment. The committee has reviewed this and prefer the statement as written. There are also recommendations in specific sections on what to do for patients who do not respond to treatment.
Midlands Thyroid Support Group	Guideline	4	8 - 9	This statement should read "The goal of treatment is to eradicate symptoms, which might be accomplished by achieving thyroid function test results within or close to the reference range. If symptoms are not eradicated upon achieving thyroid function test results within or close to the reference range, then further investigation is needed".	Thank you for your comment. We have changed 'manage symptoms' to 'alleviate symptoms. Your point about further investigations is covered by recommendations on what to do if treatment is not successful within our sections on managing and monitoring thyroid disease.
Midlands Thyroid Support Group	Guideline	4	10 - 11	This statement is ambiguous and could imply that a person is still ill, even if they do not feel ill, i.e. a medical professional could misinterpret this statement and insist that a patient is ill despite feeling well, because of the thyroid function test results. No assumptions should be made as this in turn could lead to incorrect diagnosis or treatment. We suggest that this statement should read "People may only feel well when their thyroid function test results are not within or close to the	Thank you for your comment. This bullet point addresses the notion that people with abnormal thyroid function may not have symptoms – it does not imply that we would be driving thyroid function outside the reference range with medication so that people would feel well.

				reference range. This does not necessarily mean that they are ill, well or on the correct or wrong treatment". We consider that in these circumstances, maybe where a discrepancy in thyroid levels has been identified following a routine blood test, follow up testing is carried out at appropriate intervals.	
Midlands Thyroid Support Group	Guideline	4	12 – 13	This statement is ambiguous as it does not refer to the symptoms in context, i.e. a patient would not warrant thyroid investigation if they did not have symptoms. One must therefore assume (and it is not good enough to have to assume) that this statement therefore refers to a situation where the patient has been undergoing treatment to a point where the symptoms have stopped. This needs clarification. We suggest that this statement should read "If after treatment, there is an absence of symptoms, it may be necessary to continue with treatment to ensure that symptoms do not return and, to reduce the risk of long-term complications".	Thank you for your comment. We have reworded this to state "Even when there are no symptoms, treatment may be recommended to reduce the risk of long-term complications." The purpose of the recommendation is to inform people who have been diagnosed with thyroid disease that even if they feel well treatment may be advisable.
Midlands Thyroid Support Group	Guideline	4	16 - 17	This statement is confusing as the life of thyroxine is only relevant where thyroxine (T4) mono-therapy is not successful or is over successful, for example, some patients need the addition of liothyronine (T3) and this sometimes does not work until some or all of the thyroxine (T4) has been depleted. We would suggest that this statement reads "Symptoms may lag behind treatment changes because the body needs time to adjust to them. Levothyroxine can last up to 14 days in the body and therefore, it can take a long time for any treatment adjustments to be reflected in the reduction of symptoms".	Thank you for your comment. We have amended this bullet point to read "Symptoms may lag behind treatment changes for several weeks to months." We have also amended the subsequent bullet point to read "Day-to-day changes in symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine".
Midlands Thyroid Support Group	Guideline	4	18 - 19	This statement is confusing as it does not state whether it refers to thyroid symptoms or symptoms other than thyroid. The statement should therefore read "Day to day changes in unexplained symptoms are unlikely to be due to underlying thyroid disease and should be further investigated". If the statement is intended to refer to day to changes in thyroid symptoms, we do not agree as patient experience* shows that	Thank you for your comment. We have amended this bullet point to read "Day-to-day changes in symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine". We have also amended the previous bullet point to read "Symptoms may lag behind treatment changes for several weeks to months."

				due to underlying thyroid disease, symptoms can vary on a day-to-day basis depending on the demands placed on the body, for example through other illness, diet, workload, stress, traumatic events or physical demands, e.g. exercise/increased activity. *NB References to patient experience are evidenced in the recent House of Lords dossier entitled “Case details with clear evidence that NHS England Guidance on prescribing Liothyronine is not being followed by CCGs”.	
Midlands Thyroid Support Group	Guideline	5	General	On page 5, under section 1.1.2, we feel that as there is statistically an increased risk of developing Diabetes in thyroid patients, it should be specifically mentioned as a concern and identified as a further cause for routine monitoring, that should be offered automatically, as part of the management of patients with thyroid disease. Early detection is important, even though it can be misdiagnosed, and it should not be necessary to wait until Diabetes is fully developed before anything is done about it, even if there is no evidence of Diabetes upon first diagnosis of thyroid disease. Monitoring should start straight away, and patients should be made aware of possible symptoms. For example, some symptoms of Diabetes are the same or similar to those of hypothyroidism.	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. It was not possible to review the evidence of association between thyroid disease and all possible co-existing conditions. The evidence review for who should be tested for thyroid disease found that T1DM was associated with thyroid disease; this suggests that testing for the latter in the presence of the former may be appropriate. However, that is not sufficient evidence to support routine monitoring of all people with thyroid disease for diabetes.
Midlands Thyroid Support Group	Guideline	5	General	On page 5, under section 1.1.3, we feel that an important omission has been made. Auto-immune thyroiditis should be mentioned, for example, Hashimoto’s Thyroiditis is a major cause of hypothyroidism, and auto-immune conditions can lead to other auto-immune conditions developing and also food intolerances.	Thank you for your comment. This section of the guideline is to provide information to people once they have been diagnosed with thyroid disease. We have included a recommendation on testing for thyroid dysfunction in people with auto-immune diseases.
Midlands Thyroid Support Group	Guideline	5	General	We feel that other treatment options should also be referred to in section 1.1.3, even if they are not presently available through the NHS, specifically Natural Desiccated Thyroid	Thank you for your comment. We have amended the first bullet point to state possible drug interactions with thyroid hormone replacements.

				(NDT). In our experience many people only get well again through the use of NDT and there is substantial evidence to support this and the fact that NDT is safe.	
Midlands Thyroid Support Group	Guideline	5	1 - 2	We feel that as current practice does not test all the hormones that are important by default, and that Thyroid Stimulating Hormone (TSH) testing alone is an inadequate testing method, patients should also be told of all the thyroid function tests that are available, including tests not currently available on the NHS (e.g. genetic testing), so they understand that there are other avenues to explore if they are still concerned or unwell. We would suggest a statement that reads “their underlying condition, including the role and function of the thyroid gland, what the thyroid function tests are and what they mean, and what tests can be done to investigate matters further”.	Thank you for your comment. The recommendations for testing include tests other than TSH and are based on the available evidence and committee consensus. The committee believe these tests are sufficient to provide the required information on the diagnosis of thyroid disease.
Midlands Thyroid Support Group	Guideline	5	11 - 12	There is only mention of levothyroxine (T4) and no mention of liothyronine (T3). As liothyronine is an approved treatment, although rarely prescribed, this should be included in this statement.	Thank you for your comment. We have changed ‘levothyroxine’ to ‘thyroid hormone treatment’.
Midlands Thyroid Support Group	Guideline	5	13	There is only mention of levothyroxine (T4) and no mention of liothyronine (T3). As liothyronine is an approved treatment, although rarely prescribed, this should be included in this statement.	Thank you for your comment. The committee agreed the specific issue here was how and when to take levothyroxine.
Midlands Thyroid Support Group	Guideline	6	Table	We disagree with the statement regarding risks/disadvantages of the use of radioactive iodine. We feel that the statement should read “Strong possibility of long-term or permanent hypothyroidism, requiring the need for replacement thyroid hormones, such as, but not limited to, levothyroxine (T4)”.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Midlands Thyroid Support Group	Guideline	6	Table	We consider there are omissions in the table with regard to risks/disadvantages of the use of radioactive iodine. There is a significant risk of permanent saliva gland damage and of breast iodine uptake. Recent research has also found a link	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the

				between radioactive iodine treatment and solid cancer mortality in hyperthyroidism.	recommendation on providing information to people with thyrotoxicosis.
Midlands Thyroid Support Group	Guideline	6	Table	We disagree with the statement regarding risks/disadvantages of surgery. The statement should read “Permanent hypothyroidism after total thyroidectomy, requiring the life-long need for replacement thyroid hormones, such as, but not limited to, levothyroxine (T4)”.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Midlands Thyroid Support Group	Guideline	7	General	On page 7, we feel that there is an omission under the heading “Indications for tests for thyroid dysfunction”. We feel that tests should also be offered to adults, children and young people where there are already existing blood-related family members with thyroid disease. Thyroid disease runs (genetically) in many families, and is for example, often suffered by all of the women in such a family.	Thank you for your comment. We did not find evidence to suggest that an approach involving testing all people with a family history of thyroid disease would be clinically and cost effective. However, family history of thyroid disease would be one of the factors a healthcare professional should take into account when considering the overall likelihood of thyroid disease in an individual.
Midlands Thyroid Support Group	Guideline	7	13 - 15	We disagree with the reference to “… 1 symptom alone may not be indicative of thyroid disease” as it is stating the obvious. It is most unlikely that a patient with thyroid disease will report just one symptom. In our experience all patients with thyroid disease have multiple symptoms but they, nor their doctors, are fully aware of what all the potential symptoms of thyroid disease are. There is no list of symptoms contained in the guidelines. Symptoms are listed in Evidence Review B but we consider this list should be included in the guideline for health professional reference also. If patients and doctors were aware of the extensive list of possible symptoms of thyroid disease, they would be more likely to investigate thyroid disease being the root cause and negate other unnecessary and expensive testing. It would also help prevent incorrect diagnosis, e.g. depression is a frequent symptom of hypothyroidism and in many cases the underlying hypothyroid condition is missed	Thank you for your comment. Guidelines are not intended to be a text book and it is expected that healthcare professionals will be familiar with classical description of hypo- and hyper -thyroid disease. The guideline does include specific symptoms/conditions where we found evidence for an association. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated.

				with only a diagnosis of depression being made. Depression often resolves with correct thyroid treatment. Therefore, this statement should read “Consider tests for thyroid dysfunction for adults, children and young people if there is a clinical suspicion of thyroid disease, but bear in mind that symptoms may not be indicative of thyroid disease”.	
Midlands Thyroid Support Group	Guideline	7	20 - 21	Research and observations have often revealed that a traumatic event, such as a car crash, bereavement or divorce can trigger thyroid disease. With this in mind, we feel that the statement under 1.2.3 should read “Consider tests for thyroid dysfunction for adults, children and young people with depression or unexplained anxiety, or that have recently experienced a traumatic event”.	Thank you for your comment. A previous traumatic event was not believed to be a trigger for thyroid disease by the committee and therefore was not included in the review. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated. The guideline does include specific symptoms/conditions where we found evidence for an association.
Midlands Thyroid Support Group	Guideline	8	General	On page 8, we strongly disagree with statements 1.2.7 and 1.2.8. Testing Thyroid Stimulating Hormone (TSH) alone has repeatedly proven to be insufficient as it only provides part of the picture. The inventor of this test was concerned that it would become a test that removed the need for other testing. He wanted the patient to be treated and not to rely on a single test for diagnosis. Thyroid disease is easily missed using TSH testing in isolation. Even if Free Thyroxine (FT4) testing is done, this still does not provide information about levels of the active hormone Triiodothyronine (FT3) which is what is actually used by the body as opposed to being a storage hormone. If there is insufficient active hormone present, hypothyroid symptoms will present. We feel that as soon as thyroid disease is suspected, regardless of age or whether pituitary disease is suspected, as a minimum, for first testing, Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3), Free	Thank you for your comment. The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. The committee agreed that this approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.

				Thyroxine (FT4), Thyroglobulin Antibodies (TgAbs) and Thyroid Peroxidase Antibodies (TPOAbs) should all be tested. Ideally, Vitamin D, Vitamin B12, Ferritin, Folate and Reverse Triiodothyronine (RT3) levels should also be tested. Unfortunately, RT3 testing is not currently available except through a private laboratory. This is something that we also consider needs serious address. As documented in Evidence Review C, Thyroid Function Tests, the TSH test is driven by cost saving rather than health need, we consider this over-reliance is more costly to the NHS in the long term.	These recommendations only relate to the initial tests that aid the diagnosis of thyroid disease. Subsequent testing once thyroid disease is confirmed is covered in the sections related to hypothyroidism and thyrotoxicosis respectively.
Midlands Thyroid Support Group	Guideline	9	General	On page 9, we strongly disagree with statements 1.3.1 and 1.3.2. We feel that regardless of age, if Thyroid Peroxidase Antibodies (TPOAbs) are present, they should be monitored, as changes in diet, age and lifestyle can cause levels to rise or fall. For example, if a patient researches auto-immune diseases, they might change their lifestyle through diet and/or exercise in order to improve their condition. Regular testing would confirm whether changes have been successful. Once a patient has one auto-immune disease, they are at significantly increased risk of developing other auto-immune diseases. We also feel that Thyroglobulin Antibodies (TgAbs) should be tested too, and if present, they should also be monitored for the same reasons.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee did recommend repeat testing as this would not affect a change in management. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Midlands Thyroid Support Group	Guideline	9	14 - 16	We strongly disagree with statement 1.3.4. We agree that not all people need to be routinely offered Liothyronine (T3), however, where there is a continuation or worsening of	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4

				symptoms and/or clinical evidence to confirm that treatment is not working, regardless of where that evidence has been sourced, that should always routinely result in patients being offered Liothyronine (T3). We also strongly disagree with your reference to there not being enough evidence to prove that Liothyronine (T3) offers benefits over levothyroxine (T4) mono-therapy. There is evidence that Liothyronine (T3) only or combination therapy can be and is often more effective than levothyroxine (T4) mono-therapy.	currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Hence the committee's recommendations for further research in this area.
Midlands Thyroid Support Group	Guideline	9	14 - 16	We understand that a conference is to take place on 3rd November 2019 between the American Thyroid Association, the British Thyroid Association and the European Thyroid Association to discuss the evidence-based use of Liothyronine and Levothyroxine combinations. We feel that publication of NICE guidance on thyroid disease should be delayed in order to be able to consider the findings of this conference and to include them where relevant. Should NICE guidance be published prior to considering the findings of this conference, it may be immediately out of date with national and international opinion on the best treatment protocols.	Thank you for your comment. The committee believe the conference will not be presenting new findings and will present the current evidence which is what the recommendations in this guideline are based on. .
Midlands Thyroid Support Group	Guideline	9	17 - 19	We strongly disagree with statement 1.3.5. Natural thyroid extract or Natural Desiccated Thyroid (NDT) has been successfully and safely used since the late 19th century. Many of our members, and many patients worldwide use NDT because it is the only treatment that successfully reinstates good health for them, in some cases it has been life-saving. Reports of long-term adverse effects caused by levothyroxine (T4) are well documented however, whilst we have been unable to find any significant evidence of long-term adverse effects from using NDT.	Thank you for your comment. The committee recommended against the use of natural thyroid extracts because there was no evidence of benefit over levothyroxine, they are not licensed for use in the UK and the committee was concerned about unknown adverse effects because of the high proportion of T3 to T4 in them.
Midlands Thyroid Support Group	Guideline	General	General	There are omissions in section 1.1.2. Information given to patients with thyroid disease should include the fact that thyroid disfunction usually presents with a wide variety of	Thank you for your comment. The committee considered it was not possible to develop a definitive list of symptoms that may be associated with thyroid disease.

				multiple symptoms as it can affect every bodily system. Patients should be given a list of possible symptoms which would assist them in monitoring improvement. A list of possible symptoms included in the guideline would be helpful for healthcare professionals, especially as the vast majority of patients in our group have struggled, sometimes for years, to get a diagnosis from their healthcare professional as their symptoms have not been connected and instead attributed erroneously to another condition, frequently depression, which quickly resolves when thyroid levels are normalised.	The guideline makes specific reference to testing where an association was found between some conditions/symptoms and thyroid disease. Depression is included in the guideline as a condition when thyroid assessment should be considered.
Midlands Thyroid Support Group	Guideline	General	General	In section 1.1.2 there are also omissions with regard to diet/nutrition, i.e. good and bad food choices, potential food intolerances, vitamin and mineral deficiencies. Patients need to understand that treatment might not work or might stop working if there are problems or deficiencies in these areas.	Thank you for your comment. We have mentioned the possible drug interactions with thyroid hormone replacement therapy in recommendation 1.1.4 where the committee was aware of a specific issue. The committee was not aware of specific issues with other treatments related to thyroid disease and consequently did not make statements on this.
Midlands Thyroid Support Group	Guideline	General	General	We think that the guideline should be sectioned according to age of the patient. In the instance that a General Practitioner has a young child they suspect is suffering from a thyroid disorder, in the limited time available to them, it will be necessary for them to read the whole guideline to find specific age-related guidance.	Thank you for your comment. The committee considered this, but it was felt there was too much overlap between different adult and children recommendations for this to be beneficial.
Midlands Thyroid Support Group	Guideline	General	General	There is no mention at all regarding the treatment of pregnant women in this guideline. Whilst we acknowledge that there is a new guideline in preparation by the Royal College of Obstetrics and Gynaecology, we think that both guidelines should at least be published simultaneously and cross-referenced. In instances where there is a family history of autoimmune thyroid disease, we would expect to see guidance towards conducting thyroid function tests in women who are recently confirmed as pregnant. This could reduce this risk of thyroid conditions triggering complex anti-natal conditions, ensure correct thyroid	Thank you for your comment. Pregnancy was excluded from the scope of this guideline, and we understand that the RCOG guideline will be published soon. Population screening is also outside the scope of the guideline.

				levels throughout pregnancy and reduce the risk of miscarriage, failed pregnancy and preeclampsia. Neither is there any mention of postpartum thyroiditis and necessary testing protocols to identify this.	
Midlands Thyroid Support Group	Guideline	General	General	There is no mention anywhere in the guideline of hyperparathyroidism and often resultant thyroidectomy. As above, if this is subject to a separate guideline, this needs to be published simultaneously and cross-referenced.	Thank you for your comment. Hyperparathyroidism is a different topic and therefore we have not referenced it in this guideline. There are a number of related guidelines that could be referred to. These are best identified using NICE's web site.
Midlands Thyroid Support Group	Guideline	General	General	There is no mention anywhere in the guideline of hypoparathyroidism. As above, if this is subject to a separate guideline, this needs to be published simultaneously and cross-referenced.	Thank you for your comment. Hypoparathyroidism was outside the scope of this guideline, so we have not made recommendations related to it. There is no NICE guideline on this topic.
Midlands Thyroid Support Group	Guideline	General	General	There is no mention anywhere in the guideline of cardiovascular issues being a complication of hypothyroidism. There is no acknowledgement of the advantages of treatment with T3, rather a positive discouragement to use it as a treatment. It should be acknowledged that heart failure can be a symptom of low T3, this is a serious and potentially fatal omission for some patients.	Thank you for your comment. The committee did not consider this to be a specific issue and no evidence was identified that liothyronine should be specifically considered for people with cardiovascular issues as a complication of hypothyroidism.
Midlands Thyroid Support Group	Guideline	General	General	Under testing in all sections of the draft guideline, there is no mention of a physical thyroid examination and what to do if a palpable mass is detected.	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on areas raised during scoping by stakeholders. Clinical examination was not raised as an area requiring evidence review during scoping, however the guideline includes recommendations for what imaging should be considered on discovery of enlargement or a nodule.
Midlands Thyroid Support Group	Guideline	General	General	There is no mention of the impact of thyroid disease on mental health issues contained in the guideline. As above, if this is subject to a separate guideline, this needs to be published simultaneously and cross-referenced.	Thank you for your comment. The guideline includes recommendations for testing for thyroid dysfunction in people with depression or unexplained anxiety. The aim of the recommendations overall is to improve thyroid

					disorder management, for those with and without mental health disorders.
Midlands Thyroid Support Group	Guideline	General	General	There is no mention of thyroid eye disease (TED) contained in the guideline. As above, if this is subject to a separate guideline, this needs to be published simultaneously and cross-referenced.	Thank you for your comment. Thyroid eye disease was outside the scope of this guideline, so we have not made recommendations related to it. There is no NICE guideline on this topic.
NCRI-ACP-RCP-RCR	Guideline	21	1.9 title	Our experts question whether 'thyroid enlargement' means a goitre or nodule(s)	Thank you for your comment. The committee define thyroid enlargement as "An enlargement of the thyroid gland also known as goitre, includes uniform enlargement (also known as diffuse goitre), as well as the presence of single or multiple nodules (also known as nodular or multinodular goitre)."
NCRI-ACP-RCP-RCR	Guideline	21	1.9.1, 1.9.2	Our experts question on what criteria would malignancy be 'suspected'? On the 'red flags' in bullet 2 of 1.1.5	Thank you for your comment. We do not have an exhaustive list of symptoms so have left this for clinicians to assess.
NCRI-ACP-RCP-RCR	Guideline	21 - 22	1.9.1-5	Thyroid ultrasound needs to be done by experienced operators, as does the aspiration for FNA and the subsequent cytology interpretation. Our experts' question whether there an opportunity here to give some direction as to where and who should be doing thyroid ultrasounds to reduce them happening on general lists after a GP referral and then needing repeating by a thyroid radiologist/radiographer	Thank you for your comment. NICE guidelines generally focus on what tests should be done rather than who should conduct them, allowing providers to determine how best to enact the recommendations at a local level. The level of detail you suggest is beyond the granularity with which the committee was able to approach each individual question. Definitive recommendations to this effect would require a separate evidence review and cost-effectiveness analysis to support the clinical and cost-effectiveness of only experienced operators conducting the tests in question.
NCRI-ACP-RCP-RCR	Guideline	22	1.9.7	'Non-malignant thyroid enlargement' – Our experts question on what criteria is the lack of malignancy diagnosed?	Thank you for your comment. Either those deemed of low enough risk not to require ultrasound, or those who do not then require FNA based on their ultrasound findings, or those whose FNA suggests non-malignant disease. Note This guideline does not cover malignant thyroid disease. The recommendations in this guideline do cover preliminary investigation of thyroid

					enlargement, as raised as an area for focus at scoping. The scope of the recommendations ends at the stage at which aspiration for cytology has been performed but deliberately does not extend into classification of cytology as additional complex evidence reviews would be required to make further recommendations in this area. This information will be considered for inclusion by the NICE guideline on thyroid cancer in development https://www.nice.org.uk/guidance/indevelopment/gid-ng10150
NCRI-ACP-RCP-RCR	Guideline	22	14	1.9.5. There is a brief discussion about use of ultrasound in thyroid disease. Although this is implied, it does not make it clear that this relates to thyroid nodules. There is no direct reference to either the BTA 'U' classification or TIRADS classification for ultrasound assessment of thyroid nodules, This is a significant omission.	Thank you for your comment. The 1.9.5 recommendation you flag is to use ultrasound to guide FNA. In recommendation 1.9.3 the committee recommended that an established system for grading ultrasound appearance should be used and outlined the features that should be taken into account in that system. Based on the evidence review conducted as part of the guideline, the committee did not feel it was appropriate to recommend any one system.
NCRI-ACP-RCP-RCR	Guideline	22	14	There is no discussion in the draft document about classification of thyroid FNA cytology. In the UK, pathologists and cytologists use the Royal College of Pathologists (RCPath) Thy classification terminology for thyroid FNA and for implying risk of malignancy. While this draft document does not relate to malignant disease, confirmation a nodule or thyroid lesion is benign is important and cytology is useful for this purpose. The RCPath categories are as follows *Non-diagnostic for cytological diagnosis Thy 1 (Thy1c if cystic)* *Non-neoplastic Thy 2* *Neoplasm possible Thy 3; subdivided to Thy 3f ('f' for 'follicular') and Thy 3a ('a' for 'atypia').* *Suspicious of malignancy Thy 4*	Thank you for your comment. This guideline does not cover malignant thyroid disease. The recommendations in this guideline do cover preliminary investigation of thyroid enlargement, as raised as an area for focus at scoping. The scope of the recommendations ends at the stage at which aspiration for cytology has been performed but deliberately does not extend into classification of cytology as additional complex evidence reviews would be required to make further recommendations in this area. This information will be considered for inclusion by the NICE guideline on thyroid cancer in development https://www.nice.org.uk/guidance/indevelopment/gid-ng10150

				Malignant Thy 5 The guidance is published on the Royal College of Pathologists website and should be referenced https://www.rcpath.org/uploads/assets/7d693ce4-0091-4621-97f79e2a0d1034d6/g089_guidancereportingthyroidcytology_jan16.pdf	
NCRI-ACP-RCP-RCR	Guideline	23	1.9.10	'For adults with normal thyroid function and a cyst or predominantly cystic nodule with no vascular components, offer aspiration' - a small minority of cystic thyroid nodules may harbour occult cystic thyroid carcinoma hence there needs to be a statement that 'material should be sent for cytology' and 'the cytology should be reported according to the RCPath guideline above' or words to that effect. We would advocate that all thyroid cyst fluids should be sent for cytology, not just when there is some suspicion. We would add that the aspiration of the cyst should be ultrasound-guided and any solid components should also be aspirated.	Thank you for your comment. This recommendation relates to non-malignant thyroid enlargement. It is assumed that should a clinician suspect cancer then the patient would be referred onto the thyroid cancer pathway. The guideline does recommend that fine needle aspiration should be ultrasound guided (rec 1.9.5).
NCRI-ACP-RCP-RCR	Guideline	23	1.9.11	Any treatment should also take into account the results of ultrasound and FNA.	Thank you for your comment. The indications noted here are not exhaustive and are not intended to cover the full breadth of considerations and work-up prior to intervention.
NCRI-ACP-RCP-RCR	Guideline	23	1.9.10, 1.9.11	How widely available is ethanol ablation and percutaneous thermal ablation?	Thank you for your comment. The committee acknowledges that these techniques are not always readily available hence the use of weaker recommendations. These considerations are discussed in more detail in the evidence reviews and discussion sections.
NCRI-ACP-RCP-RCR	Guideline	43	General	Investigating thyroid enlargement with normal thyroid function. It would be helpful if the guideline would specify the relevant classification systems for ultrasound of thyroid nodules, either BTA 'U' or TIRADS. There is a significant evidence base for	Thank you for your comment. The evidence reviews for this area assessed the accuracy of all available ultrasound classification systems. The committee's view of the evidence was that no one system was shown to

				both and by choosing not to specify a particular system it will make the practical application of the guidance perhaps more difficult given that the BTA 'U' system is already widely embedded in clinical practice in UK.	be definitively more accurate than any other system and therefore it was inappropriate to specify one above others.
NCRI-ACP-RCP-RCR	Guideline	43	8 onwards	Line 8 - The term 'accurate' should be defined or qualified. Neither ultrasound not cytology are 100% accurate at distinguishing benign from malignant thyroid nodules. Maybe 'reasonably accurate' would be better? Line 13 – ultrasound should only be done when 'a full assessment indicates a likelihood of malignancy' – what is meant by 'full assessment' and how is 'likelihood' defined? Should there be specific mention of focally PET-avid nodules here? Again, the accuracy of thyroid ultrasound depends on the experience of the operators. This should be mentioned.	Thank you for your comment. The wording of the rationale has been amended to reflect your point on accuracy. With regards to the following points, they represent granularity beyond the scope of the guideline in this area. The guideline scope covered a broad area; it was not possible to go into exhaustive detail in every topic, particularly if they were not prioritised by stakeholders during scoping.
NCRI-ACP-RCP-RCR	Guideline	44	3 onwards	It would be useful to include comment that the local prediction of malignancy by the different thyroid FNA reporting categories should be known from performance of regular audits, so that it can be used in consultations with patients and decision-making. The quality of FNA specimens depends on the experience of the aspirators, which could be mentioned. Best results are from concentration into a few experienced hands. As with ultrasound, the accuracy of thyroid cytology depends on the experience of the pathologists and this could usefully be commented on.	Thank you for your comment. These points represent granularity beyond the scope of the guideline in this area. The guideline scope covered a broad area; it was not possible to go into exhaustive detail in every topic particularly if they were not prioritised by stakeholders during scoping.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
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NCRI-ACP-RCP-RCR	Guideline	49	General	'Evidence review, N imaging for fine needle aspiration and evidence review O ultrasound guidance for fine-needle aspiration' -the detail of the evidence and committee's discussion could not be accessed at the time of open consultation,	Thank you for your comment. These documents were available for consultation along with all the other consultation documents.
NCRI-ACP-RCP-RCR	Guideline	7	1.1.5	Nodules are briefly mentioned on this page **'***goitre and nodules and are usually not cancerous'***.** This is one of the few areas in the document where nodules are specifically mentioned. There is also brief discussion about nodules on page 23, 1.9.11 'offer ultrasound to image palpable thyroid enlargement or focal nodularity in adults, children and young people with normal thyroid function if malignancy is suspected'	Thank you for your comment. We are not sure what point you are making. We have mentioned nodules where appropriate in the recommendations.
NCRI-ACP-RCP-RCR	Guideline	General	General	The NCRI-ACP-RCP-RCR is grateful for the opportunity to respond to the above consultation. We have liaised with the Association of British Clinical Diabetologists, the British Nuclear Medicine Society, our Joint Specialty Committee for Nuclear Medicine, and the NCRI Thyroid Cancer Subgroup, and would like to make the following comments.	Thank you for your comments. We have responded to each in turn.
NCRI-ACP-RCP-RCR	Guideline	General	General	The guidelines refer to the IR(ME)R 2017 regulations, these apply to Great Britain (GB) only. There are separate regulations in Northern Ireland (NI) – IR(ME)R(NI)2018 which should be included if the NICE guidance applies to the whole of the UK.	Thank you for your comment. NICE guidelines cover health and care in England. Decisions on how they apply in other UK countries are made by ministers in the Welsh Government, Scottish Government and Northern Ireland Executive.
NCRI-ACP-RCP-RCR	Guideline	General	General	Both GB and NI IR(ME)R regulations include a new requirement to notify the enforcing authority (CQC in England, HIW in Wales, HIS in Scotland, RQIA in NI) where an individual therapeutic exposure to ionising radiation is significantly lower than intended. If there is no, or limited, uptake of radioactive iodine during treatment, this should be notified to the enforcing authorities. Pre-treatment imaging will prevent this type of incident from happening and remove the need to notify the enforcing authorities.	Thank you for your comment. We refer to the relevant regulations within our recommendations. We did not review the evidence for pre-treatment imaging in the guideline and have not made a recommendation in this area.

Thyroid disease

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NCRI-ACP-RCP-RCR	Guideline	General	General	The title is ***Thyroid disease: assessment and management*** but this guideline deals with benign non-nodular thyroid disease and it does not deal in any depth with nodular thyroid disease where these nodules are benign but nevertheless neoplastic, e.g. follicular adenomas, or with carcinoma. For this reason the guideline title could perhaps be changed. A better title would be '***Assessment and Management of Benign Thyroid Disease'***	Thank you for your comment. The guideline context section has been amended to make it clear that the guideline does not cover managing thyroid cancer. NICE is developing a separate guideline on thyroid cancer (see https://www.nice.org.uk/guidance/indevelopment/gid-ng10150)
NCRI-ACP-RCP-RCR	Guideline	General	General	It would also be helpful if the guideline could discuss the value of cytology and histopathology for confirmation of diagnosis in benign thyroid disease (e.g. granulomatous thyroiditis, Hashimoto's thyroiditis, IgG4 disease, Riedel's thyroiditis), and confirmation that cysts are indeed benign and not occult cystic carcinomas. There are multiple other instances where pathology is useful which could reasonably be referenced and discussed. This detail could be usefully included in a revised document. Members of the NCRI Thyroid Cancer Group who are pathologist/cytologists would be happy to provide further input to a revised document should committee choose to include more pathology and cytology detail in the revised draft, david.poller@porthosp.nhs.uk and sarah.johnson8@nuth.nhs.uk Our experts question whether there should there be any comment on following up after certain ultrasound and cytology findings, or reference to the BTA Guidelines and subsequent Consensus Statements	Thank you for your comment. The scope of this guideline was to cover the preliminary investigation of thyroid enlargement but did not include detailed recommendations on cytology/histopathology. These were not raised as priority areas during scoping, NICE guidelines can only focus on a limited number of areas in order to conduct the most rigorous evidence searching and analysis. NICE is developing a separate guideline on the assessment and management of thyroid cancer (https://www.nice.org.uk/guidance/indevelopment/gid-ng10150)
NHS Central London CCG	Guideline	24	14 - 20	We support this recommendation, given the low or very low quality of much of the existing evidence on the point.	Thank you for the positive feedback.
NHS Central London CCG	Guideline	9	14	People who have decided that they want liothyronine are likely to tell prescribers, especially GPs, "I'm not a routine case" or "prescribing it for me would not be routine." So the word 'routinely' on line 14 is problematic. Because liothyronine	Thank you for your comment. The committee have used the phrase do not offer routinely, liothyronine to reflect that most people will not be considered for liothyronine. The committee agreed that it is plausible in some people

				costs thousands of pounds per patient p.a., and because people who take it often end up with TSH outside the reference range and at risk of osteoporosis and cardiac arrhythmia, please adjust the wording to help prescribers avoid prescribing it inappropriately. Is the evidence presented in Evidence Review E really sufficient to justify recommendation of **any** use of liothyronine for management of hypothyroidism? Please review this because it seems doubtful to us that it is. If your committee decides that 'routinely' should be retained on line 14, more detail is needed to help prescribers. We suggest something like: The prescribing of liothyronine is only supported if initiated by, or considered appropriate following a review by, an NHS consultant endocrinologist. GPs should not independently withdraw or adjust liothyronine treatment for patients who are stable and well on therapy, as any such changes should be overseen by an endocrinologist. This advice applies to both liothyronine monotherapy and combination therapy with levothyroxine. As noted by the British Thyroid Association (BTA) Executive Committee, 'clinicians have an ethical responsibility to adhere to the highest professional standards of good medical practice rooted in sound evidence. This includes not prescribing potentially harmful therapies without proven advantages over existing treatments'. Also 'If a decision is made to embark on a trial of levothyroxine plus liothyronine combination therapy in patients who have	who are not responding to levothyroxine that liothyronine may be beneficial either alone or in combination. They agreed in the absence of evidence and because of the high list price of liothyronine it could not be recommended but that it should also not be completely excluded. The recommendation is written to reflect this. A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).

				unambiguously not benefited from levothyroxine then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences. Many clinicians may not agree that a trial of levothyroxine plus liothyronine combination therapy is warranted in these circumstances and their clinical judgment must be recognised as being valid given the current understanding of the science and evidence of the treatments'.	
NHS England	Guideline	9	14	Point 1.3.4 of the draft NICE guideline focuses on the position in therapy for liothyronine. The national NHS England and NHS Clinical Commissioners' guidance: 'Items which should not routinely be prescribed in primary care: Guidance for CCGs' was published in November 2017 (available at https://www.england.nhs.uk/wp-content/uploads/2017/11/items-which-should-not-be-routinely-precscribed-in-pc-ccg-guidance-v2.pdf). One of the products detailed in this guidance is the oral formulation of liothyronine, and this is detailed in section 4.9 of the above document. This document states that 'The British Thyroid Association (BTA) advise that a small proportion of patients treated with levothyroxine continue to suffer with symptoms despite adequate biochemical correction. In these circumstances, where levothyroxine has failed and in line with BTA guidance, endocrinologists providing NHS services may recommend liothyronine for individual patients after a carefully audited trial of at least 3 months duration of liothyronine'.	Thank you for your comment. The recommendation has remained the same. A footnote has been added to the rationale and impact section for the recommendation 1.3.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).

				The NHS England Regional Medicines Optimisation Committee (RMOC) provides advice to the NHS in accordance with the operating model. The South RMOC was tasked with providing additional guidance for the NHS in England regarding arrangements for on-going prescribing of oral liothyronine, in the context of the 'low priority prescribing' guidance detailed above. The RMOC advice has been published and is available on https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final.pdf The RMOC guidance is consistent with point 1.3.4 of the draft NICE guideline. I would request that the RMOC guidance is noted in this context as it provides far more detailed guidance to commissioners than is present in the draft NICE guideline. I would also request that any future amendments to the draft NICE guideline regarding liothyronine should retain a consistency with the RMOC guidance.	

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NHS England	Guideline	General	General	The NHS England Regional Medicines Optimisation Committee (RMOC) has undertaken work to provide advice for the NHS, and particularly for commissioners, on the prescribing of oral liothyronine. As detailed in comment 1 above this is available on https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final.pdf, and the NHS England overarching guidance on items which should not routinely be prescribed in primary care is available at https://www.england.nhs.uk/wp-content/uploads/2017/11/items-which-should-not-be-routinely-precscribed-in-pc-ccg-guidance-v2.pdf. When considering the full NICE guideline it is consistent with the policy specified in the NHS England 'low priority prescribing' guidance, and also with the advice detailed in the RMOC guidance. I would request that this overall consistency is maintained as the final NICE guideline is developed.	Thank you for your comment. The recommendations from the consultation version have stayed the same in the final guideline. A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).
North Central London Joint Formulary Committee	Guideline	24	14 - 17	We agree that there is high need for research here however has the feasibility of undertaking a trial in this population been assessed?	Thank you for your comment. The committee informally considered the feasibility and judged it to be sufficient to make the research recommendation.
North Central London Joint Formulary Committee	Guideline	24	14 - 17	Can "not responded sufficiently to T4 alone" be expanded upon? Should this include a particular QoL measure, symptom score? Feedback from specialists is that many will they have "symptoms [which] have not responded" however not all should be considered for liothyronine.	Thank you for your comment. The committee did not consider it appropriate to provide this level of detail in the research recommendation. Clinically it is people who self-define as not responding to levothyroxine who may warrant combination therapy by the estimation of some groups. Therefore, a trial may be most useful if inclusion criteria are merely limited to those who self-define as not responding.
North Central London Joint Formulary Committee	Guideline	24	14 - 17	Should this study be restricted to patients with Hashimoto thyroiditis?	Thank you for your comment, this is intended to be primary hypothyroidism and the full research recommendation has been amended (in appendix of relevant evidence review).

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North Central London Joint Formulary Committee	Guideline	30	7 - 15	The paragraph underplays the risk and overplays the benefit associated with liothyronine. See Comment 4 for the benefit and Comment 5 for the risks.	Thank you for your comment. This section has been updated. The recommendation has also been updated as suggested in another of your comments to highlight the issue that its long-term adverse effects are uncertain.
North Central London Joint Formulary Committee	Guideline	30	10 - 11	Please comment whether any of the observed benefit (which we are unclear about, see comment 4) could be attributed to a simple dose effect rather than a liothyronine effect. If there was no (or inadequate) levothyroxine dose adjustment when liothyronine was added, then it is unreasonable to make a claim of liothyronine superiority. The higher rate of TSH suppression with combination therapy suggests that the dose adjustment of levothyroxine was inadequate.	Thank you for your comment. Overall the committee agree that there may be harms and benefits from combination therapy but that the evidence as it stands does not support a clinically important difference overall and does not warrant a recommendation for routine use.
North Central London Joint Formulary Committee	Guideline	30	10 - 11	The statement “some of the trials did show some small benefits in specific quality of life domains” provides an overly positive interpretation of the available evidence. Evidence Review 5 (page 17, line 13) states “There was evidence of a clinically important benefit of combined levothyroxine and liothyronine in terms of two aspects of quality of life”; this statement does not appear to be supported by the evidence. Evidence Review 5 (page 16 line, 1-3) shows the QoL measures considered to be positive are “life- social functioning” and “Role – emotional” however both of these have mean differences with confidence intervals spanning 0: - Social functioning = 4.64 **[-0.87** to 10.09] – low quality (page 63 line 4) - Role limits due to emotional problems = 8.70 [**-13.34** to 30.74] – very low quality (page 64, line 4)	Thank you for your comment. This section is intended to be a brief discussion of the committee’s rationale, as you have pointed out there is further information in the evidence review. The statements on evidence of benefit relate to the point estimate from trials, as you point out the confidence intervals for these benefits are wide and this is reflected in their downgrading for imprecision and therefore the overall low and very low quality of the evidence underlying the outcomes. The committee took all of this information into account when making their recommendations.

				With this data the correct interpretation should be “There was no evidence of a clinically important benefit from low and very low quality studies”. When these outcomes are combined with all other outcomes which did not show a statistically significant benefit, then the conclusion is “there is no evidence of any benefit”.	
North Central London Joint Formulary Committee	Guideline	30	13 - 14	The statement “Some evidence suggested that combination therapy with levothyroxine and liothyronine could be harmful because it may suppress the production of TSH” is a less strong statement that could be supported by the evidence. Evidence Review 5 (page 66, line 1) shows a significant increase in the number of patients who experience TSH suppression below normal (RR= 2.86 [1.54 to 5.32] – moderate quality). With this data the correct interpretation should be “There is evidence of TSH suppression from moderate quality studies which may be harmful”. It is important to acknowledge the risks with levothyroxine therapy as TSH suppression is observed in clinical practice; approximately 50% of patients in North Central London (REF: internal audit 2019) who use liothyronine (combination or monotherapy) have TSH levels below the reference range.	Thank you for your comment. This section is intended to be a brief discussion of the committee’s rationale, as you have pointed out there is further information in the evidence review. The committee took all of this information into account when making their recommendations.
North Central London Joint Formulary Committee	Guideline	9	14 - 16	This sentence does not describe the unknown safety profile of liothyronine therapy. Improved wording might be “…there is not enough evidence that it offers benefits over levothyroxine, and its long-term adverse effects are uncertain”.	Thank you for your comment. We have added the statement you suggest to the recommendation.
North Central London Joint Formulary Committee	Guideline	9	14 - 16	Please separate out recommendations for liothyronine monotherapy and liothyronine + levothyroxine combination therapy due to the differing evidence bases. NICE identified	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4

				evidence of no-benefit and potential harm with liothyronine + levothyroxine combination therapy but no evidence for liothyronine monotherapy. Approximately 20% of patients in North Central London (REF: internal audit 2019) use liothyronine monotherapy. Of those using liothyronine monotherapy, medical records state about half had an allergic reaction to levothyroxine (e.g. rash, swelling, “intolerance”) – please can the Committee take a view on (a) whether a levothyroxine allergy is possible given that it is endogenous and (b) how a patient with an apparent allergy to levothyroxine should be managed.	currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).
Royal College of General Practitioners	Guideline	General	General	The committee should consider making a recommendation to counsel patients with hypothyroidism on the symptoms and effects of too much thyroxine replacement.	Thank you for your comment. We have included a recommendation on how and when to take levothyroxine and the risks of over and under-treatment, and the committee considered that detailed advice on the benefits and risks of medication and overdose should be part of a discussion of any medication prescribed.
Royal College of Ophthalmologists	Guideline	General	General	The RCOphth supports the document and is pleased to see that its comments on the draft scope have been taken into account and included in the guideline document.	Thank you for your comment
Royal College of Paediatrics and Child Health	General	General	General	It is important to make is to ensure that young women with a history of hyperthyroidism which has resolved (either spontaneously or after definitive treatment) are advised to have TRAb antibody levels checked if they subsequently become pregnant, to help estimate the risk of neonatal thyrotoxicosis in the baby. There is no mention of pregnancy in any of the documents, whether on hypo or hyperthyroidism, it would be useful to include some guidance on this, particularly in terms of target FT4 levels pre and during pregnancy.	Thank you for your comment. The guideline does not make any statements on pregnancy as thyroid disease in pregnant women (including pre-conception and postpartum advice) was excluded during the scoping of the guideline to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists.
Royal College of Paediatrics and Child Health	Guideline	General	General	A few aspects of the implementations would have significant cost implications however, this is nothing in comparison to the poor outcomes of neglected or missed cases, such as poor	Thank you for your comment. The committee is confident that the recommendations made reflect best clinical practice and hope they will contribute to the

				growth or cardiac complications. The cost implications are nothing in comparison to the cost of serious complications.	diagnosis and management of people with thyroid disease. The committee believe that these recommendations do not miss out people and therefore do not have large cost implications. In addition, the committee considered the practical issues of implementation as part of its deliberation and following public consultation on the guideline and finalisation of the recommendation NICE undertakes a series of implementation activities.
Royal College of Paediatrics and Child Health	Guideline	General	General	Promoting awareness among patients, families, clinicians will reflect positively on proper management and early treatment for congenital hypothyroidism.	Thank you for your comment.
Royal College of Paediatrics and Child Health	Guideline	General	General	There is not much information for children and young people with thyroid disease, this is mainly because of the dearth of evidence. The discussion on TSH targets is based on adult patient experience. The risk vs the benefits of thyroid function tests are discussed in an adult context although studies have been stratified to 0-4 and 4-18 years.	Thank you for your comment. The committee agree there is not much evidence related to children. The recommendations are primarily based on the expert consensus opinion of the committee taking into account the adult evidence. While the aim of all reviews was to stratify evidence by age groups, the dearth of paediatric evidence meant this approach practically was difficult to achieve. Discussions for all sections included consideration of the similarities and differences between how the recommendations would pertain to children.
Royal College of Paediatrics and Child Health	Guideline	General	General	The testing frequency for young children is suggested at every 6-8 weeks. This information needs to be taken to the National Newborn Screening services as they are independently setting criteria for follow up frequency for children with Congenital Hypothyroidism. A testing frequency of 6-8 weeks may be challenging for many DGHs.	Thank you for your comment. The recommendations are based the expert consensus opinion of the committee taking into account the adult evidence. The committee think that until TSH has come into the normal range then this frequency of testing is advisable.
Royal College of Paediatrics and Child Health	Guideline	General	General	The treatment of hypothyroidism is based primarily on adult literature. This means that the management of children with hypothyroidism is likely to be based on the experience of the paediatrician/paediatric endocrinologist.	Thank you for your comment. The recommendations are primarily based on the expert consensus opinion of the committee taking into account the adult evidence and it is anticipated that specialist advice would be sought.

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Royal College of Paediatrics and Child Health	Guideline	General	General	The committee correctly noted that children would need to be tested more frequently than adults in the monitoring of their thyroid status. This recommendation though is pragmatic and not evidence based (in the absence of evidence).	Thank you for your comment. The committee agrees. The recommendations are primarily based on the expert consensus opinion of the committee taking into account the adult evidence.
Royal College of Paediatrics and Child Health	Guideline	General	General	The evidence for subclinical hypothyroidism is largely adult based, as expected. This infers that treatment decisions for children with subclinical hypothyroidism remains individualised.	Thank you for your comment. The committee agrees. The recommendations are primarily based on the expert consensus opinion of the committee taking into account the adult evidence. It is anticipated that most these children would be managed under specialist follow up.
Royal College of Paediatrics and Child Health	Guideline	General	General	There is considerably more evidence in the diagnosis of thyrotoxicosis in children. However, the discussion is based on evidence and does not take into account the additional benefit of undertaking scans which do not confer added benefit over standard biochemical analysis. An ultrasound was found to be useful but what is the real-life benefit of doing an ultrasound in a child with confirmed thyrotoxicosis?	Thank you for your comment. Evidence for the diagnostic accuracy of ultrasound was limited in children. Based on clinical experience, the committee agreed that there was some usefulness of ultrasound for the in determining the cause of thyrotoxicosis but only when there were palpable thyroid nodules or the cause of remained unclear following thyroid autoantibody testing and technetium scanning.
Royal College of Paediatrics and Child Health	Guideline	General	General	Is there a recommendation to check for TSH receptor activating mutations (having considered the data within the review process)?	Thank you for your comment. This was not an area prioritised for focus during scoping or in committee discussions. Consequently, we did not review the evidence and have not made recommendations in this area.
Royal College of Paediatrics and Child Health	Guideline	General	General	The committee provides good evidence of low risk with radio iodine treatment for thyrotoxicosis, suggesting the well-known treatment choice of radioiodine over surgery in teenagers and young people with thyrotoxicosis. The guideline provides useful evidence that most people tend to become hypothyroid than euthyroid following radioiodine treatment, something that needs to be discussed upfront in counselling of long-term treatment plans.	Thank you for your comment.
Royal College of Paediatrics and Child Health	Guideline	General	General	There are important conclusions which although based on adults impact the way treatment for thyrotoxic children is used, for example the increased risk of agranulocytosis with block	Thank you for your comment.

				and replace regimens. These guidelines will be valuable for discussing treatment plans with patients/families.	
Royal College of Paediatrics and Child Health	Guideline	General	General	The section on fine needle aspiration probably does not apply to children as the evidence is thin.	Thank you for your comment. The committee agree which is why we recommend that the management of children with non-malignant thyroid enlargement is discussed with a specialist multidisciplinary team.
Royal College of Paediatrics and Child Health	Guideline	General	General	Neonatal screening for congenital hypothyroidism would have the biggest impact on practice but may be challenging to implement. There needs to be national programs and financial support applied because missed cases can end up with severe consequences such as impaired intellectual and adaptive functioning. It is surprising that neonates were not in the scope.	Thank you for your comments. The management of neonates is excluded from the scope of the guideline.
Royal College of Paediatrics and Child Health	Guideline	General	General	The commenter was happy with this guideline	Thank you for your comment.
Royal College of Paediatrics and Child Health	Guideline	Section 1.7.12		"For children and young people who have stopped antithyroid drugs, consider measuring: TSH, FT4 and FT3 within 8 weeks of stopping the drug, then • TSH, FT4 and FT3 every 3 months for the first year, then TSH only every 6 months for the second year, then TSH only once a year." – again there is no recommendations for when monitoring can be stopped? If TFTs are stable by the 3rd year, it should be suggested that you can stop TFTs monitoring and advise the patient of signs/symptoms to be aware of.	Thank you for your comment. The committee believe that monitoring should continue in people who have stopped treatment to detect early signs and symptoms of relapse or complications.
Royal College of Paediatrics and Child Health	Guideline	Section 1.7.8		"Consider measuring TSH at the first postoperative assessment and then 27 once a year for adults, children and young people who have had a 28 hemithyroidectomy."- in children, management is usually with total thyroidectomy, (not a hemi).	Thank you for your comment. The committee agree that total thyroidectomy is the most likely choice of surgery in children. This recommendation provides advice on when to follow up children who do have a hemithyroidectomy. The preceding recommendation advises what to do when they have had a total thyroidectomy. Both recommendations apply to adults and children.
Royal College of Paediatrics and Child Health	Guideline	Sections 1.4.4-1.4.7	General	The recommendations for frequency of monitoring in children with primary hypothyroidism: for children aged 2 years and over and young people taking levothyroxine every 6 to 12	Thank you for your comment.

				weeks until the TSH level has stabilised within the reference range, then every 4 to 6 months until after puberty, then once a year. For children aged between 28 days and 2 years who are taking levothyroxine for primary hypothyroidism, consider measuring FT4 and TSH every 4 to 8 weeks until the TSH level has stabilised within the reference range, then every 2 to 3 months during the first year of life, and every 3 to 4 months during the second year of life. - is acceptable in view of the evidence on neuro development outcomes in congenital hypothyroidism children.	
Royal College of Paediatrics and Child Health	Guideline, diagnosing managing and monitoring	1.9.1	21	Thyroid scintigraphy is never mentioned as an important diagnostic medical imaging study.	Thank you for your comment. Scintigraphy was not considered as part of the evidence review.
Royal College of Paediatrics and Child Health	Guideline, Investigation	1.2.8	8	A consideration should be made for measuring both TSH and T4 in adults, children and young people.	Thank you for your comment. The committee consensus was that testing TSH first and only testing FT4 if TSH was outside the reference range was adequate when secondary thyroid dysfunction is not suspected.
Royal College of Paediatrics and Child Health	Guideline, Recommendations	1.1.3	5	Hypothyroidism may be underactive or resistant to thyroid hormone (RTH) or consumptive hypothyroidism.	Thank you for your comment. The guideline focuses on primary thyroid disease; although there is some consideration on appropriate testing for people when secondary thyroid disease is suspected in the recommendations prior to the one you highlight. This recommends is to provide people with hypothyroidism information related to recommendations in this guideline.
Royal College of Paediatrics and Child Health	Guideline, Recommendations	1.1.3	5	People with hypothyroidism should be provided with information about critical complications such as impaired intellectual and adaptive functioning in congenital hypothyroidism, growth retardations and cardiac problems.	Thank you for your comment. We have avoided providing a definitive list of complications and have left this for clinicians to provide.
Royal College of Paediatrics and Child Health	Guideline, treating primary hypothyroidism	1.3.3		Levothyroxine should be offered as a first–line treatment for adults, children and young people with primary hypothyroidism. It should also be offered as a secondary treatment for consumptive and tertiary hypothyroidism and on top congenital	Thank you for your comment. The guideline focuses on the management of primary hypothyroidism. Screening for congenital hypothyroidism was excluded in the scoping stage of the guideline.

				hypothyroidism as early as possible to prevent impaired intellectual and adaptive functioning. A sample management plan of CH is as follows: **A.** Initial screening test (heel prick blood sample) TSH > 40 MU/ml start levothyroxine * TSH < 40 MU/ml but above upper limit of reference range repeat serum TSH, T4 in 1-2 weeks. If TSH > 20 MU/ml start levothyroxine * if TSH 6-20 MU/ml (T4 below lower limit of reference range) start Levothyroxine or * if T4 is normal repeat the test at 4 weeks of age * if similar results of TSH and T4 either start treatment with levothyroxine and revaluate at 3-4 years of age or recheck after 6-8 weeks. **B.** If TSH is normal T4 below lower limit of reference range in initial screening test (heel prick blood sample) measure the free T4 and T3 in serum, if normal fT4 and T3 it could be a TBG deficiency or if the fT4/T3 is low then consider secondary hypothyroidism and evaluate and treat accordingly.	
Royal College of Paediatrics and Child Health	Guideline: Managing and monitoring subclinical hypothyroidism in children	Section 1.5.4 to 1.5.5		Children with subclinical hypothyroidism (defined as a serum TSH level above the upper limit of the statistically defined reference range while the serum T4 level is within the reference range, without clinical manifestations) -there is no evidence in children for treatment initiation especially if FT4 is in high-normal range. Transient hyperthyrotropenia should be interpreted with caution in newborns, to assess the risk of unnecessary treatment, including: effects on brain development, hyperactivity, advancement in bone age, and craniosynostosis (7). There is considerable controversy regarding persistent hyperthyrotropinemia (PH), again there is no evidence for treatment initiation.	Thank you for your comment. The committee think there is benefit in considering treatment for children and have made weaker ‘consider’ recommendation to reflect that the decision to treat needs to be on a case by case basis. The guideline excludes treatment for neonates.

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Society for Endocrinology	Guideline			CKS guidance should be separated and clearly distinguished from NICE as causing confusion as CKS seen as nice guidance. High risk of mixed messages	Thank you for your comment. CKS guidance is separate from NICE guidance. We are working to make this clearer.
Society for Endocrinology	Guideline	11	15	Really important to brief patients with subclinical hypothyroidism that if they are symptomatic, there is a significant chance that their symptoms are not due to thyroid disease and may not improve with treatment. Unrealistic expectations at this stage need to be managed.	Thank you for your comment. We have amended this recommendation to include symptoms of hypothyroidism
Society for Endocrinology	Guideline	15	16	I don't think it is sensible to go for RI as first line. The decision about definitive treatment is usually too much for the patient on the first consultation and while they are thyrotoxic. The quickest and most reliable way of rendering euthyroid is with anti-thyroid drugs. Once euthyroid, that is the time to explore RI or surgery.	Thank you for your comment. The committee has added a recommendation as suggested ahead of the treatment options for Graves' disease.
Society for Endocrinology	Guideline	15	16	Recent data regarding cardiovascular mortality has been published in the Lancet Diabetes and Endocrinology and may have been missed by the committee as it was fairly recent. This would argue the role for RAI and to a lesser extent surgery, in people who may not achieve good control early with anti-thyroid drugs such as high Trab smokers. There is an argument for guidance to indicate that RAI/surgery should be considered early in these people	Thank you for your comment. We believe you mean: Okosieme OE, Taylor PN, Evans C, et al. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. Lancet Diabetes Endocrinol. 2019 Apr;7(4):278-287. The study was published after the cut-off for our search and was therefore not included in the guideline. The guideline did not find evidence for this group in the evidence they reviewed.
Society for Endocrinology	Guideline	15	16	The main concern is the statement that RAI should be offered as an alternative first line treatment for Graves' disease. This is very different from practice in the UK. Although it makes the point it is a cost effective treatment for graves there are 3 points not considered: 1) Up to 50% will have a permanent treatment that they will not need and could be drug free which may have a significant impact on QOL	The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore,the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid

				2) There are a minority of people who do not feel well on levothyroxine and there is no going back with this treatment. There are very few long term effects of Carbimazole, accepting a very low level of agranulocytosis if on low dose long term medication, and possibly occasional liver toxicity (but not enough for NICE to recommend routine monitoring) and potential for long term remission or stable disease on long term low dose treatment. Whilst they mention cost effectiveness, this doesn't include long term appointments in primary and secondary care for those feeling unwell on Thyroxine. 3) Mortality - there is a comment that mortality is improved for those treated with RAI. However, if this mortality is spit into those under 45 with well controlled disease, is there really any evidence that there is a risk of adverse outcomes, if TSH remains in the normal range. Therefore, would it be more sensible to say that the treatment options should be discussed with the patient, including the advantages and disadvantages as laid out in table 1.	drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options. The committee also recommend antithyroid drugs while patients wait to be seen by a specialist, and has added a recommendation to offer antithyroid drugs to stabilise hyperthyroidism for people waiting for treatment with radioactive iodine and surgery
Society for Endocrinology	Guideline	15	16	For consistency a fixed RAI dose for a department could be recommended. Whilst there is no evidence to my knowledge that one dose is superior, than another for consistency it would be a good idea to recommend departments have a standard approach (I think most do)	Thank you for your comment. The committee has made a recommendation for research on how to administer radiation.
Society for Endocrinology	Guideline	16	19	Worth stating here that patients with an autonomous nodule need not have an US or FNA unless there are other features to suggest malignancy	Thank you for your comment. We think this relates to recommendation 1.9.1 on page 21 and not page 16 of the consultation draft of the guideline. The recommendations are intended to advise on when to do the US or FNA for people with normal thyroid function and not those with autonomous nodules.
Society for Endocrinology	Guideline	17	17	Should add something here about educating patients/carers about agranulocytosis supported by written info and reinforced at subsequent consultations.	Thank you for your comment. Recommendations related to providing information to people with thyroid disease are in section 1.1 of the guideline. Information that is

					also included in the BNF has not been mentioned in the patient information section of the guideline as all NICE guidelines recommend that clinicians use a medicine's summary of product characteristics when making decisions with patients.
Society for Endocrinology	Guideline	24		Iodine is essential for thyroid hormone and the UK has likely iodine insufficiency in pregnancy, given its mechanism of action is via thyroid hormones and the importance of good control of thyroid status in pregnancy should there not be research into iodine status of pregnant women in the UK	Thank you for your comment. The management of thyroid disease in pregnancy and the pre-conception period was outside of the scope of this guideline.
Society for Endocrinology	Guideline	24	14	Very important that this issue is addressed regarding combination thyroid hormone replacement. The research question to my mind needs to be broader. As well as DIO2 another genotype has been identified in the transporters. Thus, studies need to be done on other genotypes and other markers such as metabolomics or tissue thyroid status. Studies should be an order of magnitude larger in order to detect differences in a sub-group and special attention to whether long acting t3 is needed.	Thank you for your comment. The research recommendation is for testing in people who do not respond well to levothyroxine alone, DIO2 polymorphisms are one possible example as you flag and the one that was raised to and by the guideline committee. If further genotypes are clinically relevant they should be well represented by cohorts of people who are non-responders to levothyroxine.
Society for Endocrinology	Guideline	24	21	Also, would be tempted to include subclinical hypothyroidism and cardiovascular outcomes in younger people as a research area. Razvi JAMA internal medicine paper indicated an interaction with younger individuals with regard to cardiovascular outcomes.	Thank you for your comment. The committee has made a research recommendation along these lines.
Society for Endocrinology	Guideline	5	20	With regard to thyroid eye disease, it is not important to comment on that this should be managed in specialist centres with signposting to guidelines for this.	Thank you for your comment. As thyroid eye disease is outside of the scope of this guideline we have not made recommendations on where or how it should be managed.
Society for Endocrinology	Guideline	7	10	would recommend that in 1.2 drugs that may interfere commonly with thyroid function such as amiodarone and lithium should be included	Thank you for your comment. Drug-induced thyroid dysfunction was excluded from the scope of the guideline.

Society for Endocrinology	Guideline	9	14	"..there is not enough evidence that it offers benefits over levothyroxine monotherapy": There is ample evidence of absence of superiority of combination treatment compared to LT4, in the form of over 10 RCTs pointing in the same direction. Why be defensive? Also the point made in the next paragraph about thyroid extract (long-term adverse effects are uncertain) applies here too.	Thank you for your comment. The committee have used the phrase do not offer routinely liothyronine to reflect that most people will not be considered for liothyronine. The committee agreed that it is plausible in some people who are not responding to levothyroxine that liothyronine may be beneficial either alone or in combination and that its use is controversial, expensive and potentially harmful. They agreed in the absence of evidence and because of the high list price of liothyronine it could not be recommended but that it should also not be completely excluded. The recommendation is written to reflect this. The committee agree that in the RCT evidence identified in the guideline's evidence review there was not convincing effect of benefit for combination therapy over monotherapy, however the committee acknowledge that the trials were generally small and did not select specifically for a population of people whose disease responded insufficiently to levothyroxine monotherapy. Therefore, it remains plausible that in such subgroups there is a benefit.
Society for Endocrinology	Guideline	9	14	The trials regarding T3 are of low quality with regard to sample size, and outcomes studied. This is far from ideal given how common levothyroxine use and that around 10-15% of people are dissatisfied on treatment. ETA and ATA do recommend a trial of T3 therapy can be considered in symptomatic individuals it would be I think appropriate to include this. I also feel that this a key opportunity to highlight trials properly funded and adequately powered are urgently needed in this area..	Thank you for your comment. The committee have used the phrase do not offer routinely, liothyronine to reflect that most people will not be considered for liothyronine. The committee agreed that it is plausible in some people who are not responding to levothyroxine that liothyronine may be beneficial either alone or in combination. They agreed in the absence of evidence and because of the high list price of liothyronine it could not be recommended. We agree that more research is needed and have made a recommendation for research in this area.

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Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	Again, it is noted that many of the studies used are of low or very low quality, with only a few of moderate and one of high quality.	Thank you for your comment. It is important to note that GRADE terminology (low or very low etc.) reflects the quality of the evidence underlying the outcome and does not necessarily mean the studies themselves are low or very low quality. Factors that are included in the GRADE rating are risk of bias, imprecision, indirectness, inconsistency and publication bias.
Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	The NICE committees own statement: The committee noted that the doses of radioactive iodine used in most studies were lower than what would be used in the UK currently. Qualitatively, higher doses would be expected to lead to more hypothyroidism and euthyroidism and less hyperthyroidism. Higher doses could also lead to more adverse events, although these were not identified in this review. Would seem to support the need for further research specifically for this issue.	Thank you for your comment. We agree more research is needed.
Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	Overall though we on the SRP medical sector committee support this document as it is for publication.	Thank you for your comment
Stourbridge Thyroid Support Group	Guideline	1	4	This heading is not ideal. We feel it should read “Thyroid Disease: Diagnosis, Assessment and Management”. Assessment and management implies that diagnosis has already been made somewhere, and if so, by who and when and what was the diagnosis? This heading is therefore ambiguous, and could be misunderstood or ignored by a medical professional who is looking for help with diagnosis specifically, based purely on the wording in a heading.	Thank you for your comment. We have amended the guideline context section to make it clear that the guideline covers investigation of suspected thyroid disease.
Stourbridge Thyroid Support Group	Guideline	10	General	We strongly disagree with statements 1.4.1 and 1.4.2. Symptoms happen for a reason and if they are persistent, it is indicative of a shortage of active hormone (Triiodothyronine or FT3). Thyroid Stimulating Hormone (TSH), however good a diagnostic tool, does not tell us how much active hormone is present. Once a patient is being treated with Levothyroxine (T4), their TSH level will drop, regardless of how much active	Thank you for your comment. The committee agreed that FT3 doesn’t help determine if treatment should change as it is a short acting hormone so will be very different on different days. Symptoms give a better indication. Recommendation 1.4.1 has been edited to reflect this and states “Aim to maintain TSH levels within the reference range when

				hormone is actually available for use at a cellular level. If there is not enough active hormone available, symptoms will persist. Because many patients also have reduced ability to convert the inactive hormone into the active one, it is especially important to be able to quickly identify how much FT3 is present. Statement 1.4.1 should therefore be changed to “Aim to eradicate symptoms whilst maintaining TSH and Triiodothyronine (FT3) levels close to or within their reference ranges, when treating primary hypothyroidism with Levothyroxine”. Statement 1.4.2 should therefore be changed to “Be aware that the TSH level can take up to 6 months to normalise for people who have had a very high TSH level and/or a very low Triiodothyronine (FT3) level before starting their treatment, or that have experienced a prolonged period of untreated hypothyroidism. Take this into account when adjusting the dose of Levothyroxine or Liothyronine”.	treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing but avoid using doses that cause TSH suppression or thyrotoxicosis.” Liothyronine is not routinely recommended and is therefore not included in this recommendation.
Stourbridge Thyroid Support Group	Guideline	10	General	We also strongly disagree with statements 1.4.3 and 1.4.4. As mentioned previously, symptoms happen for a reason and if they are persistent, it is indicative of a shortage of active hormone (Triiodothyronine or FT3). Thyroid Stimulating Hormone (TSH) is a good diagnostic tool but it does not provide all the information that is needed. Once a patient is being treated with Levothyroxine (T4), their TSH level will drop, regardless of how much active hormone is actually available for use at a cellular level. If there is not enough active hormone available, symptoms will persist. TSH testing does not confirm how much active hormone is available at a cellular level and because many patients also have reduced ability to convert the inactive hormone into the	Thank you for your comment. The committee agreed that FT3 doesn’t help determine if treatment should change as it is a short acting hormone so will be very different on different days. Symptoms give a better indication. Recommendation 1.4.1 has been edited to reflect this and states “Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing but avoid using doses that cause TSH suppression or thyrotoxicosis.”

				active one, it is especially important to be able to quickly identify how much FT3 is present. It is pointless trying to keep the TSH level in range if there is still not enough active hormone available for the body to function, and the patient remains ill. Doctors have been treating the TSH level alone for far too long and it is not addressing the situation, as people are remaining ill as a result. There are now well over 100,000 people on UK forums alone, that are complaining about their treatment and the failings of the TSH test. Statement 1.4.3 should therefore be changed to “For adults who are taking Levothyroxine and/or Liothyronine for primary hypothyroidism, consider measuring TSH, Thyroxine and Triiodothyronine (FT3) every 3 months until symptoms have been significantly reduced or completely eradicated, and/or all three levels have stabilised within or close to the reference range, and then once a year. Statement 1.4.4 should therefore be changed to “For children aged 2 years and over and young people taking Levothyroxine and/or Liothyronine for primary hypothyroidism, consider measuring TSH, Thyroxine and Triiodothyronine (FT3): - every 6 to 12 weeks until symptoms have been significantly reduced or completely eradicated, and/or all three levels have stabilised within or close to the reference range, then - every 4 to 6 months until after puberty, then once a year”.	Liothyronine is not routinely recommended and is therefore not included in these recommendations.
Stourbridge Thyroid Support Group	Guideline	10	2 - 4	We would like clarification on statement 1.3.6. If we have assumed the meaning of this statement correctly, and we should not have to make assumptions, we feel it would be better if it were reworded to “Consider starting Levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight for	Thank you for your comment. The recommendation has been edited to state “Consider starting levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight per day (rounded to the nearest 25 micrograms) for

				adults under 65 with primary hypothyroidism and no history of cardiovascular disease".	adults under 65 with primary hypothyroidism and no history of cardiovascular disease
Stourbridge Thyroid Support Group	Guideline	11	General	We also strongly disagree with statements 1.4.5 and 1.4.6. As mentioned in previous comments, symptoms happen for a reason and if they are persistent, it is indicative of a shortage of active hormone (Triiodothyronine or FT3). Thyroid Stimulating Hormone (TSH) is a good diagnostic tool but it does not provide all the information that is needed. Once a patient is being treated with Levothyroxine (T4), their TSH level will drop, regardless of how much active hormone is actually available for use at a cellular level. If there is not enough active hormone available, symptoms will persist. TSH testing does not confirm how much active hormone is available at a cellular level and because many patients also have reduced ability to convert the inactive hormone into the active one, it is especially important to be able to quickly identify how much FT3 is present. It is pointless trying to keep the TSH level in range if there is still not enough active hormone available for the body to function, and the patient remains ill. Doctors have been treating the TSH level alone for far too long and it is not addressing the situation, as people are remaining ill as a result. There are now well over 100,000 people on UK forums alone, that are complaining about their treatment and the failings of the TSH test. Statement 1.4.5 should therefore be changed to "For children aged between 28 days and 2 years who are taking Levothyroxine and/or Liothyronine for primary hypothyroidism, consider measuring TSH, Thyroxine and Triiodothyronine (FT3):	Thank you for your comment. The evidence on patients being unable to convert T4 to T3 remains controversial. T3 is a short acting hormone and measurements of FT3 will be very variable on different days and at different times. There are currently no good tests available to measure the tissue level of active thyroid hormone. The guideline evidence review did not identify that measurements including reverse T3 and SHBG are useful in this setting.

				- every 4 to 8 weeks until symptoms have been significantly reduced or completely eradicated, and/or all three levels have stabilised within or close to the reference range, then - every 2 to 3 months during the first year of life, and - every 3 to 4 months during the second year of life". Statement 1.4.6 should therefore be changed to "Consider measuring TSH, Thyroxine and Triiodothyronine (FT3) for adults, children and young people who continue to have symptoms of hypothyroidism after starting on Levothyroxine and/or Liothyronine".	
Stourbridge Thyroid Support Group	Guideline	11	16 - 18	Under statement 1.5.1, symptoms are not being taken into account. If symptoms are present, then there is a problem and treatment should begin. Delaying supportive/preventative treatment could result in an increase and/or worsening of symptoms and a higher risk of associated illnesses and conditions developing, such as Diabetes, depression, gallstones, fertility problems, weight gain and fatty liver disease.	Thank you for your comment. This recommendation has been edited to encompass your point and now includes reference to symptoms: "When discussing whether or not to start treatment for subclinical hypothyroidism, take into account features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous thyroid surgery or raised levels of thyroid autoantibodies."
Stourbridge Thyroid Support Group	Guideline	11	20 - 23	Statement 1.5.2 also ignores symptoms. Thyroid Stimulating Hormone (TSH) testing alone is not a good long-term diagnosis tool. We would also point out that there is no evidence that there is a recognised and agreed starting point for initiating treatment based on TSH alone. Each person is different and the hormone levels that are right for them are unique to them. It is also worrying that the possibility of secondary thyroid disease being the cause is not being considered for further investigation at this stage. We also dispute the reference range for TSH, as it was based on research that was significantly flawed, because non healthy patients were used along with healthy patients to set the reference range, and therefore the conclusions are unreliable.	Thank you for your comment. Recommendations in section 1.4 of the guideline provide clarification on what should be done for children and adults in whom symptoms persist.

				Our TSH reference range in the UK is amongst the widest in the world. It discourages correct diagnosis on two grounds: firstly because the range is too wide and, secondly, because it does not give the whole picture. Many of our members, and patients worldwide, do not regain their health until their TSH level is below 2.5 mIU/litre.	
Stourbridge Thyroid Support Group	Guideline	12	General	Statement 1.5.3 does not make any sense to us at all. In our opinion, the reference to age ranges of under or over 65 do not matter. The differences between statements 1.5.2 (on page 11) and 1.5.3 imply that if you are over the age of 65 and you have symptoms, then symptoms are ignored, but if you are under the age of 65, symptoms are taken into account. Have we misunderstood this statement, and if we have, then clarification is required? Symptoms should never be ignored. We already disagree with statement 1.5.2 and we feel that if it were changed to include our recommendations, it would apply to any adult of any age. Therefore, lines 1 - 5 on page 12 should be removed, and lines 6 - 9 should be tagged on to the end of statement 1.5.2. Please also see the next comment (comment 33), which also criticises lines 6 - 9 though.	Thank you for your comment. The committee agreed that recommendation 1.5.2 applies to everyone regardless of symptoms. A person over 65 with a TSH over 10 should be considered for treatment. The agreed not to make a recommendation for people over 65 with a TSH of less than 10 as there is no evidence of benefit and the potential for harm with treatment.
Stourbridge Thyroid Support Group	Guideline	12	General	Statements 1.5.4 and 1.5.5 again focus on Thyroid Stimulating Hormone (TSH) testing alone, as a means of monitoring. We must re-emphasis the pointlessness of testing TSH alone. Triiodothyronine (FT3) and Thyroxine (FT4) levels need to be tested to gain more information, to understand what is going on. Are there conversion problems? We would add that it seems unethical to us, to restrict increased or alternative treatment options purely based on clinical results alone, ie symptoms can not only be dreadful, but be debilitating, and allowing patients to suffer as a result of inaction and/or wrong treatment is immoral. We would also comment that there is little point in having any kind of reference if it is ignored and patients are left to suffer as a result?	Thank you for your comment. The committee agreed that FT3 is a very poor measurement of hypothyroidism. The committee also agreed that to diagnose subclinical hypothyroidism FT4 would have had to have been measured. These recommendations use TSH level as a parameter for deciding when to offer treatment.

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Stourbridge Thyroid Support Group	Guideline	12	6 - 9	We are unhappy with this guidance, as we have mentioned previously that testing Thyroid Stimulating Hormone (TSH) levels alone does not give enough information. If symptoms are present, there is a problem. Therefore, if symptoms persist, testing of Triiodothyronine (FT3) and Thyroxine (FT4) levels is required, to gain more information. If FT4 is towards the top of range with no symptom improvement, but FT3 is low in range, this suggests that conversion from inactive to active hormone is poor. It is our experience, learned from our members and patients worldwide, that approximately 15% of adults are unable to eradicate symptoms with Levothyroxine alone. Approximately 1.5% of these patients have also managed to go on to identify one or more genetic faults that are known to impede or even block conversion of the inactive hormone to the active hormone.	Thank you for your comment. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Stourbridge Thyroid Support Group	Guideline	13	General	Statements 1.5.7, 1.5.8 and 1.5.9, do not make any reference to symptoms or the testing of Triiodothyronine (FT3). This means that there is still too much focus on Thyroid Stimulating Hormone (TSH) levels. We also must remind the committee that there is no evidence that there is a recognised and agreed point where treatment should begin with regard to the TSH range. Each child, young person or adult is unique. The most important hormone to test for is Triiodothyronine (FT3), and the objective should be to eradicate symptoms.	Thank you for your comment. These recommendations relate to children who are not receiving treatment or have had treatment stopped and therefore they are unlikely to have symptoms. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Stourbridge Thyroid Support Group	Guideline	13	4 - 6	We feel that there are omissions in statement 1.5.6, pertaining to our previous arguments surrounding symptoms, Thyroid Stimulating Hormone (TSH) and Triiodothyronine (FT3). This statement should be changed to “For adults with untreated subclinical hypothyroidism or adults who have stopped Levothyroxine or Liothyronine treatment for subclinical	Thank you for your comment. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no

				hypothyroidism, and who are symptom free, consider measuring TSH, FT3 and FT4:"	value in testing FT3 for people with subclinical hypothyroidism.
Stourbridge Thyroid Support Group	Guideline	14	7 - 9	We disagree with statement 1.6.1. Measuring TSH Receptor Antibodies (TRAbs) alone will not necessarily correctly confirm Graves' Disease. It is important to test for all thyroid antibodies, including but not restricted to Thyroglobulin Antibodies (TgAbs) and Thyroid Peroxidase Antibodies (TPOAbs). Testing for Thyroid Stimulating Immunoglobulin (TSIAbs) should also be considered. TPOAbs are found in approximately 95% of patients with Hashimoto's Disease, but they are also found in between 50% and 80% of patients with Graves' Disease and we are aware of cases where patients have been diagnosed as having Graves' Disease and were treated for it, when in fact, they were actually suffering from Hashimoto's Thyroiditis, which can cause a short but debilitating period of hyperthyroidism whilst in its early stages.	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Stourbridge Thyroid Support Group	Guideline	14	17	Further to our comment 37, we feel that technetium scanning should be considered if testing for thyroid antibodies (TSH Receptor Antibodies (TRAbs), Thyroglobulin Antibodies (TgAbs), Thyroid Peroxidase Antibodies (TPOAbs) and Thyroid Stimulating Immunoglobulin (TSIAbs) proves negative, ie testing for all thyroid antibodies should be carried out first.	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Stourbridge Thyroid Support Group	Guideline	15	General	We strongly disagree with statements 1.6.8, 1.6.9 and 1.6.10. We have knowledge of cases where patients were not given a choice between radioactive iodine and antithyroid drugs, and sadly, they were left with a totally non-functioning thyroid gland, lots of horrible side-effects from the treatment and permanent hypothyroidism. In some of these cases, patients were knowledgeable and would have preferred to try antithyroid drugs first, in order to try to retain a functioning thyroid gland, but they were not given the option. In some of	Thank you for your comment. The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore,the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a

				these cases however, patients simply didn't understand the risks involved until it was too late. We feel that in most cases, if the patient fully understood the risks involved, eg that they will risk becoming hypothyroid for the rest of their life, they would also prefer to try to save their thyroid gland, if at all possible. It also makes sense to us to at least try antithyroid drugs before considering treatment with radioactive iodine, even if there is a strong chance that the antithyroid drugs will not work. Either way, because the consequences of radioactive iodine treatment could be life-changing in a very negative way, patients need to have a say in how they are treated. They are the ones that will have to live with the consequences of the treatment - not the doctor or specialist. Recent research has also found links between radioactive iodine treatment and solid cancer mortality in hyperthyroidism (referred to in comment 17), and this is yet another reason why patients must be given a choice. This is absolutely not a decision for the doctor or the specialist to make, as they will not have to live with the consequences of the treatment, and whilst they might not wish to admit it, they could even find themselves too easily influenced by cost, putting the patient's needs last. The patient must be given a choice of radioactive iodine OR antithyroid drugs. Clearly, if antithyroid drugs do not work, then there may be no choice but to consider radioactive iodine or surgery.	particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options. The committee has also added a recommendation immediately preceding the treatment options for Graves' disease to highlight the importance of discussing treatment: "Ensure that people can actively participate in decisions about treatment by following the recommendations in the NICE guideline on patient experience in adult NHS services. This includes presenting information about possible outcomes in a way the person can understand."
Stourbridge Thyroid Support Group	Guideline	15	1 - 3	We disagree with statement 1.6.6. Because of the risks involved with using antithyroid drugs, and the fact that there is a chance that they are inappropriate, we feel that only a specialist should be able to consider commencing their use. However, this does not stop a doctor from consulting with a specialist, and we believe it is a good idea to do so, in order to discuss what treatment, if any, is appropriate whilst the patient	Thank you for your comment. The committee believe it is appropriate for the GP to start treatment and anticipate that GPs will talk to a specialist before initiating treatment on a case by case basis if they are unsure of what to do.

				is waiting for their assessment. Starting treatment as early as possible is always a good idea, provided it is the correct treatment.	
Stourbridge Thyroid Support Group	Guideline	16	10 - 15	In light of recent research linking radioactive iodine with solid cancer mortality in hyperthyroidism, we would suggest that statement 1.6.13 needs review.	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Stourbridge Thyroid Support Group	Guideline	16	19 - 21	In light of recent research linking radioactive iodine with solid cancer mortality in hyperthyroidism, we would suggest that statement 1.6.15 needs review.	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort

					matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Stourbridge Thyroid Support Group	Guideline	17	General	In light of recent research linking radioactive iodine with solid cancer mortality in hyperthyroidism, we would suggest that statements 1.6.17 and 1.6.18 need review.	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at

					length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Stourbridge Thyroid Support Group	Guideline	19	General	We disagree with statements 1.7.3 and 1.7.4. Thyroid Stimulating Hormone (TSH) testing alone is inadequate. We do not understand why hypothyroid patients that were hyperthyroid previously should be treated any differently to other hypothyroid patients. Why should it be any different for patients who become hypothyroid as a consequence of radioactive iodine treatment to those who are hypothyroid for other reasons? It does not matter why a patient is hypothyroid, they are hypothyroid, and this means that what matters most is the testing of Triiodothyronine (FT3) levels, along with any other appropriate tests.	Thank you for our comment. In patients who develop hypothyroidism following treatment for hyperthyroidism the TSH concentration may remain low or undetectable for some time and measurement of FT4 andFT3 help guide treatment in this situation. This is different from those who develop autoimmune hypothyroidism in whom the TSH will be raised at diagnosis.
Stourbridge Thyroid Support Group	Guideline	19	1 - 3	There is too much reliance on keeping Thyroid Stimulating Hormone (TSH) levels within the reference range and there is no reference to symptoms. Upon becoming hyperthyroid, the body's cells become accustomed to higher levels of Triiodothyronine (FT3), so it is important to keep these levels relatively high to eradicate symptoms for most patients. Maintaining FT3 levels at the top of range whilst keeping TSH levels within range is sometimes impossible. If symptoms persist, there is something wrong and the FT3 levels are not right for that patient.	Thank you for your comment. The guideline recommends that initially TSH, FT3 and FT4 are monitored. Once the patient becomes hypothyroid we recommend that the guidance on monitoring hypothyroidism is followed. This guidance suggests that TSH and FT4 should be measured if symptoms are ongoing.
Stourbridge Thyroid Support Group	Guideline	19	6	Statement 1.7.2 refers to following recommendations in statement 1.3.6. In comment 26, we have asked for clarification on 1.3.6.	Thank you, we have responded to that comment
Stourbridge Thyroid Support Group	Guideline	19	7	Statement 1.7.2 refers to following recommendations in statements 1.4.1 to 1.4.6. In various comments, we have expressed disagreement with these statements.	Thank you, we have responded to those comments in turn
Stourbridge Thyroid Support Group	Guideline	19	22 - 25	Statement 1.7.7 refers to following recommendations in statements 1.3.6 and 1.4.1 to 1.4.6. In various comments, we	Thank you, we have responded to those comments in turn

				have expressed disagreement and/or a need for clarification with these statements.	
Stourbridge Thyroid Support Group	Guideline	19	26 - 28	There is once again too much emphasis on Thyroid Stimulating Hormone (TSH) testing. Triiodothyronine (FT3) and Thyroxine (FT4) should also be tested, especially if symptoms persist or have worsened.	Thank you for your comment. This has been amended to recommend measuring TSH and FT4 at 2 and 6 months post-surgery, then TSH annually. If TSH is below the reference range FT4 (if not already measured) and FT3 should also be measured.
Stourbridge Thyroid Support Group	Guideline	22	18 - 19	We disagree with statement 1.9.7. If there are no symptoms, and there appears to be normal thyroid function, then there is indeed no need to offer treatment to adults with non-malignant thyroid enlargement. However, even if symptoms are only mild, it does not matter whether there appears to be normal thyroid function or not, we feel that treatment should be considered, as symptoms should never be ignored, no matter how mild they are.	Thank you for your comment. In the absence of evidence, the committee agreed that mild symptoms alone were not enough to warrant treatment unless a person has difficulty in breathing of there are clinical concerns.
Stourbridge Thyroid Support Group	Guideline	31	1 - 2	We find it hard to understand why the committee was unable to find evidence to support the use of iodine and selenium supplements, and we also question why they are not considering other supplements too. There are numerous papers published on the subject of supplements, and it has been found that selenium deficiency in particular causes problems, as it decreases the production of thyroid hormones, because it decreases the function of selenoproteins, in particular, in the iodothyronine deiodinases (DIOs), which are a family of enzymes that remove specific iodine atoms, and are responsible for the conversion of Thyroxine (FT4) to Triiodothyronine (FT3). We can provide evidence.	Thank you for your comment. There was no evidence that met the protocol criteria for these evidence reviews. While there may be some published research into these treatments which will have its merits, it is not of the nature required to make definitive recommendations on treatment in a NICE guideline in this context.
Stourbridge Thyroid Support Group	Guideline	31	11 - 17	Under the heading “Why the committee made the recommendations”, patients complain about the Thyroid Stimulating Hormone (TSH) reference range and the fact that some patients only feel better when their TSH levels are in the lower half of that range. There are many references throughout the guidelines that focus on keeping TSH levels	Thank you for your comment. The recommendations have been reworded to reflect this feedback.

				close to or within range and not enough focus on other hormone levels and symptoms. It is not always possible to keep Thyroxine (FT4) and Triiodothyronine (FT3) levels in range and symptoms eradicated whilst keeping TSH in range. We agree with these comments and cover this in our other comments too.	
Stourbridge Thyroid Support Group	Guideline	31	11 - 17	Under the heading "Why the committee made the recommendations", concerns have also been raised about the reference to the increased cost involved by having to increase medication to achieve a TSH level in the lower half of range. It is felt that this is a short-sighted approach by many patients, as Levothyroxine (T4) is very cheap and therefore, an increased dose of Levothyroxine is justifiable, especially if it alleviates or eradicates symptoms completely, helping to fully restore the patient's health, compared to the costs involved in trying to investigate and treat the symptoms instead, and allowing the patient to suffer in the meantime. Again, we agree with these comments and believe that this applies to the use of Liothyronine (T3) too, although in the case of T3, currently, for the wrong reasons, it is expensive in the UK at this time. It is not expensive in other countries though and if it were being sold at a fair price, it could be more cost-effective in the long-run. The pricing issue needs to be resolved, and not used as an excuse for denying T3 to patients, who would definitely benefit from its use.	Thank you for your comment. This NICE guideline is written from the perspective of the UK NHS and PSS, and therefore takes account of current UK prices available across the NHS. Liothyronine is subject to CMA investigation and a cross reference to the CMA investigation has now been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). However, until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline. The guideline states that liothyronine should not be routinely prescribed as no clinically important difference was identified for health-related quality of life, between T4 and T4/T3. There was a clinically important harm of combined levothyroxine and liothyronine for quality of life-role physical functioning and TSH suppression. There was a clinically important benefit of combined levothyroxine and liothyronine for quality of life-social functioning and quality of life-role-emotional. Overall, the committee agreed that the evidence was generally suggestive of combined therapy having no important effect on quality of life and the small and contradictory benefits and harms in subdomains of quality of life were

					more likely to reflect the low quality of the underlying evidence. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).
Stourbridge Thyroid Support Group	Guideline	37	13 - 17	Under the heading “How the recommendations might affect practice”, we, and many patients worldwide, are concerned about the strong possibility that radioactive iodine will end up becoming the preferred and even, the only option provided to patients, based on cost, and not what is best for the patient. There are many associated risks with radioactive iodine treatment and, as mentioned in other comments, the patient has to live with the long-term consequences of any treatment, therefore they should be offered as many options as possible.	Thank you for your comment. The committee is aware of the potential risks associated with radioactive iodine treatment. Decision making has been based on the committee’s clinical expertise and by evidence of the highest quality available of the clinical and cost-effectiveness of radioactive iodine as first-line treatment for thyrotoxicosis. In particular, the safety of radioactive iodine relative to various cancer diagnoses including breast, respiratory and thyroid cancer diagnoses was demonstrated. Furthermore, the benefit that radioactive iodine being a definitive treatment could bring to patients was considered to outweigh potential harms.
Stourbridge Thyroid Support Group	Guideline	4	7	A good response to treatment depends on the patient being given the most appropriate treatment for them. This line should read “Thyroid disease usually responds well to **correct** treatment”. Patients who do not improve are clearly not on the right treatment.	Thank you for your comment. The committee has reviewed this and prefer the statement as written. There are also recommendations in specific sections on what to do for patients who do not respond to treatment.
Stourbridge Thyroid Support Group	Guideline	4	8 - 9	Symptoms are there for a reason and are rarely imagined. If symptoms persist, after receiving treatment that should eradicate them, then there is something wrong still. This statement should therefore read “The goal of treatment is to eradicate symptoms, which might be accomplished by achieving thyroid function test results within or close to the	Thank you for your comment. We have changed ‘manage symptoms’ to ‘alleviate symptoms. Your point about further investigations is covered by recommendations on what to do if treatment is not successful within our sections on managing and monitoring thyroid disease.

				reference range. If symptoms are not eradicated upon achieving thyroid function test results within or close to the reference range, then further investigation is needed".	
Stourbridge Thyroid Support Group	Guideline	4	10 - 11	This statement is ambiguous and could therefore be interpreted incorrectly. It could imply that a person is still ill, even if they do not feel ill, giving a medical professional a reason to insist that a patient is ill, despite them feeling well, purely based on their thyroid function test results. This in turn could lead to wrong or inappropriate treatment. We would suggest that this statement is changed to "People may only feel well when their thyroid function test results are not within or close to the reference range. This does not necessarily mean that they are ill, well or on the correct or wrong treatment".	Thank you for your comment. These bullet points are for clinicians to provide information to people with thyroid disease of what they might experience.
Stourbridge Thyroid Support Group	Guideline	4	12 - 13	This statement is ambiguous as it does not refer to the symptoms in context, ie a patient would not warrant thyroid investigation unless they have, or have had symptoms. One must therefore assume (and it is never good enough to have to assume) that this statement refers to a situation where the patient has been undergoing treatment to a point where their symptoms have stopped. This needs clarification. We would suggest that this statement be changed to "If after treatment, there is an absence of symptoms, it may be necessary to continue with treatment to ensure that symptoms do not return and, to reduce the risk of long-term complications".	Thank you for your comment. We have reworded this to state "Even when there are no symptoms, treatment may be recommended to reduce the risk of long-term complications." The purpose of the recommendation is to inform people who have been diagnosed with thyroid disease that even if they feel well treatment may be advisable.
Stourbridge Thyroid Support Group	Guideline	4	16 - 17	We feel that this statement is confusing, as this appears to be a reference more appropriate for hyperthyroidism than hypothyroidism. It is hard to see how the life of Thyroxine (FT4) is relevant in hypothyroidism, unless treatment changes are required, ie situations where Levothyroxine (T4) mono-therapy has not been successful or has been over-successful, for example, some patients need the addition of Liothyronine (T3), and T3 sometimes does not work unless FT4 levels have	Thank you for your comment. We have amended this bullet point to read "Symptoms may lag behind treatment changes for several weeks to months." We have also amended the subsequent bullet point to read "Day-to-day changes in symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine".

				been reduced first. We would suggest that this statement reads “Symptoms may lag behind treatment changes because the body needs time to adjust to them. Thyroxine can last up to 14 days in the body and therefore, it can take a long time for any treatment adjustments to be reflected in the reduction of symptoms”.	
Stourbridge Thyroid Support Group	Guideline	4	18 - 19	Traumatic events and changes in diet, lifestyle, workload, stress levels and general constitution affect all of us, whether we are ill or not, and symptoms can present as a result. Symptoms should always be taken into consideration when diagnosing a patient, but possible causes of symptoms, especially erratic symptoms, should be investigated. One cannot assume that underlying thyroid disease is or isn’t the cause without taking all circumstances into account.	Thank you for your comment. We have amended this bullet point to read “Day-to-day changes in symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine”. We have also amended the previous bullet point to read “Symptoms may lag behind treatment changes for several weeks to months.”
Stourbridge Thyroid Support Group	Guideline	5	General	Under section 1.1.2, we feel there are omissions. Patients should also be provided with a list of symptoms, so they can monitor improvements or worsening of symptoms and not be guided by clinical evidence alone. They should also be told about places where they can get further information and support, eg Thyroid UK and Thyroid Patient Advocacy.	Thank you for your comment. The committee considered it was not possible to develop a definitive list of symptoms that may be associated with thyroid disease. The guideline makes specific reference to testing where an association was found between some conditions/symptoms and thyroid disease.
Stourbridge Thyroid Support Group	Guideline	5	General	Under section 1.1.2, we feel there are also omissions with regard to diet and nutrition, ie good and bad food choices, potential food intolerances, and deficiencies in vitamins and minerals. Patients need to understand that treatment might not work or might stop working if there are problems in these areas.	Thank you for your comment. Diet and nutrition were excluded from the scope, so we have made no statements about them within the patient information recommendations.
Stourbridge Thyroid Support Group	Guideline	5	General	Under section 1.1.2, we feel that there is a testing requirement that has not been mentioned for consideration. Thyroid disease is associated with an increased risk of developing Diabetes, so it should be specifically mentioned as a concern, and singled out as a further reason for routine monitoring, that should be offered automatically, for all patients with thyroid disease. Early detection is important, even though Diabetes	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. It was not possible to review the evidence of association between thyroid disease and all possible co-existing conditions. The evidence review for who should be tested for thyroid disease found that T1DM

				can be misdiagnosed, and it should not be necessary to wait until Diabetes is fully developed before anything is done about it, even if there is no evidence of Diabetes upon first diagnosis of thyroid disease. We believe that monitoring should start straight away, and patients should be made aware of what symptoms to look out for. For example, some symptoms of Diabetes are the same or very similar to those of hypothyroidism.	was associated with thyroid disease; this suggests that testing for the latter in the presence of the former may be appropriate. However, that is not enough evidence to support routine monitoring of all people with thyroid disease for diabetes.
Stourbridge Thyroid Support Group	Guideline	5	General	Under section 1.1.3, we feel that other treatment options should also be referred to, even if they are not currently available through the NHS, specifically Natural Desiccated Thyroid (NDT). It is our experience that many people have only regained their health through the use of NDT, and there is a lot of evidence to support this and the fact that NDT is safe, and certainly no less safe than Levothyroxine (T4). We can provide evidence.	Thank you for your comment. We have amended the first bullet point to state possible drug interactions with thyroid hormone replacements.
Stourbridge Thyroid Support Group	Guideline	5	General	Under section 1.1.3, we feel that an important omission has been made. Auto-immune Thyroiditis should be mentioned. For example, Hashimoto's Thyroiditis is a major cause of hypothyroidism, and auto-immune conditions can lead to extensive food intolerances and the development of other auto-immune conditions.	Thank you for your comment. This section of the guideline is to provide information to people once they have been diagnosed with thyroid disease. We have included a recommendation on testing for thyroid dysfunction in people with auto-immune diseases.
Stourbridge Thyroid Support Group	Guideline	5	1 - 2	Because current practice does not test all the most important thyroid hormones by default, and we believe that Thyroid Stimulating Hormone (TSH) testing alone is an inadequate testing method, patients should also be told about all the thyroid function tests that are available, so they understand that there are other avenues to explore if they feel they have a need to. Patients should be made aware of other types of testing that could help them with the management of their condition for example, even if they are not available through the NHS.	Thank you for your comment. The recommendations for testing include tests other than TSH and are based on the available evidence and committee consensus. The committee believe these tests are sufficient to provide the required information on the diagnosis of thyroid disease.

				We would suggest re-wording this statement to "- their underlying condition, including the role and function of the thyroid gland, what the thyroid function tests are and what they mean, and what tests can be done to investigate matters further".	
Stourbridge Thyroid Support Group	Guideline	5	11 - 12	There is only mention of Levothyroxine (T4) and no mention of Liothyronine (T3). As Liothyronine is an approved treatment, although seldom given, this should be included in this statement.	Thank you for your comment. We have changed 'levothyroxine' to 'thyroid hormone treatment'.
Stourbridge Thyroid Support Group	Guideline	5	13	There is only mention of Levothyroxine (T4) and no mention of Liothyronine (T3). As Liothyronine is an approved treatment, although seldom given, this should be included in this statement.	Thank you for your comment. The committee agreed the specific issue here was how and when to take levothyroxine.
Stourbridge Thyroid Support Group	Guideline	6	Table	We disagree with the statement regarding risks/disadvantages of the use of radioactive iodine. The statement should be re-worded to "Strong possibility of long-term or permanent hypothyroidism, requiring the need for replacement thyroid hormones, such as, but not limited to, Levothyroxine (T4)".	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Stourbridge Thyroid Support Group	Guideline	6	Table	We also feel there are omissions in the table with regard to risks/disadvantages of the use of radioactive iodine. There is a significant risk of permanent saliva gland damage and a risk of breast iodine uptake. Recent research has also found a link between radioactive iodine treatment and solid cancer mortality in hyperthyroidism. We can provide evidence.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Stourbridge Thyroid Support Group	Guideline	6	Table	We disagree with the statement regarding risks/disadvantages of surgery. The statement should be reworded to "Permanent hypothyroidism after total thyroidectomy, requiring the life-long need for replacement thyroid hormones, such as, but not limited to, Levothyroxine (T4)".	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. A bullet point has been included

					mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Stourbridge Thyroid Support Group	Guideline	7	13 - 15	We are confused by the statement under 1.2.1. There is possible contradiction. How can there be a clinical suspicion of thyroid disease if no tests have been done yet and they are only just being considered, or have they been done already? Are symptoms being included under the description “clinical suspicion”? Clinical results are mostly gained through tests, including blood tests etc, so this implies that clinical tests have aroused suspicion. Therefore, surely there is no such thing as clinical suspicion unless tests have been carried out already, which perhaps do not conclusively provide a diagnosis? Clarification is required. We would also add that we disagree with the reference to “… 1 symptom alone may not be indicative of thyroid disease”. Based on our experience, this is stating the obvious, as it is most unlikely that a patient will be blaming thyroid disease based on just one symptom. All patients with thyroid disease have multiple symptoms but as most people, including doctors, do not know what all the symptoms are, it can be incredibly difficult to attribute certain symptoms to thyroid disease. Some symptoms are very vague and could be attributable to many conditions, but when there are a lot of these vague symptoms, a pattern is formed that we associate with thyroid disease. Until a list of symptoms is widely accepted as part of the diagnosis process, this will continue to be a problem, and thyroid conditions will go undiagnosed. We can provide a list of known symptoms for thyroid disease, which comes directly from patients themselves, and extensive references, research and observations. If patients and doctors were aware of all the	Thank you for your comment. A person may present with symptoms that suggest they may have thyroid disease. The GP will decide whether they think a person’s thyroid function needs to be tested using these recommendations and their experience. Guidelines are not intended to be a text book and it is expected that healthcare professionals will be familiar with classical description of hypo- and hyper -thyroid disease. The guideline does include specific symptoms/conditions where we found evidence for an association. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated. We are happy with the recommendation as it is written

				symptoms to consider, they would more quickly see how many relevant symptoms are being presented that would suggest that thyroid disease is the root cause. Therefore, this statement should be reworded to “Consider tests for thyroid dysfunction for adults, children and young people if there is a suspicion of thyroid disease based on symptoms, but bear in mind that symptoms may not be indicative of thyroid disease”.	
Stourbridge Thyroid Support Group	Guideline	7	20 - 21	Research and observations have often revealed that a traumatic event, such as the death of a loved one, a failed marriage, major surgery or a car accident can trigger thyroid disease. With this in mind, we feel that this statement under 1.2.3 should read “Consider tests for thyroid dysfunction for adults, children and young people with depression or unexplained anxiety, or that have recently experienced a traumatic event”.	Thank you for your comment. A previous traumatic event was not believed to be a trigger for thyroid disease by the committee and therefore was not included in the review. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated. The guideline does include specific symptoms/conditions where we found evidence for an association.
Stourbridge Thyroid Support Group	Guideline	8	General	On page 8, we strongly disagree with statements 1.2.7 and 1.2.8. Testing Thyroid Stimulating Hormone (TSH) alone does not provide enough information for diagnosis, assessment or monitoring. The creator of this test was concerned that the TSH test might end up being used solely for diagnosis, instead of carrying out other important tests. He wanted the patient to be treated - and not to rely on one test for diagnosis. It is too easy to not diagnose thyroid disease when it is present through using TSH testing alone. Free Thyroxine (FT4) and Triiodothyronine (FT3) levels need to be tested too. If there is not enough active hormone present (FT3), hypothyroid symptoms will be evident, and there will be a strong possibility that thyroid disease is there. We feel that as soon as thyroid	Thank you for your comment. The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. The committee agreed that this approach to

				disease is suspected, regardless of age or whether secondary thyroid dysfunction is suspected, as a minimum, Thyroid Stimulating Hormone (TSH), Free Triiodothyronine (FT3), Free Thyroxine (FT4), Thyroglobulin Antibodies (Tabs) and Thyroid Peroxidase Antibodies (TPOAbs) should all be tested. Ideally, Vitamin D, Vitamin B12, Ferritin and Reverse Triiodothyronine (RT3) levels should also be tested, but unfortunately, testing for RT3 is not currently available except through a private laboratory. This is something that also needs to be acknowledged and addressed.	testing would be both clinically and cost effective for the diagnosis of thyroid disease. These recommendations only relate to the initial tests that aid the diagnosis of thyroid disease. Subsequent testing once thyroid disease is confirmed is covered in the sections related to hypothyroidism and thyrotoxicosis respectively.
Stourbridge Thyroid Support Group	Guideline	9	General	We strongly disagree with statements 1.3.1 and 1.3.2. We feel that regardless of age, if Thyroid Peroxidase Antibodies (TPOAbs) are present, they should be monitored, as changes in diet, age and lifestyle can cause levels to rise or fall. Changes should be noted, as for example, if a patient researches auto-immune diseases, they might intentionally change their lifestyle through diet and/or exercise in order to try to improve their condition. Regular testing would confirm whether changes have been successful or not. Once a patient has one auto-immune disease, they are at a significantly increased risk of developing other auto-immune diseases, so it is important to check the antibody levels from time-to-time to ensure that there are no major changes, especially increases in antibody levels. We also feel that Thyroglobulin Antibodies (TgAbs) should be tested too, and if they are present, they should also be monitored for the same reasons.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee did recommend repeat testing as this would not affect a change in management. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Stourbridge Thyroid Support Group	Guideline	9	14 - 16	We strongly disagree with statement 1.3.4. We agree that not all people need to be routinely offered Liothyronine (T3), however, where symptoms are getting worse and/or clinical evidence appears to confirm that treatment is not working, regardless of where that evidence has been sourced, that	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for

				should always routinely result in patients being offered T3. We also strongly disagree with your reference to there not being enough evidence to prove that T3 offers benefits over Levothyroxine (T4) mono-therapy. There is plenty of evidence that T3 only or combination T3/T4 therapy can be, and often is more effective than T4 mono-therapy. We can provide evidence.	T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Hence the committee's recommendations for further research in this area.
Stourbridge Thyroid Support Group	Guideline	9	17 - 19	We strongly disagree with statement 1.3.5. Natural thyroid extract or Natural Desiccated Thyroid (NDT) has been successfully and safely used since the late nineteenth century. Many of our members and indeed many patients worldwide, use NDT because it is the only treatment that has worked well for them, successfully reinstating good health. Reports of long-term adverse effects caused by Levothyroxine (T4) are well documented however, whilst we have been unable to find any significant evidence of long-term adverse effects from the use of NDT.	Thank you for your comment. The committee recommended against the use of natural thyroid extracts because there was no evidence of benefit over levothyroxine, they are not licensed for use in the UK and the committee was concerned about unknown adverse effects because of the high proportion of T3 to T4 in them.
Stourbridge Thyroid Support Group	Guideline	General	General	On pages 7 and 8, under the heading "Indications for tests for thyroid dysfunction", we feel there is an omission. We believe that tests should also be offered to adults, children and young people where there are already existing blood-related family members with thyroid disease. Thyroid disease often runs (genetically) in many families, and is for example, often suffered by all of the women in such a family.	Thank you for your comment. We did not find any evidence to support case finding in families.
Stourbridge Thyroid Support Group	Guideline	General	General	On pages 20 and 21, under the headings "Monitoring of antithyroid drugs" and "Managing and monitoring subclinical hyperthyroidism", we feel that there is still far too much emphasis on Thyroid Stimulating Hormone (TSH) testing, and not enough consideration is given to symptoms or levels or Triiodothyronine (FT3).	Thank you for your comment. While the committee agreed that TSH would be a sufficient test for the majority of people, symptoms should of course be taken into account in any individual interaction between a person and a healthcare professional. Other tests are recommended alongside TSH in the early stages post-treatment of hyperthyroidism until TSH becomes an appropriate sole biochemical marker for monitoring.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

Stourbridge Thyroid Support Group	Guideline	General	General	On pages 28 and 29, under the heading “Why the committee made the recommendations”, and throughout all the guidelines and evidence reviews, there appears to be too much reliance on the Thyroid Stimulating Hormone (TSH) test. There is a great deal of concern from our members and patients around the world about how the TSH test is not being used appropriately. We are very concerned too. Through their experience and our own, and the experience of many other support groups and organisations, too many people are not being diagnosed with secondary or central hypothyroidism, when they should be, because of the reliance on Thyroid Stimulating Hormone (TSH) testing alone. Dr Robert Utiger was a pioneering doctor in the field of endocrinology, and was also the creator of the TSH test. He also helped develop other thyroid tests too. Dr Utiger, with all of his background knowledge, said that he hoped that doctors will still practice medicine and treat the patient - not the TSH levels. He believed that the best way to evaluate whether a patient’s metabolism is causing their symptoms or not, is to measure body temperature and heart rate and to offer a therapeutic trial of T3. He did not want his test to be used as a substitute for all other possible tests and to be considered more important than symptoms. To get a full picture of what is actually happening, TSH needs to be taken into account, but it also needs to be taken in context. TSH only reveals part of the picture. Even if Free Thyroxine (FT4) testing is performed too, this still does not provide information about Triiodothyronine (FT3) levels, and this is the active hormone that is actually needed at a cellular level by the body. If there is not enough active hormone present, hypothyroid symptoms will exist, and there is a strong possibility that thyroid disease is present too. Reverse	Thank you for your comment. The committee agrees that symptoms form an important part of the clinical picture. NICE guidance is not intended to be exhaustive and the recommendations do not list all the actions that a healthcare professional should follow during monitoring and the consideration of symptoms is of course important. The committee do consider that in the majority of cases TSH is a sufficient sole biomarker for the most people if they are well and their thyroid function has stabilised following any acute treatment (e.g. in hyperthyroidism). While other tests may have theoretical benefits, there is no evidence to suggest routine use of these tests would form a cost-effective monitoring strategy and expanding their use would certainly have resource implications. The recommendations have been amended somewhat during this consultation phase to emphasise the importance of symptoms and expand the use of additional tests like FT4 in certain situations.

				Triiodothyronine (RT3) levels and various thyroid antibody levels reveal a lot about what is going on too. If further testing reveals more questions than answers, there are definitely many more tests that can be done to give an even larger picture, such as testing for important vitamin and/or mineral deficiencies. It might also be a good idea to encourage patients to keep a diary to keep notes on dietary changes, basal body temperature and heart rate. Symptoms are probably the most important clues of all though. If symptoms are present, there is a situation that needs to be addressed. When a patient visits their doctor for diagnosis, they are not presented with a list of symptoms. We understand that most thyroid related symptoms are vague, but there are so many symptoms that are caused by thyroid conditions that it is not so much about what symptoms a patient has but more about how many symptoms a patient has. To have most of the symptoms on a symptoms list, no matter how vague those symptoms are, this would strongly indicate that a thyroid condition or problem is present. This does not necessarily mean that there is thyroid disease, but it does mean that the patient is genuinely ill, perhaps through a deficiency of Vitamin D or Vitamin B12. That is why it is so important to treat the patient based on symptoms foremost, and to not rely on TSH alone. We can only estimate, but we believe that it is possible that the TSH test fails to recognise and correctly diagnose up to 85% of all thyroid patients.	
Stourbridge Thyroid Support Group	Guideline	General	General	There are many references throughout the guidelines to palpable mass detection, but there is no mention of who should be doing this, how and when. Not all medical professionals are trained in how to do this and most patients are never checked for a palpable mass as a result.	Thank you for your comment. The committee expect that all medical professionals who will be assessing a neck mass will have been appropriately trained.

Thyroid disease

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Stourbridge Thyroid Support Group	Guideline	General	General	Reverse Triiodothyronine (RT3) is not given consideration anywhere in these guidelines. We feel that it is an invaluable diagnosis tool though, because RT3 levels rise and fall with bad and good inactive to active hormone conversion, respectively.	Thank you for your comment. RT3 was included in the protocol for which tests should be performed when thyroid dysfunction is suspected and there was no evidence to support its clinical or cost effectiveness. In addition, this test is only available in a few UK centres. The committee therefore agreed that it was not appropriate to make consensus based recommendations to drastically expand the amount of RT3 in the UK.
Stourbridge Thyroid Support Group	Guideline	General	General	There are four types of thyroid antibody that we feel should be tested, to help give a clearer picture of what is going on. These are TSH Receptor Antibodies (TRAbs), Thyroglobulin Antibodies (TgAbs), Thyroid Peroxidase Antibodies (TPOAbs) and Thyroid Stimulating Immunoglobulin (TSIAbs). Testing all four types avoids the risk of misdiagnosis caused by the patient having more than one type of thyroid antibody.	Thank you for your comment. The committee searched for evidence across the spectrum of thyroid antibody tests including all those you mention and generally found insufficient evidence to support their use beyond that of TPOAbs and TRAbs in the indications listed in the recommendations.
Stourbridge Thyroid Support Group	Guideline	General	General	Many patients with thyroid conditions are puzzled at the lack of diagnosis methods used at an NHS thyroid consultation, compared to a private one. A lot could be learned from private practice, where patients are often given full thyroid panel blood tests that do not rely on levels of Thyroid Stimulating Hormone (TSH) alone, and they are asked to fill in a full medical questionnaire and keep a diary of dietary changes, heart rate and basal temperature. On top of this, it is common to present the patient with symptom lists and supplement recommendations, to help the patient understand their symptoms and recognise them, and how best to support their condition. Sometimes, adrenal hormone testing and sex hormone testing is suggested, along with genetic assessment. The patient leaves the consultation with lots of information and support.	Thank you for your comment. The committee made recommendations based on the best available evidence and committee consensus. Commenting on what happens in private practice is beyond the remit of this guideline.
Stourbridge Thyroid Support Group	Guideline	General	General	Treatment with Liothyronine (T3) is discouraged and treatment with Natural Desiccated Thyroid (NDT) is dismissed completely	Thank you for your comment.

				in these guidelines. This is a blinkered approach to these two very valid alternative treatment options. Many patients do not recover their full health through Levothyroxine (T4) alone. Many need the addition of Liothyronine (T3) or to solely use T3. Some patients do not do well on T4 only, T3 only or T3 in combination with T4, and find that NDT is the only treatment that significantly reduces or even eradicates their symptoms. We believe that more research is needed to understand why one person is best suited to a particular treatment over another, and why different brands of those treatments are not as good as each other too. It cannot be coincidence that so many people feel better, and even thrive on NDT. Saying there is not enough evidence is not an excuse to ignore facts. We should do the research and create the evidence. However, there is evidence that NDT is better suited to certain patients, and there is no evidence that we can find to suggest that NDT or T3 are any more dangerous or "less safe" than T4. NDT has been used for over 100 years and if it were that dangerous, how come it has not been withdrawn, and why is it so popular still? If it did not work, people would not buy it, and it is often the preferred choice by many specialists in other countries?	The recommendations are based on clinical evidence available and the research was searched for evidence to support use of T3 and thyroid extract. We did not find evidence to support the routine use of T3 or the use of thyroid extract. We agree that more research is required and have made research recommendations for liothyronine. We have not made a research recommendation for thyroid extracts as NICE cannot make a research recommendation if a product is not licensed.
Stourbridge Thyroid Support Group	Guideline	General	General	We feel that Liothyronine (T3) and Natural Dessicated Thyroid (NDT) should be mentioned in these guidelines, along with their proper use, even if they are less likely to be prescribed, and this is for two reasons. Firstly, the doctor or specialist does not have the right to deny a patient the treatment they need, and in the absence of professional approval, a patient might purchase the treatment they need privately. This does not mean that they should not be monitored, and it should not be permissible to turn a patient away because their treatment option is not liked by the medical practitioner. Secondly, there	Thank you for your comment. The recommendations are based on clinical evidence available and the research was searched for evidence to support use of T3 and thyroid extract. We did not find evidence to support the routine use of T3 or the use of thyroid extract. The committee have made research recommendations in this area.

				are instances where doctors and specialists are prescribing these alternative treatments, although it is rare. However, perhaps opinion will also change in the future and these alternatives will be more frequently prescribed. Including references to T3 and NDT in these guidelines will mean some small adjustments to the guidelines as discussed in many of our comments. We would also add that these guidelines do not reflect final guidance in “Prescribing of Liothyronine”, published by the Regional Medicines Optimisation Committee in June 2019.	The recommendations are based on available evidence and committee consensus and written independently of the Regional Medicines Optimisation Committee recommendations.
Stourbridge Thyroid Support Group	Guideline	General	General	We cannot see any references to patients with congenital thyroid disorders. Is there going to be a separate guideline for this and if so, it should at least be referred to, even if it does not exist yet. Patients in this category are more likely to need alternatives to Levothyroxine (T4) mono-therapy treatment. They also need special consideration regarding calcium levels. If no guideline is available at this time, some basic guidelines should be included within these guidelines.	Thank you for your comment. The committee believe these recommendations will apply to people with congenital thyroid disorders as well. It is also anticipated that children will be under specialist care.
Stourbridge Thyroid Support Group	Guideline	General	General	Many patients who have undergone a thyroidectomy have expressed concern that they are not given any special considerations with regard to their treatment, although we believe it is widely acknowledged that if treatment practices improved, as per our recommendations and comments, they too would see the benefits, and may find that fewer special considerations would be required.	Thank you for your comment. The recommendations on the management of hypothyroidism and subclinical hypothyroidism will also apply to patients who have had a thyroidectomy.
Stourbridge Thyroid Support Group	Guideline	General	General	We cannot see any references to parathyroid conditions in these guidelines. Is there going to be a separate guideline for this and if so, it should at least be referred to, even if it does not exist yet. Such conditions can have serious consequences for the thyroid and calcium levels. Patients in this category need support and monitoring too.	Thank you for your comment. NICE has developed a guideline on diagnosis and management of primary hyperparathyroidism including monitoring following surgery (https://www.nice.org.uk/guidance/ng132)

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Stourbridge Thyroid Support Group	Guideline	General	General	We cannot see many references to women who are trying to conceive or that are pregnant or nursing. We acknowledge that there is going to be a new guideline soon, however, we feel that a reference to this fact should be in the guidelines, along with some basic guidance that can be used in the meantime, until the new guideline has been produced.	Thank you for your comment. This was outside the scope of this guideline, and we understand that the RCOG guidance will be published soon.
Stourbridge Thyroid Support Group	Guideline	General	General	In light of recent research that has found a link between radioactive iodine treatment and solid cancer mortality in hyperthyroidism, we feel that this needs urgent investigation and a possible review, especially where children and young adults are concerned.	Thank you for your comment. If you are referring to the study published by Kitahara et al 2019 in JAMA, this study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
Stourbridge Thyroid Support Group	Guideline	General	General	We cannot see references to cardiovascular issues being a complication of hypothyroidism in these guidelines. It should be acknowledged that heart failure can be a symptom of low	Thank you for your comment. These recommendations are not a comprehensive guide to all aspects of thyroid disease management but focus on key questions

				Triiodothyronine (FT3), and this is a serious and potentially fatal omission for some patients.	prioritised during scoping with stakeholders and informed by committee discussions. NICE guidelines can only focus on a limited number of areas in order to conduct the most rigorous evidence searching and analysis.
Stourbridge Thyroid Support Group	Guideline	General	General	We could not see any references to Thyroid Eye Disease or the impact of thyroid disease on mental health in these guidelines. Are there going to be separate guidelines that cover these conditions?	Thank you for your comment. Thyroid eye disease was excluded in the scope and therefore no recommendation has been made in this area.
Stourbridge Thyroid Support Group	Guideline	General	General	We are saddened to note that the committee is rather small for such a complex subject, and that there are no members who represent the people who have to live with thyroid conditions and understand how badly they can affect people who have them, and their family and friends.	Thank you for your comment. The committee constitution is aimed to ensure adequate expertise for the areas included in the scope. The guideline committee included lay members who are people who have personal experience of thyroid disease and also have a wider experience of representing the interests of people with thyroid disease. The lay committee members have been fully involved throughout the development of the guidance.
Stourbridge Thyroid Support Group	Guideline	General	General	We are also saddened by the poor layout of the guidelines that make it difficult for a medical practitioner to follow, and we are dismayed at the prioritising of costs above patient health. Good treatment leads to better health and poor treatment leads to worse health in the long run. Therefore pennies spent now can save thousands of pounds in the future.	Thank you for your comment. The guideline is produced in a number of formats with a shorter version including recommendations and an explanation of why they were developed and separate more detailed reviews of evidence. NICE guidelines are required to consider cost effectiveness but evidence for clinical benefit is assessed before cost effectiveness is considered. Cost effectiveness analysis does include long term implications of treatment decisions.
TEAMeD	Guideline	25	6	This section (Long-term effectiveness and safety of radioactive iodine therapy) should include the development of regimes to minimise the side effects (eg optimal combination with short term antithyroid drugs) including radiation thyroiditis, post-I-131 hypothyroidism, weight gain and thyroid eye disease.	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee

					considers there is a need for further research. The suggestion you make here does not meet these criteria.
TEAMeD	Guideline	5	20	We suggest the following text be added to the fourth bullet point ('the risk and impact of thyroid eye disease…'): '….and the importance of smoking cessation in reducing this risk', and include signposting to NHS smoking cessation resources. All studies including RCTs have shown that smoking increases the risk of thyroid eye disease. (eg Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131.Träisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nyström E, Ponjavic V, Taube A, Törring O, Wallin G, Asman P, Lundell G; Thyroid Study Group of TT 96.J Clin Endocrinol Metab. 2009 Oct;94(10):3700-7) We would also suggest that the phrase include specific reference to Graves' disease as only those with thyrotoxicosis due to Graves' disease are at risk of eye disease e.g. suggested wording "the risk and impact of thyroid eye disease in people with Graves' disease, and the importance of smoking cessation in reducing this risk".	Thank you for your comment. We have not included advice on smoking cessation as we did not review the evidence for this. The committee consider advising people to stop smoking is generic advice given to all people. We have amended the bullet point to read "• the risk of and impact of different treatment options on new and existing thyroid eye disease (for example, radioactive iodine may precipitate or worsen thyroid eye disease)"
The Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	It is the overall view of the committee that this guidance is a fair and balanced document. We consider that further work is needed to compare fixed patient dose versus individualised, and it is unfortunate that the quality of the current studies is considered low or very low.	Thank you for your comment. It is important to note that GRADE terminology (low or very low etc.) reflects the quality of the evidence underlying the outcome and does not necessarily mean the studies themselves are low or very low quality. Factors that are included in the GRADE rating are risk of bias, imprecision, indirectness, inconsistency and publication bias.
The Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	There is little comment on the effects of the radiation dose absorbed and perhaps the recent study noting a possible increase in breast cancer and some other cancers from	Thank you for your comment. This study was raised by a number of stakeholders. The study was published after the final search for evidence for the guideline and also

				treatment with radioactive iodine particularly for younger people should be referenced and considered (published July 2019). Several of the studies included do note site specific cancers as being an outcome, but the NICE committee concludes the risk is not clinically impactful.	does not strictly match the inclusion criteria for either of the evidence reviews relating to radioactive iodine as it fails to compare a radioactive iodine treated group with a non-radioactive iodine group (either hyperthyroidism treated with some other modality or age/sex/cohort matched healthy controls).The study finds a marginal increase in overall cancer diagnoses in people who are treated with higher radioactive iodine doses compared with those treated with lower doses. The effect is statistically significant but small and the study has a number of limitations including the formula used to assess exposure, the lack of useful control group and relatively limited set of confounders controlled for (e.g. not including smoking). While the guideline itself does not reference the study for the reasons listed in the third sentence of this response, the committee discussed it at length during the consultation phase and agreed that due to its various limitations it did not have a significant impact on the recommendations in the guideline.
The Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	This would support the suggestion for further study taking dosimetry into account, especially since the need for such treatments is expected to increase, to ensure the management of these conditions is within the UK principle of ALARP CIP (as low as reasonably practicable consistent with intended purpose).	Thank you for your comment. We agree which is why we made the research recommendation.
The Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	The UK has a duty to meet the requirements of the BSS directive of 2013 for treatments to be planned and verified and though this may cost more in terms of time and effort, there would be potential benefits to the patient.	Thank you for your comment. The committee was aware of this and took it into consideration when recommendations related to radioactive iodine. The recommendations cross refer to the 2017 regulations on medical exposure to ionising radiation.
The Society of Radiological Protection – The Medical Sector Committee	Guideline	General	General	The section ‘Management of thyrotoxicosis: drugs vs surgery vs radioactive iodine’ notes some units are more proactive in	Thank you for your comment, the text you are referring to is an introduction and the aim of the

				management of the condition (especially for young people), and perhaps clearer guidance would be beneficial.	recommendations overall is to provide clearer guidance to ensure that inconsistency between units is reduced.
The Thyroid Trust	Equality Impact Assessment	1	2.1	Women's health issues are recognised by the WHO to be under addressed, this needs to be acknowledged. In our view, the Equality Impact Assessment is glib and wrongly slanted and must be revised, to acknowledge that gender health inequality is a factor in thyroid disease. We know that conditions which affect mostly women are poorly studied and that, because thyroid disorders affect more women than men, they can tend to be taken less seriously than they should be.	Thank you for your comment. We have reviewed the recommendations in light of your comments. A new recommendation has been added about menopausal women: "1.2.5 Be aware that in menopausal women symptoms of thyroid dysfunction may be mistaken for menopause". We have checked the rest of the guideline and do not consider that any of the recommendations discriminate against women in any way.
The Thyroid Trust	Evidence Review E	16	26	This guideline misses some key points related to patients' experiences. The NICE methodology, focusing only on RCTs and academic evidence, combined with the way in which the guidelines are 'designed by a committee' will in our view, be limiting if it is rigidly adhered to.	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Looking at RCTs ensures the recommendations made are based on the best available evidence. The aim of the recommendations is to provide guidance toward what constitutes best clinical practice and not to replace clinical judgment in the management of individual patients.
The Thyroid Trust	Evidence Review E	16	26	Some other NICE Guidelines may cover older medicines that are known to be effective but have little or less research than the thyroid hormone treatments used to treat hypothyroidism. We don't know of specific examples, but we would ask that NICE considers this issue and how it may be addressed in other Guidelines. We acknowledge the difficulty is that there's limited incentive (funding) to do research on older medicines, such as	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Looking at RCTs ensures the recommendations made are based on the best available evidence. We have made a key research recommendation on levothyroxine-liothyronine combination therapy for hypothyroidism.

				liothyronine and thyroxine, which have gone off patent, as there's less money to be made in producing them. If the NICE methodology will only look at academic research RCTs etc (much of which is industry funded), using committee members' experience, to plug the gaps, is not a sufficiently robust process. The experience of the wider clinical community, where a relatively small number of specialists can be classed as thyroid experts, as well as patient experiences, such as those detailed in The Liothyronine Dossier, must be added to the committee's experiences, or the Guideline will be too narrow. The NICE methodology risks misses important evidence on drugs that are off patent.	
The Thyroid Trust	Evidence Reviews	General	General	We are unclear as to whether the committee have discussed the Common Themes in the Liothyronine Dossier patient stories? We strongly recommend that they do so and consider the patient experiences before finalising this Guideline. We can also offer access to The Thyroid Trust Registry which is available for researchers and has over 60 detailed stories in database form, including year of birth and age at diagnosis.	Thank you for your comment. The committee is aware of the general patient experience and view on liothyronine and has had input on this from its lay members during guideline development, and from stakeholders both during this consultation and at scoping. We appreciate the offer of additional evidence but in order to justify a deviation from the current recommendation, randomised controlled trials demonstrating significant benefits of combination therapy would be required.
The Thyroid Trust	Evidence Reviews	General	General	The research into combined levothyroxine / liothyronine therapy is inconclusive. Half the studies substitute L-T3 for L-T4 in a 1:4 or 1:5 ratio based on their relative serum potency. Basic pharmacokinetics indicate the ratio patients swallow will most likely not be reflected in the blood, due to different absorption rates and elimination half-lives. All the studies fail to select appropriate cohorts – patients who fail to do well on levothyroxine. None of the studies attempted to determine the L-T3 dose patients required. The researchers decree that the patients must suffer from primary hypothyroidism (and no other form of hypothyroidism) and this	Thank you for your comment. The committee agree that there are limitations to the current evidence base, hence the research recommendation. Overall the committee agree that the current recommendation on combination therapy, twinned with a recommendation for further research, is justified based on the available evidence.

				must be corrected by small amounts of L-T3, contrary to clinical experience. Demanding patients respond according to unproven theory is not good science.	
The Thyroid Trust	Guideline	10	2	This sounds like a very positive recommendation. We believe there are thousands of patients currently left on 25mcg, 50mcg or 75mcg levothyroxine, becoming increasingly unwell and GP's refusing to increase the dose despite ongoing hypothyroid symptoms. It would be good to see this dose by weight message highlighted in communications when the Guideline is published.	Thank you for your comment. The committee agree which is why they made the recommendation.
The Thyroid Trust	Guideline	10	10	Based on clinical experience and patient reported outcomes, on Levothyroxine, we would suggest that the usual reference range is too wide for many patients To alleviate all hypothyroid symptoms we know that many patients on Levothyroxine need their TSH to be under 2, or indeed less than 1. Frequently patients need TSH under 1 and many find TSH becomes suppressed on almost any dose of Levothyroxine. http://www.pathology.leedsth.nhs.uk/pathology/ClinicalInfo/Biochemistry/EndocrinologyampDiabetes/ThyroidFunctionTests.aspx *See Box - Thyroxine Replacement Therapy in Primary Hypothyroidism* ***TSH 0.2-2.0 - sufficiently replaced. Over 2.0 likely under replacement*** If TSH becomes suppressed when patients are on less than recommended dose of 1.6mcg per kilo, we would suggest that FT4 and FT3 and vitamin levels should be tested. Annual monitoring of FT4 and FT3 and vitamin levels should continue with patients whose TSH is under 0.2. If FT4 and FT3 are	Thank you for your comment. We have amended the first recommendation (1.4.1) to state "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing."

				within range and patient is well, low TSH does NOT appear to indicate they are over treated	
The Thyroid Trust	Guideline	10	10	It is important that this is amended, to include “and restore wellbeing” and to highlight the potential importance of dose titration for patient wellbeing when patient feels unwell within the reference range	Thank you for your comment. We have amended the first recommendation (1.4.1) to state “Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing.”
The Thyroid Trust	Guideline	10	16	For cases where patients are hard to treat, might we suggest including testing SHBG sex hormone binding globulin for tissue health which we understand used to be used routinely to check for hypo or hyperthyroidism. If this test result is fine, we believe it may show good tissue health and may give clinicians peace of mind, regarding monitoring patients who report they only feel well with a suppressed TSH.	Thank you for your comment. The review for this area looked for evidence relating to SHBG and found no evidence that including this in testing strategies was a clinically or cost effective approach, therefore the committee did not include it in its recommendations.
The Thyroid Trust	Guideline	10	17	We would suggest revising this to add “and symptoms have resolved” after “until the level has stabilised within the reference range”, otherwise the monitoring criteria is meaningless.	Thank you for your comment. Recommendation 1.4.3 has been amended to clarify what stabilisation of TSH means and recommendation suggesting testing of TSH and FT4 if symptoms are not resolved has been moved up to immediately follow this: 1.4.3 For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised (2 similar measurements within the reference range 3 months apart), and then once a year. 1.4.4 Consider measuring FT4 as well as TSH for adults who continue to have symptoms of hypothyroidism after starting levothyroxine.
The Thyroid Trust	Guideline	11	11	We would suggest, based on patient and clinician experiences, that only testing TSH and FT4 may be inadequate if symptoms remain. Frequently key nutrient levels become very deficient as direct result of hypothyroidism and conversion of FT4 to	Thank you for your comment. TSH and FT4 are recommended. The committee noted that FT3 measurements are not useful in managing

				FT3 can be poor. TSH will often be extremely low and FT4 near top of range in such cases. Full testing of TSH, FT4 and FT3 plus vitamin D, folate, ferritin and B12 should be arranged by GP. If symptoms remain after vitamin levels are improved patient should be referred to endocrinologist for further evaluation. Recommending test tests at primary care level will reduce the need for expensive secondary care referrals and lengthy delays in resolving symptoms.	hypothyroidism as T3 is a short acting hormone and measurements will be very different on different days. Vitamins and minerals were not included as part of the review question and not mention of them has been made.
The Thyroid Trust	Guideline	11	11	Why the use of the word “consider” here – surely it is important to measure FT4 in this instance and direction should also be given on when to measure FT3 and when it may be appropriate to consider treatment with liothyronine	Thank you for your comment. TSH and FT4 are recommended. The committee noted that FT3 measurements are not useful in managing hypothyroidism as T3 is a short acting hormone and measurements will be very different on different days.
The Thyroid Trust	Guideline	11	14	Frequently we hear of patients who are diagnosed as subclinical with very debilitating symptoms who are only prescribed a very low dose of Levothyroxine, (25mcg or 50mcg) and left with high, but just within range, TSH results and FT4 or FT3 not tested. When symptoms remain in these cases, we would strongly recommend the dose of levothyroxine should be increased and bloods retested after 6-8 weeks. If symptoms remain when TSH is low in range, under 1, then FULL thyroid and vitamin testing should occur. Low vitamin D, folate, B12 and Ferritin are all extremely common and very often need to be supplemented. A high percentage of auto immune patients are either coeliac (5%) or gluten intolerant (over 70%) yet the NHS rarely tests for coeliac or discusses possible link to gluten intolerance with patients. See our research recommendations. Any thyroid patients, with raised antibodies and ongoing symptoms should be tested for coeliac. If coeliac test is	Thank you for your comment. The diagnosis of subclinical hypothyroidism is internationally agreed as a biochemical diagnosis. The guideline recommends adjustment of levothyroxine dosage even if TSH is in the reference range until there is optimal well-being and the testing of TSH and FT4 if symptoms continue. No evidence was identified for more frequent testing than 3 monthly in patients with subclinical hypothyroidism In the final guideline we have added a link to the NICE guideline on coeliac disease (NG20), which recommends testing for coeliac disease in people with a diagnosis of autoimmune thyroid disease.

				negative GP should discuss that patient might wish to try a gluten free diet, for three to six months, to see if there's noticeable benefit.	
The Thyroid Trust	Guideline	11	18	Add reference to 'presence of clinical symptoms which may suggest underlying thyroid disease'	Thank you for your comment. This recommendation has been edited to encompass your point and now includes reference to symptoms: "When discussing whether or not to start treatment for subclinical hypothyroidism, take into account features that might suggest underlying thyroid disease, such as symptoms of hypothyroidism, previous thyroid surgery or raised levels of thyroid autoantibodies."
The Thyroid Trust	Guideline	11 - 12	15 - 9	Why no mention of any other treatment option for patients who do not respond to initial treatment?	Thank you for your comment. No evidence was identified for further treatments. The committee also agreed that if symptoms do not improve then they may be due to other causes.
The Thyroid Trust	Guideline	12	6 - 9	Strongly suggest adding recommendation to titrate dose until T4 is at upper end of the range and TSH less than 1 before concluding that thyroxine may not be a useful treatment. Also strongly recommend adding testing T3 if TSH goes below 1 and symptoms persist, to see if the issue is non conversion. We make these recommendations based on experienced clinicians' advice and patient reported outcomes. We are concerned if these recommendations are not made then patients will be left with unresolved symptoms, which can be crippling.	Thank you for your comment. The committee agreed that if symptoms persist when TSH is within the reference range then levothyroxine should be stopped as it is possible that the symptoms are due to causes other than hypothyroidism.
The Thyroid Trust	Guideline	12	19	greater awareness of signs and symptoms needed, we would suggest they ought to be listed here and wherever symptoms are referred to in the Guideline, alternatively they need to be detailed and signposted very clearly elsewhere under a specific heading.	Thank you for your comment. The committee considered it was not possible to develop a definitive list of symptoms that may be associated with thyroid disease. The guideline makes specific reference to testing where an association was found between some conditions or symptoms and thyroid disease.
The Thyroid Trust	Guideline	13	7	As above, we believe it is important to include a mention of symptoms, which can be a sign of underlying thyroid disease.	Thank you for your comment. These recommendations relate to children who are not receiving treatment or

					have had treatment stopped and therefore they are unlikely to have symptoms.
The Thyroid Trust	Guideline	13	7	There is no recommendation as to treatment here, just measuring TSH & FT4. Clinicians tell us they would find this frustrating. Is the guideline saying just stop treatment and monitor even though symptoms may be present?	Thank you for your comment. These recommendations relate to what to do for people who are not receiving treatment or have had treatment stopped and therefore they are unlikely to have symptoms. The guideline does not recommend stopping treatment if it is working.
The Thyroid Trust	Guideline	14	24	The meaning of “supportive treatment” for hyperthyroidism is not clear, the wording appears to assume a degree of understanding which may not be there (as with previous references to signs of underlying thyroid disease).	Thank you for your comment. Supportive treatment has been defined with the example of beta-blockers.
The Thyroid Trust	Guideline	15	10	We recommend that patients are enabled to make an informed choice between RAI and surgery A minority of patients report life-changing consequences of RAI although the reasons for this are not yet understood. We note the recommendation for research, number 4, ‘Long-term effectiveness and safety of radioactive iodine therapy’ demonstrating the need for greater understanding of the risks and benefits of this treatment option. We note that 20% of patients after complete thyroidectomy or RAI may need addition of small dose of T3 to regain full health. There is evidence that T3 blood serum levels do not return to pre surgery levels with levothyroxine alone.	Thank you for your comment. This is included as part of our recommendations.
The Thyroid Trust	Guideline	19	9	Add “and are not showing symptoms of hypothyroidism” as criteria, if TSH is in range but patient feels unwell they should not simply have TSH monitored further action is required to restore wellbeing, such as levothyroxine dose titration and/or possible testing of T3.	Thank you for our comment. This recommendation has been amended to recommend measuring TSH and measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range.
The Thyroid Trust	Guideline	19	26	We would strongly suggest that further tests are required if patient is symptomatic.	Thank you for your comment. This has been amended to recommend measuring TSH and FT4 at 2 and 6 months post-surgery, then TSH annually. If TSH is below the

					reference range FT4 (if not already measured) and FT3 should also be measured.
The Thyroid Trust	Guideline	20	4	After the word “range”, add: “and patient feels well”. It is not sufficient to imply that TSH in range is the sole goal of treatment, indeed extensive patient reported experiences tell us that this stance, when taken by clinicians, can be harmful to patient outcomes.	Thank you for your comment. The committee believed this was sufficient for the majority of people and they also assumed that a person with significant symptoms will seek medical advice and may be tested more frequently if needed.
The Thyroid Trust	Guideline	24	11	We recommend adding the following Research Recommendations: • Understanding Quality of Life issues and impacts for thyroid patients • Gut function and autoimmunity • Gluten intolerances and thyroxine absorption How many patients are taking liothyronine or NDT for hypothyroidism and are satisfied with it, having previously suffered, and how else should they be treated?	Thank you for your comment. NICE guidelines make research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The areas you have suggested do not meet these criteria.
The Thyroid Trust	Guideline	24	11	Further to point 71 - to address the scant evidence base, retrospective research, into patient experiences and responses to different treatments, should be conducted through large scale patient surveys with thyroid patients who are well and less well, to gauge relative success of treatment options and lifestyle choices.	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
The Thyroid Trust	Guideline	25	16	We would suggest that more research needs to be done into the mental health aspects of thyroid disease. Thyroid patients report experiences ranging from depression and anxiety to psychosis and dementia like symptoms.	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee

					considers there is a need for further research. The suggestion you make here does not meet these criteria.
The Thyroid Trust	Guideline	25	16	Further to our comment 16, we would also suggest adding to Research Recommendations, that the NHS collates and analyses any such genetic test data, to help build understanding of the genetic aspects of thyroid disease.	Thank you for your comment. NICE guidelines make research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The area you have suggested does not meet these criteria.
The Thyroid Trust	Guideline	29	3	It is not known how many people may suffer from secondary hypothyroidism but we know that often patients wait years for a diagnosis because doctors are not aware it is a possibility. In our opinion, something more needs to be said about diagnosis and treatment of secondary hypothyroidism in the NICE Guideline.	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The focus of this guideline was on primary thyroid disease, although some recommendations reference investigation strategies for secondary thyroid disease.
The Thyroid Trust	Guideline	30	20	The American Thyroid Association surveyed 12,500 patients with hypothyroidism in 2018 and found that that 15% of patients report impaired quality of life on levothyroxine treatment alone. PMID:2962097. Given these findings, from a large sample size, it is not reasonable for treatment options, other than standard levothyroxine, to be withheld from patients who need them.	Thank you for your comment. Evidence of benefit from other treatments was not identified and therefore not recommended. Furthermore, the committee agreed there is the potential for harm with other treatments as their long-term adverse effects are unknown. Although liothyronine is not recommended for routine use the guideline does not completely rule its prescription out.
The Thyroid Trust	Guideline	31	9 onwards	There is no mention here of resolving symptoms, it is vital that doctors do not have the impression that symptoms do not matter and that they can treat hypothyroidism purely by paying attention to numerical blood test results. Long clinical experience of specialists in the field, as well as patient reported outcomes, indicate that, for many patients, if symptoms are not resolved once TSH is in the range, they may be resolved with a titrated dose and lower TSH. It is vital this is flagged up in the NICE guidelines.	Thank you for your comment. The recommendations have been reworded to reflect this feedback.

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The Thyroid Trust	Guideline	32	15	See The Thyroid Trust Registry for possible evidence? Patient reported experiences indicate subclinical hypothyroidism can include low T3 and/or fine tuning of levothyroxine dose plus other interventions such as Vit D and gluten free can make a profound difference	Thank you for your comment. There was no evidence that met the protocol criteria for the relevant evidence reviews. While there may be some published research into these issues which will have its merits, it is not of the nature required to make definitive recommendations on treatment in a NICE guideline in this context.
The Thyroid Trust	Guideline	4	8	The use of the word 'manage' here is ambiguous. We are concerned that the goal of treatment not positioned as being to resolve symptoms, we would prefer the clear wording used in the British Thyroid Association 2015 hypothyroidism guidance - "to restore wellbeing".	Thank you for your comment. We have changed 'manage symptoms' to 'alleviate symptoms.
The Thyroid Trust	Guideline	4	14	We would suggest revised emphasis here, so that GPs and patients are alert to the possibilities of titrating dose, for potentially profound differences to patient wellbeing - this is key for many patients we hear from.	Thank you for your comment. We have adjusted the wording to facilitate dose titration: Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal well-being.
The Thyroid Trust	Guideline	5	8 - 13	Given the rationale for the guideline - that it is important for people to understand the disease etc...- we think it is important patients with hypothyroidism should told that T3 and NDT and levothyroxine dose titration are possible treatment options for hypothyroidism. All of these are very important to those patients who need them Many patients and their carers are unaware of treatment options and greater awareness amongst health professionals is badly needed.	Thank you for your comment. We reviewed each of these medications as part of the guideline development and found the best evidence of effectiveness for levothyroxine which is why this is recommended. NDT and liothyronine were also reviewed, and the rationale behind not recommending these is included within the guideline. The committee therefore considers that information about these treatment options has been presented in a transparent way.
The Thyroid Trust	Guideline	5	9	We would strongly suggest also providing information on: causes of hypothyroidism including autoimmunity and include an explanation of "Hashimotos" benefits and risks of treatment- and treatment options. Patients tell us these are the questions they most need answers to.	Thank you for your comment. The guideline focuses on primary thyroid disease; although there is some consideration on appropriate testing for people when secondary thyroid disease is suspected in the recommendations prior to the one you highlight. This recommends is to provide people with hypothyroidism information related to recommendations in this guideline.

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The Thyroid Trust	Guideline	5	11	What are the interactions – we would suggest listing these here, or link to? Also include interactions with supplements, particularly iron and calcium	Thank you for your comment. There are many interactions with levothyroxine. NICE guidelines assume that prescribers will use a medicine's summary of product characteristics to inform decisions made with individual patients.
The Thyroid Trust	Guideline	5	11	Brands of thyroid hormones are not interchangeable for some patients. Some people may feel less well with different formulations of levothyroxine. The reason for this is not clear but might relate to differences in fillers and bulking agents between the various manufacturers' tablets. We would suggest that the Guidelines should mention this and patients should be advised, where possible to stay on the same manufacturer's formulation of thyroid hormones. https://academic.oup.com/jcem/article/98/2/511/2833067 Until better data become available, we would suggest the 2013 AACE/ATA/TES recommendations on LT4 treatment are included in the Guideline. These state that physicians should: alert patients that preparations may be switched at the pharmacy; encourage patients to ask to remain on the same preparation at every pharmacy refill; and make sure patients understand the need to have their TSH retested and the potential for dosing readjusted every time their LT4 preparation is switched The new Teva, lactose free formulation of Levothyroxine, with mannitol, for example, is known to upset some patients.	Thank you for your comment. We did not investigate brands of levothyroxine, so we have not made a recommendation related to brands
The Thyroid Trust	Guideline	5	14	We would strongly suggest including 'hyperthyroidism' in this heading as people often do not realise the three terms mean the same thing.	Thank you for your comment. The committee believe thyrotoxicosis is the correct term to use here and not hyperthyroidism. Both these terms are defined in the section "Terms used in this guideline".

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The Thyroid Trust	Guideline	6	1	In table 1, we consider that the risk of hypoparathyroidism following surgery is understated and recommend expanding this to explain that this may require life-long monitoring and treatment with vitamin D and calcium tablets.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
The Thyroid Trust	Guideline	6	2	Add that hypothyroidism can sometimes be hard to manage and have severe affect on QoL. TTT have seen many anecdotal reports of patients who say they may not have had treatment had they known how hellish hypothyroidism could be for them and that they were unprepared by their doctors.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
The Thyroid Trust	Guideline	7	12	Why no mention of the specific symptoms which could indicate a need for testing, or = a clinical suspicion that thyroid disease may be present? GPs and patients should be aware of common symptoms and they should be detailed here.	Thank you for your comment. Guidelines are not intended to be a text book and it is expected that healthcare professionals will be familiar with classical description of hypo- and hyper -thyroid disease. The guideline does include specific symptoms/conditions where we found evidence for an association. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated.
The Thyroid Trust	Guideline	7	21	Instead of referring simply to anxiety or depression, we would suggest that ‘anyone presenting with any mental health symptoms’ should have their thyroid checked, as per British Thyroid Association 2015 guidance. Mental health impacts of thyroid hormone imbalance can include psychosis and dementia like symptoms.	Thank you for your comment. No evidence was identified for anyone with mental health symptom. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated.

					The guideline does include specific symptoms/conditions where we found evidence for an association.
The Thyroid Trust	Guideline	8	7 - 20	The tests listed are 'surrogate markers' (a measure of effect of a specific treatment that may correlate with a real clinical endpoint but does not necessarily have a guaranteed relationship). For patients it's the signs and symptoms (how they feel) that matter most. These should be listed in the guideline in our view. (See overall point 1.1 above).	Thank you for your comment. These recommendations relate to the initial tests to use when thyroid dysfunction is suspected. Further tests are recommended once thyroid disease is confirmed. Guidelines are not intended to be a text book and it is expected that healthcare professionals will be familiar with classical description of hypo- and hyper -thyroid disease. The guideline does include specific symptoms/conditions where we found evidence for an association. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated.
The Thyroid Trust	Guideline	8	6	We would suggest that a section should be added detailing tests that should be done for other possible causes of symptoms, that may be similar to symptoms of a thyroid condition – particularly where treatment for a thyroid condition has not resolved symptoms – Vitamin D, Vitamin B12, etc.	Thank you for your comment. The guideline only covers investigations for diagnosing thyroid disease. Diagnosing other conditions is beyond the scope of this guideline.
The Thyroid Trust	Guideline	8	12 and 19	We are pleased to see the recommendation to test Ft3 in hypothyroidism if TSH is below the reference range – this indicates to us that T3 should always now be checked if patient is symptomatic but TSH appears suppressed, which makes sense, there is no point testing T3 when everything else is out of kilter as it will always be out of kilter too, if everything else seems fine, that is the time to test T3 and consider possible T3 treatment.	Thank you for your positive comment.

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The Thyroid Trust	Guideline	8	6	We are pleased to see a clear recommendation to test FT3 when TSH is below the reference range however in the subsequent section on managing hypothyroidism, page 9, from line 2, there needs to also be guidance on when to consider using T3 treatment otherwise “hard to treat” hypothyroid patients will continue to be ignored or end up seeking alternative practitioners or self-treating options which may be unsafe.	Thank you for comment. No evidence was identified to recommend the use of liothyronine, so the committee recommend against its routine use. Clinicians can still decide to offer it on a case by case basis.
The Thyroid Trust	Guideline	8	23	We would suggest that clinicians consider genetic testing for patients who may show signs of being unable to convert T4 to T3.	Thank you for your comment. We did not find evidence to recommend this.
The Thyroid Trust	Guideline	8	7	TSH only gives part of the picture, why not routinely measure TSH and FT4?	Thank you for your comment. The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
The Thyroid Trust	Guideline	9	2	We would strongly suggest that the guideline needs to include advise to consider using careful levothyroxine dose titration for “hard to treat” hypothyroid patients. We know that even small adjustments can be transformational for those patients whose conditions are finely tuned.	Thank you for your comment. We have amended the first recommendation on follow up and monitoring of primary hypothyroidism to read “Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal well-being.”
The Thyroid Trust	Guideline	9	2	We recommend including a mention that some patients may be intolerant to changing manufacturer of levothyroxine and may	Thank you for your comment. We did not cover different brands of levothyroxine and anticipate the clinicians will

				need to be prescribed specific formulations including in some cases liquid thyroxine, for those intolerant, or allergic, to fillers.	refer to the summary of product characteristics regarding interactions and medicinal forms.
The Thyroid Trust	Guideline	9	2	As the guideline only considers primary hypothyroidism. It should be made clear that there are multiple causes of hypothyroidism e.g. primary, central, resistance to thyroid hormone, endocrine disruption, subnormal TSH secretion (down-regulated axis) etc. It should be stated the guidelines do not apply to any condition other than uncomplicated primary hypothyroidism and that more complex cases may require a specialist referral.	Thank you for your comment. We have made it clear in the headings and recommendations the conditions being considered. With regard to investigations this applies to any type of hypothyroidism, with regard to management we have headed the section as 'primary hypothyroidism' and added 'primary hypothyroidism' to the recommendations.
The Thyroid Trust	Guideline	9	5	We are concerned that there is no mention here of testing Thyroglobulin antibodies. It is most common with autoimmune thyroid disease to have high TPO Abs or high TPO Abs and high TGAbs. Some patients with hypothyroidism report to patient organisations that they ONLY have high Thyroglobulin antibodies and they therefore have often struggled to get diagnosed. It's less common, but we believe that it may not be rare to only have high TG antibodies: Reference: https://www.healthline.com/health/antithyroglobulin-antibody#results *If you have high levels of antithyroglobulin antibodies in your blood, it may be a sign of serious autoimmune disorder, such as Graves' disease or Hashimoto thyroiditis*	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
The Thyroid Trust	Guideline	9	11	We suggest it would be useful for NHS research to test all patients who are well and stable on T4/T3 combination (and also consider testing patients who are currently on NDT.) We note that some NHS thyroid specialists endocrinologists already offer DIO2 testing on NHS and NHS prescription of T3 if a patient tests positive and also investigate gut and gluten issues.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line

				A negative result should not exclude a T3 trial.	with current practice. The committee also agreed that it would not be appropriate to recommend repeating tests when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
The Thyroid Trust	Guideline	9	12	We are aware of increasing numbers of patients being issued short prescriptions and in some cases being forced to ring or drive around many pharmacies every 1 or 2 months in search of whichever formulation of Levothyroxine or Liothyronine they require, which is inconvenient and an inefficient use of the health service resources as well as patient time. May we suggest that the Guideline explicitly states that once a patient is established on a stable dose they should be issued with prescriptions for 3 months at a time. Some patients have reported that their surgery will only issue 1 months supply at a time, saying they are incentivised by their CCGs not to prescribe for longer.	Thank you for your comment. This is not within NICE's remit, so we are unable to make a recommendation related to prescriptions.
The Thyroid Trust	Guideline	9	14	We are concerned that the draft Guideline does not acknowledge the profound difference to quality of life that treatment with liothyronine makes for some patients, who are unable to live normally without it. The following quote is typical of patients we hear from very regularly and those who submitted their stories for The Liothyronine Dossier. While the genetic link is unproven and unlikely to be the only reason some patients may need this treatment, there is no denying that for some patients, liothyronine is necessary and life changing: "The addition of 15mcg of T3 a year ago to my existing prescription of 100mcg of T4 for autoimmune underactive thyroid has been life changing. I have a heterozygous DIO2 gene impairment resulting in a decreased ability to convert synthetic Levothyroxine to active T3 and I would like the incredible improvement in the following symptoms after adding in T3 recognised by NICE: fatigue, anxiety, depression, brain	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).

				fog, general aches and pains, wellbeing. My quality of life has improved immeasurably after the addition of T3 and I have returned to work full time having had to stop work due to immense brain fog. I think it is extremely worrying that NICE do not recognise the beneficial impact that T3 can have."	
The Thyroid Trust	Guideline	9	14	why is FT3 testing recommendation not followed up with recommendation for when a trial of liothyronine may be appropriate or what other treatment may be recommended for patients with low T3 when TSH and FT4 blood tests are "optimal" but symptoms remain. Given the patient stories in Thyroid Trust registry and liothyronine dossier, showing many patients reporting losing years of their lives till liothyronine treatment restored QoL, the guidelines should say more about when T3 treatment may be considered.	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients(including those already taking liothyronine).
The Thyroid Trust	Guideline	9	14	Given the patient stories in Thyroid Trust directory and liothyronine dossier showing many patients reporting losing years of their lives till liothyronine treatment restored QoL, the guidelines should say more about when T3 treatment may be considered.	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).
The Thyroid Trust	Guideline	9	14	We note that many doctors are currently being told by their CCGs that NHS England does not permit liothyronine to be	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there

				prescribed, which is incorrect – where there is a medical need, NHS England and The Department of Health and Social Care have confirmed, this treatment should be available.	is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients(including those already taking liothyronine).
The Thyroid Trust	Guideline	9 - 10	11 (p10) to 14 (p11)	Why no mention of any other treatment option for patients who do not respond to initial treatment?	Thank you for your comment. No evidence was identified to support recommendations for alternative treatments for levothyroxine.
The Thyroid Trust	Guideline	General	General	Thyroid disease has many aetiologies and presentations. This guideline should emphasise the need for a choice of treatment options that best suit individual patients.	Thank you for your comment. We have made the recommendations based on the available evidence and committee consensus. Where evidence suggests a choice of treatments we have made this clear in the recommendations and have also included links to the NICE patient experience guideline which makes recommendations about shared decision-making. .
The Thyroid Trust	Guideline	General	General	We note that observational data has been discounted on the whole but that the committee's own observations are used extensively, in the absence of robust evidence from large clinical trials. This would seem to be somewhat biased. We feel that for these guidelines to be successful it will be vital to incorporate the experiences and practical insight from patients and other clinicians	Thank you for your comment. NICE guidelines are developed to produce recommendations based on the best available evidence, for some categories of reviews it is appropriate to restrict this solely to randomised controlled trials. For others, including the review on the safety of radioactive iodine, including non-randomised evidence is appropriate. The composition of the committee and the stakeholder feedback exercise are designed to supplement and optimise the use of the evidence included in the reviews. Where insufficient evidence is available to make strong recommendations, the committee considers making weak

					recommendations based on their consensus and supplementing that with recommendations for further research.
The Thyroid Trust	Guideline	General	General	The Guideline needs to reference NICE Guidance on Medicines Optimisation (NG5), and Medicines Adherence (CG76), which stresses the importance of patient involvement in the decision on a medicine.	Thank you for your comment. Where evidence suggests a choice of treatments we have made this clear in the recommendations and have also included links to the NICE patient experience guideline which makes recommendations about shared decision-making. .
The Thyroid Trust	Guideline	General	General	The Guideline needs to cross reference the NICE Guideline on Multi-morbidity (NG56), as this is common and may affect the treatment decision.	Thank you for your comment. We have added this to the section on related NICE guidelines in the methods chapter.
The Thyroid Trust	Guideline	General	General	We believe the guidelines should also reference the latest RMOC guidance on prescribing liothyronine (published 15th July 2019, replacing the November 2018 version) and the BTA 2016 guidance for GPs and endocrinologists, on liothyronine switching and prescribing.	Thank you for your comment. A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine, cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).
The Thyroid Trust	Guideline	General	General	While we appreciate that pregnant and postpartum women are out of scope for this Guideline, we believe that the link with successful pregnancy and thyroid disorders is too important to not be mentioned at all in the NICE Guidelines. We would suggest that the new guidance, currently being developed, by the Royal College of Obstetricians & Gynaecologists, should be referenced prominently somewhere in the NICE Guideline: as it is in the Scope document.	Thank you for your comment. We are aware of the forthcoming RCOG guidance, and will include a link to it from the guideline when that guidance publishes.
The Thyroid Trust	Guideline	General	General	As Thyroid Eye Disease is mentioned several times in the Guideline we would suggest that there should be some mention of the need for a specialist referral in the case of suspected thyroid eye disease and perhaps a link to a	Thank you for your comment. Thyroid eye disease was excluded from the scope, so no recommendations are made in relation to its management. Thyroid eye disease

				resource where signs and symptoms are detailed, since so many Thyroid Eye Disease patients currently wait a long time to be diagnosed and properly treated. http://www.clinmed.rcpjournal.org/content/15/2/173.abstract	is mentioned in recommendations where there is the potential for it to be an adverse effect of treatment.
The Thyroid Trust	Guideline	General	general	Mental health impacts can be severe when a thyroid disorder is not well managed and this should be made very clear in the Guideline, this aspect appears to be entirely missing from the draft. The risk is that clinicians treating thyroid patients with mental health symptoms may not make the connection. It has been said previously that anyone with any mental health symptoms should have their thyroid checked. http://www.thyromind.info/ This appeared to be a sensible statement and worth repeating.	Thank you for your comment. The guideline includes recommendations for testing for thyroid dysfunction in people with depression or unexplained anxiety. The aim of the recommendations overall is to improve thyroid disorder management, for those with and without mental health disorders.
The Thyroid Trust	Guideline	General	General	There are several references to using the TSH reference range as a diagnostic range or a therapeutic target. There is no evidence base for these statements. Many patients who have a TSH within the reference interval are hypothyroid. Some patients require a low TSH to resolve signs and symptoms of hypothyroidism. Some patients have a very narrow therapeutic range within the TSH reference interval. There is no evidence that biochemistry reflects clinical presentation in all cases. The guidance should assert the superiority of clinical response over biochemistry. Serum is the intermediate space; it does not consistently reflect intracellular hormone status.	Thank you for your comment. We have amended our first recommendation on monitoring and follow up of primary hypothyroidism to state “Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal well-being.”
The Thyroid Trust	Guideline	General	General	Approximately 3% of UK population are prescribed Levothyroxine If a patient remains unwell on levothyroxine, once dose has been increased high enough to bring TSH under 1 and all four vitamins optimal (and gluten free if applicable) then they should be entitled to an NHS referral to a thyroid specialist endocrinologist and option of a trial of T3, yet across many areas of the UK this is not happening	Thank you for your comment. We have made recommendations for this guideline based on the available evidence. No clinical evidence was identified to recommend the routine use of liothyronine. It is beyond the remit of this guideline to comment on BTA guidance and Department of Health and Social Care policy.

				https://www.british-thyroid-association.org/sandbox/bta2016/bta_response_to_the_nhs_england_consultation_for_website.pdf For patients with hypothyroidism who are not on liothyronine but wish to trial it, the principles guiding decision-making should follow those outlined in the BTA statement [1]. Combination treatment with Levothyroxine and Liothyronine should only be initiated and supervised by accredited endocrinologists [1]. Patients experiencing symptomatic benefit on a combination Levothyroxine and Liothyronine regimen should be able to continue such therapy prescribed from primary care. There are numerous reports from patients of seeing endocrinologist and being advised that despite clinical need they are unable to be prescribed T3 on NHS for variety of reasons, such as: 1)Initial 3 month prescription via hospital, but the refusal of GP to cover ongoing prescribing, care and cost 2) Endocrinologist applies for individual funding request on patients behalf, but this is refused 3) Endocrinologist can't prescribe at all 4) Endocrinologist would monitor patient if the patient sources T3 from abroad 5) Endocrinologist advises patient to buy T3 from abroad, but no ongoing monitoring 6) A private prescription written in a way that enables the patient to access to cheap T3 from EU 7) A private prescription that is deliberately only written to access UK T3 and therefore financially beyond most patients	

				All of these reasons are unacceptable. The Department of Health and Social Care must take decisive action on the price, then doctors can do their jobs and not have to waste time filling in individual funding requests and being forced to deny thyroid patients access to the treatment they need.	
The Thyroid Trust	Guideline	General	General	In relation to the guidelines for hypothyroidism, one of our commenters observed:, the proposed guidelines are consolidating practices that have been discredited over the past two decades. They fail to address large-scale patient dissatisfaction with hypothyroidism therapy and restrict the options available to patient and physician.	Thank you for your comment. We have made recommendations for this guideline based on the available evidence. We only found evidence to recommend the routine use of levothyroxine.
The Thyroid Trust	Guideline	General	General	In response to the question: 'Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why'. The treatment of those patients with hypothyroidism who do not respond well to levothyroxine monotherapy is the area of current practice which needs to change most. The NHS is currently paying far more for liothyronine than other markets but as the cost is being brought down, this should not be a barrier for treatment for those who cannot thrive on levothyroxine alone. It's widely accepted in medical circles that approximately 10-15% of patients do not recover full health on Levothyroxine mono- therapy https://www.sciencedaily.com/releases/2016/10/161012132038.htm and https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4980994/ "….authors have questioned the efficacy of l-thyroxine monotherapy	Thank you for your comment. The costs of T3 is outside the control of NICE. NICE guidelines are based on current UK prices available across the NHS. T3 is subject to CMA investigation, which is now cross referenced in the discussion (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct), but until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline.

				because about 10% to 15% of patients are dissatisfied as a result of residual symptoms of hypothyroidism” 10% -15% remaining unwell on Levothyroxine is approximately 200,000-300,000 patients in the UK. UK Thyroid support groups are inundated with dissatisfied patients, most of whom are only prescribed Levothyroxine and many of whom are on very low doses with seemingly no regard given to resolving their symptoms. Thousands of UK patients on Levothyroxine remain unwell, often with severely curtailed life, frequently unable to work or contribute to society...these patients’ situations cannot be overlooked by the Guideline.	
The Thyroid Trust	Guideline	General	General	In response to the question ‘ Would implementation of any of the draft recommendations have significant cost implications?’ The cost implications of prescribing liothyronine, where it is required, will be mitigated considerably by more effective procurement of this generic medicine by the Department of Health, to bring the price into line with other countries and in line with overall NHS procurement whereby this country generally pays a lower price than most other markets for most medicines. This work is underway and we are advised that the price is coming down rapidly but liothyronine is still perceived as being prohibitively expensive by many local health authorities. It should be borne in mind that patients who require liothyronine and do not have it prescribed are likely to cost the health service and society dearly, since without treatment they often describe themselves as “unable to function” and are likely to visit their doctors much more often, with many other tests and	Thank you for this information. NICE guideline can only use the current prices rather than future prices; a cross reference to the CMA investigation has been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). Purchasing medications and the cost of T3 are beyond the remit and scope of this guideline. The guideline states that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients.

				treatments being given, often for many years. See The Liothyronine Dossier and The Thyroid Trust Registry for case examples.	
The Thyroid Trust	Guideline	General	General	In response to the question: What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) We would suggest that where patients' symptoms are unresolved, clinicians are directed to seek guidance from the British Thyroid Association and/or centres of excellence in thyroid care, where there are clinicians who are skilled at resolving symptoms in thyroid patients (as per recent new NICE parathyroid guidelines).	Thank you for your comment. Seeking guidance from the British Thyroid Association is outside the remit of the guideline. The committee anticipate that clinicians will seek specialist advice when required and the guideline recommends seeking specialist advice in some situations.
The Thyroid Trust	Guideline	General	General	Are there any considerations related to ethnicity and treatments of thyroid disorders? Even if there aren't, we believe this should be noted in the guideline and in the Equality Impact Assessment.	Thank you for your comment. This was not raised as an issue related to thyroid disease. We have noted this in the latest EIA form.
Thyroid Cancer Alliance	Guideline	10	10	This rationale states that the aim of treating hypothyroidism with L-T4 is to maintain TSH levels within the reference range. We propose adding "and at a level at which the patient feels 'well'". Patients on L-T4 tell us that even a small adjustment can be beneficial and that they frequently feel better when the TSH is at the lower end of the reference range.	Thank you for your comment. We have amended the first recommendation (1.4.1) to state "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing."
Thyroid Cancer Alliance	Guideline	10	17	We are concerned that this recommendation may imply that FT4 should 'never' be measured in adults. We recommend incorporating the wording from page 11 here to add that if adult patients continue to feel unwell on L-T4 then FT4 should also be measured.	Thank you for your comment. No evidence was identified for FT4 testing for all people. The committee noted that in some situations when people have symptoms there may be benefit of FT4. This was recommended in the first draft of the guideline. We have moved this up to immediately follow the recommendation on testing people on levothyroxine. 1.4.3 For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised (2 similar

					measurements within the reference range 3 months apart), and then once a year. 1.4.4 Consider measuring FT4 as well as TSH for adults who continue to have symptoms of hypothyroidism after starting levothyroxine.
Thyroid Cancer Alliance	Guideline	11	11	We note that the Guidelines recommend here to consider measuring FT4 as well as TSH for adults, children and young people who continue to have symptoms of hypothyroidism after starting levothyroxine. However, the guidelines already recommend testing FT4 as well as TSH in children and young people on page 10. It would therefore be helpful to the flow of content to expand the statement about testing adults on page 10 referenced above.	Thank you for your comment. We agree and have changed this recommendation to apply to adults only and moved it next to the adult recommendation.
Thyroid Cancer Alliance	Guideline	24	14	We are encouraged to note that the guidelines committee has made a key research recommendation to assess the clinical and cost effectiveness of L-T4 and L-T3 combination therapy compared with L-T4 alone for people with hypothyroidism whose symptoms have not responded sufficiently to L-T4 alone. We agree this is important.	Thank you for your comment and positive feedback.
Thyroid Cancer Alliance	Guideline	30	4	This rationale explains that combination treatment with levothyroxine and liothyronine did not offer any important health benefits compared with levothyroxine monotherapy “and was significantly more expensive”. Our organisation is concerned that some UK patients who are refused combination L-T4 and L-T3 therapy are obtaining liothyronine from abroad, sometimes without the knowledge of their physicians, which means they may not be being properly monitored or managed. While it is arguably not in the remit of the Committee to lobby for a reduction in price, it would be helpful to mention that liothyronine is considerably cheaper in other countries and that it is hoped that prices in the UK will be reduced to European levels in the near future.	Thank you for your comment. Liothyronine is subject to CMA investigation and a cross reference to the CMA investigation has now been added in the committee discussion in the evidence report (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). However, until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).

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Thyroid Cancer Alliance	Guideline	5	11 - 13	We recommend including advice to physicians and patients to stay with the same preparation of levothyroxine where possible and to rerun thyroid function tests after 6-12 weeks in the event of a forced changeover (for example, if a particular preparation is unavailable). Patient organisations in France and the Netherlands for example have reported on issues when patients switch between brands or when the manufacturer changes the formulation. See also the ATA position statement https://www.thyroid.org/thyroxine-products-joint-position-statement/.	Thank you for your comment. We did not investigate brands of levothyroxine, so we have not made a recommendation related to brands
Thyroid Cancer Alliance	Guideline	6	1	In table 1, we consider that the risk of hypoparathyroidism following surgery is understated and recommend expanding this to explain that in some cases, this may require life-long monitoring and treatment with vitamin D and calcium tablets (often under the supervision of an endocrinologist).	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Cancer Alliance	Guideline	9	14	We note the advice not to offer L-T3 “routinely” either alone or in combination with L-T4. We acknowledge that L-T4 therapy remains the standard of care for hypothyroidism and works for the majority of patients. However, we are concerned that GPs may lean too heavily on this advice which fails to acknowledge that a proportion of patients on L-T4 continue to suffer with symptoms. We propose expanding this statement to mention that in some cases, and under initial supervision by an endocrinologist, a trial of L-T4 with L-T3 may be warranted (as recommended by the European Thyroid Association and British Thyroid Association guidelines).	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine). A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical

					Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).
Thyroid Cancer Alliance	Guideline	9	14	We hope this section will be reviewed to align with the latest advice from NHS England Regional Medicines Optimisation Committee (RMOC) "Guidance on the Prescribing of Liothyronine" June 2019 (version 2.6) which has just been released.	Thank you for your comment. A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine cross referring to the guidance you refer to
Thyroid Patient Advocacy	Equality Impact Assessment	General	General	It is beyond belief that no equalities issues have been identified during this process so far. The guidelines as TPAUK comments within this document confirm, that there are many inequalities that are experienced by people with thyroid conditions. One example is by not addressing the problems of the people who do not return to optimal health on levothyroxine (or T3) they are not treating all thyroid patients as equal. Thyroid patients who do not do well on levothyroxine find themselves in a situation whereby they have to purchase their own medication perhaps via the internet because they are refused help and left to suffer. They are monitored by TSH and their symptoms ignored. How can this be treating thyroid patients equally? Women in particular are not treated equally and very often dismissed as being menopausal or put on anti depressants when in fact they are hypothyroid. Older people are at times told that they don't need treatment because there is no need at their age and they might only be in their sixties – hardly old today. t	Thank you for your comment. The aim of the equality impact assessment is to ensure that people with protected characteristics are not systematically discriminated against as a result of the recommendations. NICE has a duty to eliminate unlawful discrimination and advance equality of opportunity. As well as people with protected characteristics defined in the Equality Act health inequalities and inequities in access to health, public health and care services associated with socioeconomic factors and with other forms of disadvantage are also included. We have reviewed the recommendations in light of your comments. A new recommendation has been added about menopausal women: "Be aware that in menopausal women symptoms of thyroid dysfunction may be mistaken for menopause". We do not consider that anything else in the guideline discriminates against women or older people in any way.

				Many thyroid patients do not get told the cause of their condition even when they ask. They are diagnosed with a life long condition without any thought as to how that might psychologically impact on them and their family. In fact they are often told that hypothyroidism is easy to treat and just take a pill and you will be fine. For a percentage of those with hypothyroidism this is just not the case and therefore these people are not treated as equals when it comes to health care for their thyroid issues.	
Thyroid Patient Advocacy	Evidence Review A	5	2 - 3	The use of the "words thyroid" disease is imprecise. It is hypothyroid people who are being alluded to, as the three studies used in this review are on attitudes and perceptions of hypothyroidism of patients and doctors. The word "should" implies obligation, duty or correctness, what hypothyroid patients should be told. Why not simply do a survey of a survey of a representative number of them and find out what they want to know rather than relying on studies that are biased in favour of the current method of treatment: management by tsh and levothyroxine-only?	Thank you for your comment. The aim of this review was to capture the type of information that people with thyroid disease, not limited to hypothyroidism, could benefit from. Following NICE processes for guideline development, qualitative studies looking at the views of people diagnosed with thyroid disease, their families, carers or health professionals were sought, quality assessed and reviewed to ensure the recommendations made are based on the best available evidence. The committee is aware that the studies meeting the review protocol were particularly relevant to people with hypothyroidism and have used their clinical expertise to make recommendations that are relevant to the whole population of people with thyroid disease.
Thyroid Patient Advocacy	Evidence Review B	10	1	In section 1.4.3 Quality assessment of clinical studies included in the evidence review it is clear that the predictor (outcome) were all looked at separately. It would be useful for studies to look at clusters of predictors to see if having more than one from a list would be more accurate and that if having a larger number of predictors increased accuracy still further.	Thank you for your comment. We agree that a cluster of predictors could have higher predictive accuracy and searched for such evidence, unfortunately no evidence of this nature was found.
Thyroid Patient Advocacy	Evidence Review B	18	24	The committee noted that no one symptom of thyroid disease was a good predictor for	*Formatting issue: Response on ID 75. Note for NICE: IDs 72 to 75 look like they should be one comment*

Thyroid Patient Advocacy	Evidence Review B	18	25	thyroid dysfunction, with positive predictive values varying but generally around 10%. The	*Formatting issue: Response on ID 75. Note for NICE: IDs 72 to 75 look like they should be one comment*
Thyroid Patient Advocacy	Evidence Review B	18	26	symptoms of thyroid disease are often non-specific (for example tiredness, cognitive	*Formatting issue: Response on ID 75. Note for NICE: IDs 72 to 75 look like they should be one comment*
Thyroid Patient Advocacy	Evidence Review B	18	27	impairment). But clusters of symptoms do make it more like likely that thyroid disease is involved so if a patient has a number of symptoms all associated with thyroid disease then they should be tested however it should be noted that a TFT is not a definitive method for diagnosing hypothyroidism so that reliance should be placed on clinical judgment and symptoms . No consideration was given to a symptom scoring system . Symptoms strongly associated with hypothyroidism eg slowed ankle reflexes or high cholesterol were not included.	Thank you for your comment. We agree that a cluster of symptoms could have higher predictive accuracy and searched for such evidence, however no evidence of this nature was found. The guideline is not intended to replace clinical judgment which should always be employed during clinical practice. Recommendation 1.2.1 particularly points clinicians towards testing for thyroid dysfunction based on their clinical suspicion of thyroid disease. The committee is aware of the wide variety of symptoms associated with thyroid disease and it would not have been possible to examine every possible symptom. Thus, the committee agreed on a list of symptoms to be examined within the present review where recommendation making could be most impactful.
Thyroid Patient Advocacy	Evidence Review B	19	4	No relevant economic studies were found which rather undermines the whole document as we are not clear about the long term economic benefits because we cannot weigh the costs testing more people and thus potentially identifying more hypothyroid people against the costs to the NHS of them going on to develop more severe conditions or simply the cost to the NHS of treating their unresolved symptoms individually. It was noted in Section [F] Monitoring Thyroid Disease page 15, line 19 improved early detection of uncontrolled thyroid disease could result in improved treatment, survival time and QoL.	Thank you for your comment. As this is a prognostic question, which aims to identify the factors suggestive of thyroid disease that might require further investigation, no economic evidence was sought. The committee reviewed the clinical evidence along with the unit costs of the test to help them make a recommendation. As you correctly mentioned long term health outcomes and costs are needed to work out the cost effectiveness of these tests, but as this was not possible the committee used their expert knowledge and current practice to make recommendations.
Thyroid Patient Advocacy	Evidence Review B	19	8	The committee noted that if patients were sent for testing with only 1 symptom then extra costs might be incurred but again no stress was put on the fact that patients with a cluster of symptoms or depression/auto immune disease or a family	Thank you for your comment. The committee agree that having multiple symptoms or co-existing conditions makes the likelihood of thyroid disease higher. As per the recommendations on tests, the committee consider

				history of thyroid diseases are candidates for testing but, particularly for hypothyroidism, that the test should not be considered definitive and that doctors will need to rely on their clinical judgment. Another method of diagnosis is through response to treatment. If a person's symptoms improve with treatment, then that is an indication in itself. This method is used in situations where diagnosis by other means is difficult or not conclusive. For instance diagnosing asthma in children under 5.	that TSH testing in the first instance is sufficient to diagnose hypothyroidism when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is, if TSH is above the reference range measuring FT4 in the same sample and if TSH is below the reference range measuring FT3 in the same sample. The committee agreed that this approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease.
Thyroid Patient Advocacy	Evidence Review B	19	13 - 14	It is muddling to talk about using TFTs to monitor existing hypothyroidism here as this has not really been mentioned in the preceding pages. A return of symptoms would also be another reason to order TFTs	Thank you for your comments. We agree and have deleted this sentence. It is anticipated that people experiencing symptoms are likely to be tested.
Thyroid Patient Advocacy	Evidence Review B	32 - 39	Table 14	Table 14 Ankle reflexes and high cholesterol not included in literature searches.	Thank you for your comment. Thyroid disease can be associated with a variety of symptoms and it would not have been possible to examine every possible symptom or sign. As a result the committee agreed on a prioritised list of symptoms and signs that would include those where recommendation making (either for or against testing) would be most impactful.
Thyroid Patient Advocacy	Evidence Review B	47 - 59	2	The papers presented in the clinical evidence tables all contain examples of the different ways that hypothyroidism and sub clinical hypothyroidism are defined, with most not excluding any form of central hypothyroidism or poor conversion. TSH has been assumed unquestioningly to be a marker for hypothyroidism with no discussion of how it might not be or the implications if it is not. TSH is a pituitary hormone and a proxy for T4 levels and to a lesser extent for T3 levels. If TSH is used to select subjects without reference to symptoms then the subjects are being selected on the basis of a compromised	Thank you for your comment. The committee is confident that TSH is an acceptable marker of thyroid disease particularly in the context of large cohort studies. TSH levels were not part of the inclusion criteria that the included papers used to derive their sample (these can be found in Appendix D of the evidence review). The fact that papers have used different values has not been considered to affect the extent to which findings can be meta-analysed where possible to observe the diagnostic accuracy of tests.

				variable. Almeida 2011 on page 47- sub clinical hypothyroidism if TSH>4 and FT4 <10 Canaris 2000 on page 49 - euthyroid if TSH 0.3-5.1 Canaris 2013 on page 50 - only TSH tested and those above 5.5 considered hypothyroid Cappola 2006 on page 52 - FT4 only tested if TSH out of range so participants with central hypothyroidism not excluded. SCH if TSH >4.5mU/L and 20mU/L or TSH >4.5mU/L with FT4 below normal (0.7ng/dL) Engum 2005 on page 54 - Thyroid autoimmunity: TSH carried out in all women and 50% of men. T4 measured if TSH abnormal. TPOAb measured in all samples with TSH >/= 4.0mU/l (n=1700) and in randomly selected samples from people with normal TSH who answered no to symptom survey (n=745). 995 were TPOAb positive of which 78 had normal thyroid function, 15 had decreased TSH levels, 902 had elevated TSH levels. T4 was normal in 784 individuals; T4 was decreased in 157 individuals. Feldthusen 2015 on page 55 Hypothyroidism: TSH> 3.7mU/L, FT4 and FT3 below the reference range SCH: TSH> 3.7mU/L, FT4 and FT3 in the reference range Fleiner 2016 on page 57 - Hypothyroidism: TSH> 4.5mU/L, FT4 and FT3 below the reference range Guimaraes 2009 on page 59 Hypothyroidism: TSH > 4mU/L, FT4<0.7ng/dL SCH >4mU/L, normal FT4	

				The fact that different levels were chosen to indicate hypothyroidism and subclinical hypothyroidism and the lack of reference to symptoms makes comparing these papers rather difficult. All these papers are done on the assumption that TSH indicates thyroid function and draw cut-off levels for hypothyroidism and subclinical hypothyroidism from 95% reference ranges. None tested all parameters in all subjects including healthy controls so conditions are imposed before the trial. An ideal paper would measure TSH, TT4, FT4, FT3, TPO and Tg antibodies and a symptom score. It would also look at the relationship between TSH, FT4 and FT3 as they should not be independent variables, and FT4:FT3 ratio.	
Thyroid Patient Advocacy	Evidence Review B	5	1	Would this section not be better called Diagnosis? As it is there is bias in the implication that the way thyroid disease is diagnosed is only through blood tests and specifically TSH levels.	Thank you for your suggestion. We can assure you that the wording used in the title had no impact on the recommendations regarding diagnosis and investigation of thyroid disease.
Thyroid Patient Advocacy	Evidence Review B	5	6	However thyroid disease was diagnosed successfully before the advent of blood testing using a constellation of signs and symptoms including those presented at line 15 in the table 1. Although for hypothyroidism two important symptoms, a slow ankle reflex and high cholesterol have been missed out, as have alterations to sex hormone binding globulins and low heart rate, high or low blood pressure and oedema, particularly of the face. No thought was given to using or developing a symptoms scoring list. In the research presented later in this section	Thank you for your comment. The studies included were the only ones identified that met the pre-specified protocol criteria. These reported the predictive accuracy of no more than one symptom. We agree that a cluster of symptoms could have higher predictive accuracy and searched for such evidence, however no evidence of this nature was found. The committee is aware of the wide variety of symptoms associated with thyroid disease and it would not have been possible to examine every possible symptom. Thus, the committee agreed on a list of symptoms to be examined within the present

				pretty much no individual symptom was shown to have a connection with hypothyroidism but no studies were done on groups of symptoms. Perhaps the studies needed to use some form of Canonical correspondence analysis to identify clusters of symptoms associated with the disease. This should be recommended. There are many available references for lists of symptoms associated with thyroid disease. Here is one mentioning symptoms associated with hypothyroidism. *Primary thyroid axis disorders can be associated with a wide range of psychiatric manifestations ranging from depression and anxiety to overt psychosis. Regardless of the precise aetiology, hypothyroidism leads to a number of clinical manifestations, including slowed mentation, forgetfulness, decreased hearing, cold intolerance, and ataxia. Decreased energy, weight gain, depression, cognitive impairment, or overt psychosis ('myxedema madness') may also result. Due to the overlapping symptoms with major depression, thyroid hormone deficiency must be ruled out when evaluating patients with depression.* *…..It is important to note that occult primary hypothyroidism is among the leading medical causes of refractory depression.* *Psychiatric Manifestations of Thyroid Dysfunction* *D.A. Gutman, C.B. Nemeroff, in Encyclopedia of Neuroscience, 2009*	review on which recommendations might be most impactful.
Thyroid Patient Advocacy	Evidence Review B	5	7	Clinical experience varies considerably from doctor to doctor which thus makes consistency difficult. The implications here are that the blood tests will unequivocally confirm or deny the diagnosis. In fact currently the thyroid function tests measure where hormones are in relation to a 95% population reference range. Particularly for hypothyroidism where the cut-off between 'healthy' and hypothyroid lies is subject to debate.	Thank you for your comment. We hope the recommendations will support consistency in clinical practice. Issues with clinical experience of individual doctors are outside the remit of this guideline.

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Thyroid Patient Advocacy	Evidence Review B	5	8	A number of the co-existing conditions , for example fibromyalgia and CFS, may actually be caused by undiagnosed hypothyroidism or forms of tissue hypothyroidism that will be missed if this definitions used in this guidance are followed for example poor conversion of T4 to T3 or thyroid hormone resistance.	Thank you for your comment. The diagnosis of other conditions is outside the remit of this guideline.
Thyroid Patient Advocacy	Evidence Review B	5	11	The worry here is that doctors will use or be forced to use the information in the NICE guidelines to replace their clinical knowledge in the way that the existing clinical knowledge summaries are currently used.	Thank you for your comment. The aim of NICE guidelines is not to replace clinical knowledge but to provide guidance for clinicians that is based on the best available evidence.
Thyroid Patient Advocacy	Evidence Review B	5	15	Table 1 Ankle reflex and high cholesterol, two common symptoms associated with hypothyroidism were not included in table 1 or apparently in the literature searches. Family history of thyroid disease is important to aid diagnosis as susceptibility to thyroid disorders is often inherited, but becomes more so with research indicating that the thyroid hormone status of a mother can alter how her child's body responds to thyroid hormone when it reaches adulthood. *Anselmo J, Scherberg NH, Dumitrescu A M and Refetoff S, Reduced sensitivity to Thyroid Hormone as a Transgeneration Epigenetic Marker transmitted along the Human Male Line. Thyroid, vol. 29, No 6 https://doi.org/10.1089/thy.2019.0080* *Pakkila F et al, Maternal Thyroid Dysfunction During Pregnancy and Thyroid Function of her Child in Adolescence, J Clin Endocrinol Metab. 2013 Mar; 98(3): 965–972.*	Thank you for highlighting those research findings. We do agree with the information you provide that family history can be important for diagnosis and hence, family history was included in the symptoms or signs investigated as potential indications for testing. Although no evidence was identified to support a recommendation to particularly test people with family history, the recommendations made do not contradict this and in the presence of other signs or symptoms a clinician might decide to offer testing to people with family history of thyroid disease. In regards to ankle reflex and high cholesterol, the committee acknowledges that thyroid disease can be associated with a variety of symptoms and it would not have been possible to examine every possible symptom or sign. As a result, the committee agreed on a list of symptoms to be examined within the present review on which recommendations might be most impactful.
Thyroid Patient Advocacy	Evidence Review C	10	1	The committee did not acknowledge that this cascade approach leaves a proportion of sufferers undiagnosed and no suggestion is made about how their situation will be remedied.	Thank you for your comment. The committee is confident that the recommended cascade approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease and that TSH is an

				The use of TSH to monitor thyroid disease is not workable. The argument is completely circular. How do you develop ranges that mean anything for a disease that is diagnosed with a blood test? This is totally self-confirming since everyone who does not fit with the test is excluded and told they don't have a thyroid dysfunction. What if we are measuring the wrong thing? What if people with CFS, fibromyalgia even ME actually have a thyroid dysfunction that is not picked up using the current TFTs?	appropriate initial measure in the investigation and monitoring of thyroid disease. The committee has acknowledged that tests may need repeating and this is reflected in the recommendations in section 1.2. Making specific recommendations for the diagnosis of people with other co-morbidities is outside the remit of the guideline.
Thyroid Patient Advocacy	Evidence Review C	5	1	This section [C] Thyroid Function Tests and previous section Indications for testing would be better combined into a section [?]Diagnosis which would include all methods for diagnosis without bias towards thyroid function tests which cannot and should not be used in isolation to diagnose thyroid diseases. Note what was said in Section [G] page 17 line 21-23 *It was raised that an overreliance on TSH levels in decision making about treatment that is most often the case in clinical practice may be problematic, and that other factors, including patients' symptomatology are to influence their need for treatment.*	Thank you for your comment. It was agreed by the committee that examining those topics separately would be most appropriate. The point raised in Evidence review G has been captured by the recommendations, where the importance of symptoms in determining treatment has been highlighted (e.g. recommendation 1.4.1).
Thyroid Patient Advocacy	Evidence Review C	5	2	The whole section is somewhat confused as to whether the use of thyroid function tests in the monitoring of treatment for thyroid disease should be included in this section. Where are the references used to support what is said in sections 1.2 and 1.7.1.3? This section indicates bias as no consideration is given to other methods of diagnosing thyroid diseases such as symptoms, auto antibodies, thyroid gland scans and biopsies and metabolic rate testing. Note again what is said in section [G] Subclinical	Thank you for your comment. What is said in sections 1.2 and 1.7.1.3 are based on the committee's consensus. The committee agreed that when thyroid disease is suspected, which may be due to symptoms, thyroid function tests would be required at first to confirm the presence of underlying thyroid disease. The importance of antibody testing has been particularly acknowledged within the present guideline with the diagnostic accuracy of antibody testing examined in separate evidence reviews (reviews D and H) as the committee agrees that antibody testing would be an appropriate method of testing for people with confirmed

				Hypothyroidism, page 17, lines 21-25. Why is that not considered here? *It was raised that an overreliance on TSH levels in decision making about treatment that is most often the case in clinical practice may be problematic, and that other factors, including patients' symptomatology are to influence their need for treatment. The committee felt that a trial period of treatment of 6 months would be appropriate for symptomatic patients with TSH lower than the 10 cut-off.* This review should have included a discussion of the validity of using thyroid function tests to give a definitive diagnosis of thyroid disease and whether the ranges for TFTs allow any decision to be made about whether someone has a thyroid disorder or not given that the ranges are merely 95% population reference ranges. *It should also be noted that there is no published literature to support the reference values supplied by manufacturers with their assays and it remains unclear how these ranges are derived. Indeed, only minimal information is available in assay manuals. For the four methods with the largest user groups in the UKNEQAS for thyroid hormones, expected values are derived from the measurements of TSH on 'euthyroid' individuals with the caveat that individual laboratories should provide their own local reference ranges (Table 1). It is unclear of how many laboratories actually do heed this advice.* *The upper limit of the reference range for thyroid-stimulating hormone should not be confused with a cut-off to define subclinical hypothyroidism*	hypothyroidism or thyrotoxicosis to confirm the cause of their thyroid disease. The point raised in Evidence review G has been captured by the recommendations, where the importance of symptoms in determining treatment has been highlighted (e.g. recommendation 1.4.1 also related to 1.5.2).

				Ahmed Waise, Hermione C Price Annals of Clinical Biochemistry: International Journal of Laboratory Medicine, 2009, https://doi.org/10.1258/acb.2008.008113 What about testing thyroid auto antibodies? These are significant in hyperthyroidism but can also indicate hypothyroid disease in apparently euthyroid cases.	
Thyroid Patient Advocacy	Evidence Review C	5	8 - 9	The high analytical sensitivity and specificity are irrelevant if they do not successfully diagnose hypothyroidism . Note in Section [F] Monitoring Thyroid Disease, page 13, line 10 that it says *The committee noted that reference ranges are ranges and that for each individual person there will be variability as to what exact TSH targets are most appropriate for them.* This shows that the committee understands the individuality associated with optimal hormone levels particularly for hypothyroid people. In addition to the problems caused by individuality and 95% population ranges from which it is difficult to ensure that hypothyroid people are excluded, the use of TFTs to diagnose hypothyroidism depends on the definition of hypothyroidism being a shortage of thyroid hormones in the bloodstream not a shortage of thyroid hormones in the tissues/cells. There are many sufferers who have hypothyroidism that is relieved by treatment with thyroid hormones but who have been excluded from diagnosis since the recent reliance on TFTs as can easily be seen by visiting one of the many internet forums that try to help those let down by the current system of diagnosis and treatment.	Thank you for your comment. The committee's acknowledgment of the fact that individuals may have a different optimal TSH level has now been captured in the recommendations relevant to treatment of primary hypothyroidism (1.4.1). The guideline did not specifically review evidence relating to diagnostic criteria for thyroid disease as the reference standard for diagnosis is thyroid function tests and so no alternative can perform better by accuracy measures. Therefore, the committee overall agreed it was most appropriate to address this aspect of the scope by considering which specific tests had most benefit. NICE recommendations are not intended to cover every possible aspect of a disease area and the committee agree that clinical signs and symptoms are an important part of diagnosis. Please note that the recommendations aim to provide guidance to clinicians towards the management of patients according to best clinical practice that would be appropriate for the majority of patients with thyroid disease. They cannot cover every possible scenario such as thyroid hormone resistance and do not replace clinical judgment in the management of patients according to their individual characteristics and needs.

				An understanding of the normal relationship between serum levels of free T4 (FT4) and TSH is essential when interpreting thyroid tests. Needless to say, an intact hypothalamic-pituitary axis is a prerequisite if TSH measurements are to be used to determine primary thyroid dysfunction (19). A number of clinical conditions and pharmaceutical agents disrupt the FT4/TSH relationship. *National Academy of Clinical Biochemistry Laboratory medicine Practice Guidelines vol13, 2002 Laboratory support for the clinical diagnosis of thyroid disease* But even this may now be confounded by the discovery of thyroid hormone resistance (THR) in children and grandchildren of mothers with altered hormone levels during pregnancy. Anselmo et al and Pakkila F et al.	
Thyroid Patient Advocacy	Evidence Review C	5	9 - 10	Clinical utility can be disputed since the tests only diagnose those that they diagnose and anyone else is deemed not to have a thyroid disorder. Although the test may accurately measure levels of circulating hormones this does not inform about how to read the results there is still much disagreement about what constitutes hypothyroidism as can be shown b the many different upper reference ranges. These reference ranges are population reference ranges and only reveal where the results for 95% of a theoretically healthy population lies. How a population is determined to be free of thyroid disease when thyroid disease itself is now only diagnosed by blood test is not often mentioned but certainly does not allow for the exclusion of those with central hypothyroidism. Very little reference is made to symptoms and often it is remarked that some hypothyroid people actually have no symptoms curiously it is never mentioned that this could be to do with different set points, good conversion etc. The opposite, that you may	Thank you for your comment. The committee is confident that the recommendations made reflect best clinical practice. Please note that the aim of the recommendations is to provide guidance to clinicians on the best approach to diagnosing thyroid disease in the majority of people they are likely to encounter and cannot cover every possible scenario in regard to diagnosis in individual patients. The diagnosis of central hypothyroidism is outside the scope of the guideline. The potential variability in TSH targets that would be most appropriate for individual patients and the importance of symptoms have been acknowledged by the committee and reflected in the now amended recommendation about the treatment of primary hypothyroidism (1.4.1). The committee is also confident of their definition of subclinical hypothyroidism which has been based on

				people may have symptoms of hypothyroidism with blood tests within the 95% population reference ranges, is rarely mentioned yet any visit to internet thyroid forums reveals that the exist. Arbitary levels for the division between hypothyroidism and subclinical hypothyroidism are often used. Plenty of examples of this are seen in the papers presented here for instance in indications for testing. For instance a TSH of over 10 is considered to be definitive but no reasons are offered for this number. It is suspiciously neat. No reference is made to whether a person is suffering symptoms at this point. These things have become fixed in clinical practice and are never questioned as they should be by good science.	consensus. They acknowledge the importance of symptoms for treatment and have amended recommendation 1.5.2 and 1.5.4 to reflect that.
Thyroid Patient Advocacy	Evidence Review C	5	18	If TSH is used to diagnose/monitor thyroid diseases then a patient never reaches the point at which pituitary deficiency or impaired homeostatic mechanism is considered because a thyroid disorder has been dismissed using the TSH and the symptoms attributed to fibromyalgia/CFS or in the worst case a somatoform disorder.	Thank you for your comment. Please note that the aim of the recommendations is to provide guidance for clinicians on the diagnosis and management of thyroid disease according to what constitutes best clinical practice. The recommendations cannot cover every possible scenario such as pituitary deficiency or impaired homeostatic mechanisms as they aim to be applicable to the majority of patients, for whom the committee is confident TFTs would be appropriate.
Thyroid Patient Advocacy	Evidence Review C	5	22	Diseases are always rare if you don't diagnose them and the bias here is that if TSH is within a population reference that thyroid disease is not present. Once this situation is arrived at how does anyone ever get their central hypothyroidism diagnosed? Or when as in on line 20 there has been longstanding thyroid disease that causes the homeostatic mechanism to be impaired. Where are the references for these introductory statements? *However, prolonged stress is invariably associated with decreased hypothalamic–pituitary–thyroid (HPT) activity in*	Thank you for your comment. This section is a brief introduction to the area that is then reviewed more fully in the document. Central hypothyroidism is outside the scope of this guideline. Section 1.2 of the evidence review serves as a chapter introduction and the information provided here is based on the committee's expertise. Please note that the aim of the present recommendations is to provide guidance on what constitutes best clinical practice in the diagnosis and management of thyroid disease in the majority of

				humans and experimental animals.128–130This leads to decreased metabolic activity, which contributes to energy conservation during chronic stress. *The Hypothalamic–Pituitary–Adrenal Axis and Neuroendocrine Responses to Stress* *Greti Aguilera, in Handbook of Neuroendocrinology, 2012* *Interestingly, for reasons not fully understood, maternal thyroid function also appears to imprint upon future thyroid function in the offspring. A recent student by Pakkila and colleagues investigated maternal thyroid status from mothers in early pregnancy, and compared these to thyroid test concentrations in the offspring at a mean age of 16 years. Boys of hypothyroid mothers had higher TSH concentrations than those of euthyroid mothers, and children of hyperthyroid mothers had lower TSH concentrations than those of euthyroid mothers.102* *Erik K. Alexander, Susan J. Mandel, in Endocrinology: Adult and Pediatric (Seventh Edition), 2016*	people. They cannot cover every possible scenario such as diagnosis in cases where homeostatic mechanisms have been impaired, and they are not to replace clinical judgment in the diagnosis and management of individual patients according to their specific characteristics and needs. The committee is confident that the recommended approach to confirming thyroid dysfunction through TFTs reflects best practice and would be applicable to the vast majority of patients. Thank you for the references you highlight. Both the potential influence of maternal thyroid function on the TSH levels of their offspring and the influence of stress on thyroid function are outside the scope and remit of this guideline. Hence relevant literature such as the references you kindly provide was not considered.
Thyroid Patient Advocacy	Evidence Review C	5	31	Many GP surgeries cannot get FT3 tested for individuals where symptoms persist despite reasoned requests because the TSH is inside an population reference range	Thank you for your comment. Repeating tests for thyroid dysfunction including FT3 where clinically appropriate if symptoms persist or new symptoms develop has been recommended by the committee (recommendation 1.2.9)
Thyroid Patient Advocacy	Evidence Review C	5	33	Using an out of population reference range TSH to cascade to testing FT4 or FT3 automatically misses out those with central hypothyroidism, those with impaired homeostatic mechanisms and those with poor conversion of T4 to T3 (which becomes especially relevant in those treated with Levothyroxine as this is known to produce a lower T3 to T4 ratio than in healthy subjects converting their own hormones.	Thank you for your comment. Please note that central hypothyroidism is outside the scope of this guideline. The aim of the present recommendations is to provide guidance to clinicians on the management of thyroid disease according to what constitutes best clinical practice. They do not replace clinical judgment in the management of individual patients based on their specific characteristics and needs and cannot cover all

				In fact, other markers of thyroid hormone economy might not be fully normalised in patients given levothyroxine; the basal metabolic rate can remain subnormal, lipid abnormalities can persist, and the serum T4:T3 ratio is raised, with relatively lower serum T3 concentrations. Notably, less attention has been given to the raised T4:T3ratio because serum TSH dominates as the therapeutic target and the medical community has dogmatic confidence in the deiodinases to appropriately regulate tissue T3 generation. *McAninch E A, Bianco A C, 2015, New insights into the variable effectiveness of Levothyroxine monotherapy for hypothyroidism. The Lancet Diabetes and Endocrinology, volume 3, Issue 10, 756-758*.	possible scenarios such as impaired homeostatic mechanisms or poor T4 to T3 conversion.
Thyroid Patient Advocacy	Evidence Review C	5	44 - 48	TSH and to a certain extent FT4 are only proxies as the active hormone is T3.	Thank you for your comment. TSH is widely accepted as the most sensitive indicator of thyroid status. The guideline also recommends testing FT4 when TSH is above the reference, and FT4 and FT3 when TSH is below the reference range.
Thyroid Patient Advocacy	Evidence Review C	5	48	TSH alone is not suitable for monitoring treatment in hypothyroidism or hyperthyroidism and the inclusion of tests for FT4 and FT3 the active hormone should not be ruled out where clinically necessary, that is where testing of TSH alone does not equate to symptoms. Since we have a section about monitoring should all reference in this section be to use for diagnosis? All the way through section 1.2 no mention of the relationship of TFTs to symptoms was mentioned but for patients symptoms are paramount. There are papers mentioning how some patients have no symptoms and yet have out of range TFTs and papers mentioning that people who are apparently euthyroid may also have symptoms. No consideration is ever	The committee agrees that there are cases where FT4 and FT3 testing would be appropriate and the possibility of conducting those tests in addition to TSH has not been ruled out. The circumstances under which these tests would be appropriate in the investigation of thyroid disease have been specified in the recommendations. Regarding monitoring patients following treatment for hypothyroidism, the committee agreed that looking at TSH is sufficient and measuring FT4 would only further contribute to monitoring of children and young people and people who continue to experience symptoms (recommendations 1.4). Regarding monitoring following treatment for hyperthyroidism, where measuring TSH,

				given to the fact that the TFTs, in the way they are currently used, may just not actually being doing the job for a proportion of thyroid disease sufferers. This problem is solved for the medical profession by saying that these people do not have a thyroid disease but this is not a solution for the patient who is then left in limbo. Definition of hypothyroidism would be better if it were lack of thyroid hormone in the tissues which would encompass those with primary, secondary and tertiary hypothyroidism as well as those who have post thyroid gland failures such as poor conversion of T4 to T3 and thyroid hormone resistance. *Definition* *Hypothyroidism is a clinical syndrome resulting from a deficiency of thyroid hormones, which results in a generalised slowing of metabolic processes. Central hypothyroidism is the result of anterior pituitary or hypothalamic hypofunction. It may be the result of congenital, neoplastic, inflammatory, infiltrative, traumatic, or iatrogenic aetiologies. It is characterised by decreased thyroid-stimulating hormone secretion in turn causing decreased thyroid hormone synthesis and release.* https://bestpractice.bmj.com/topics/en-gb/36	FT4 and FT3 would be appropriate has been specified (recommendation 1.7.1) Please note that section 1.2 constitutes a chapter introduction and that the committee acknowledges the importance of symptoms and how these should impact follow-up and monitoring, including which TFTs should be conducted has been captured in the recommendations (e.g. recommendations 1.4.1; 1.4.6; 1.5.1). Thank you for highlighting this reference. The committee are confident of their definition of hypothyroidism; the aim of the present guideline was to cover primary hypothyroidism and central hypothyroidism is outside the scope of the present guideline,
Thyroid Patient Advocacy	Evidence Review C	6	9	Table 1 Should this include people being treated for thyroid disease as well as those being investigated?	Thank you for your suggestion. This reflects the criterion set for the population of studies to be included in the review. This had been set in advance to ensure the studies that are relevant to the review question that was about the investigation of people with thyroid disease are identified by the search and included in the review and has been most appropriate for this purpose.
Thyroid Patient Advocacy	Evidence Review C	6	12	No relevant clinical studies were found so what was he recommendation based on?.	Thank you for your comment. The committee used their clinical experience to make a consensus

					recommendation. More detail is provided in the committee discussion of the evidence report.
Thyroid Patient Advocacy	Evidence Review C	8	3	The committee need to provide references for this. Although testing TSH and FT4 may reveal those with obvious primary hypothyroidism it will miss out a significant proportion of people who have thyroid disease but an unreactive TSH due to HP axis dysfunction as mentioned elsewhere in this evidence review page 5 line 18-21. '*However there are notable exceptions when serum TSH concentration alone may not accurately reflect thyroid hormone production. This is most frequently encountered when the homeostatic mechanism has been impaired by long standing primary thyroid disease' .* This is clearly a harm to these people. What strategy is put in place for these people? If TSH and FT4 come back within the population reference range the first time will TSH, FT4 and FT3 be tested a second time to ensure that they are picked up. What about thyroid auto antibodies?	Thank you for your comment. Please note that the aim of the present recommendations is to provide guidance on what constitutes the best clinical practice in the diagnosis and management of the majority of patients with thyroid disease. They cannot cover every possible scenario such as the diagnosis of people with people with HP axis dysfunction and they do not replace clinical judgment in the diagnosis and management of individual patients according to their specific characteristics and needs. The committee is confident that the recommended approach to confirming thyroid dysfunction through TFTs reflects best practice and would be applicable to the vast majority of patients. Repeating tests for thyroid dysfunction including FT4 and FT3 where appropriate has been recommended if symptoms worsen or new symptoms develop (recommendation 1.2.9). The committee agreed that antibodies are to be measured after thyroid disease has been confirmed via TFTs to confirm the cause of thyroid disease and guide treatment.
Thyroid Patient Advocacy	Evidence Review C	8	6 - 10	It is important to determine whether the patient has symptoms too! Sub clinical hypothyroidism is not subclinical if the patient has symptoms.	Thank you for your comment. The importance of symptoms in determining treatment for subclinical hypothyroidism has been captured in the relevant recommendations (1.5)
Thyroid Patient Advocacy	Evidence Review C	8	14	'….and fewer primary or autoimmune causes' Fewer not less here.	Thank you for your comment. This has been amended.
Thyroid Patient Advocacy	Evidence Review C	8	18	No economic evidence was presented so that it is not possible to determine whether it is economically valid to restrict testing to the strategy suggested as it is not possible to work out the ongoing cost to the NHS of further testing for potentially spurious diseases because thyroid disease has been ruled out	Thank you for your comment. As no economic evidence was found the unit costs of the thyroid function tests were presented to the committee. It was not possible to calculate the cost-effectiveness of the different testing strategies and

				or the potential cost to the NHS of treatment further disease developing from undiagnosed thyroid disease or the cost to the patient, families carers etc. of ongoing undiagnosed thyroid disease.	therefore the committee made recommendations in line with current practice.
Thyroid Patient Advocacy	Evidence Review C	8	21	Where are the references to support the consensus recommendations? Are they subject to the high standards that the other papers used in the review were subject to?	Thank you for your comment. In cases where evidence has not been sufficient the committee has used their collective experience to make consensus recommendations. This follows the process detailed in the guidelines manual on making recommendations. Similarly, the expertise of stakeholders is taken in to account through the consultation process.
Thyroid Patient Advocacy	Evidence Review C	8	23	The costs of the blood tests are only one part of the equation. Where are the costs for treating say heart disease that might develop if a patient is missed by this strategy of testing? Or the costs to patients (and to society) if they are left too ill to work?	Thank you for your comments. The committee did consider the impact of testing on downstream resource use in addition to the cost of the test itself. The recommendations are based not only on costs, but the clinical evidence presented in the review. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease. In addition, as reported in the Manual for developing NICE Guidelines (https://www.nice.org.uk/process/pmg20/chapter/introduction-and-overview), “productivity costs and costs borne by people using services and carers that are not reimbursed by the NHS or social services should not

					usually be included in any analyses". This is for different reasons, for example time off work is implicitly incorporated in QALY. Also if we included productivity costs in our analyses we would favour those interventions aimed at the working population and would discriminate against the elderly, children, unemployed people and people with disabilities.
Thyroid Patient Advocacy	Evidence Review C	8	40 - 41	How are people suspected of secondary thyroid disease to be identified since they will have been ruled out using a TSH test? What about those with poor T4 to T3 conversion? Or THR?	Thank you for your comment. The guideline recommends suggest both TSH and FT4 if secondary disease is suspected.
Thyroid Patient Advocacy	Evidence Review C	8	43	Here again we seem to have switched back to monitoring treatments which is very confusing as the arguments are not exactly the same. Once diagnosed and started on treatment a patient would usually be testing every 5-6 weeks after a dose adjustment to monitor progress. Dose will need to be titrated to try and remove symptoms although often it is only titrated to get blood test results into wide population reference ranges. The current recommendations are that those who are elderly or with a heart condition should be started at a relatively low dose which is titrated upwards. These people will need regular tests to ensure that Levothyroxine is being converted and that their HP axis appears to be functioning.	Thank you for your comment. The line you refer to is associated with the diagnosis of thyroid disease. The management and monitoring of people with hypothyroidism has been addressed in a separate evidence review chapter (chapters E and F) and the committee is confident that the recommendations made reflect best clinical practice. Please note that considering the time it can take for TSH to return to the reference range, 5-6 week testing was considered unnecessarily frequent except in children or young people.
Thyroid Patient Advocacy	Evidence Review C	8	47	What is considered unnecessary? For the patient the goal is to return to symptom free and that would outweigh any cost savings to the NHS that results in the patient remaining with unresolved symptoms.	Thank you for your comments. We have now deleted the reference to reducing excessive testing, so as to give greater emphasis to avoiding misinterpretation of test results.
Thyroid Patient Advocacy	Evidence Review C	9	1	Current practice leaves a proportion undiagnosed, and if treated, badly managed.	Thank you for your comment. The committee is confident that the recommendations made reflect best clinical practice and hope they will contribute to the diagnosis and management of thyroid disease.
Thyroid Patient Advocacy	Evidence Review C	9	2	A consistent approach by all laboratories would be helpful as long as it was flexible enough not to prevent testing of any parameter when requested.	Thank you for your comment. The interpretation of tests is outside the remit of this guideline. The committee agrees that symptoms may lead to clinical suspicion of

				Interpretation of the tests is critically important. The tests as currently used are self-confirming and do not successfully diagnose those with hypothyroidism. Diagnosis needs to be based on symptoms and this can be supported but not decided by thyroid function tests and antibody tests. Trial of treatment is another possible route to diagnosis which has some precedents. *Hypothyroidism is a common condition of thyroid hormone deficiency, which is readily diagnosed and managed but potentially fatal in severe cases if untreated. The definition of hypothyroidism is based on statistical reference ranges of the relevant biochemical parameters and is increasingly a matter of debate. Clinical manifestations of hypothyroidism range from life threatening to no signs or symptoms. The most common symptoms in adults are fatigue, lethargy, cold intolerance, weight gain, constipation, change in voice, and dry skin, but clinical presentation can differ with age and sex, among other factors. The standard treatment is thyroid hormone replacement therapy with levothyroxine. However, a substantial proportion of patients who reach biochemical treatment targets have persistent complaints. In this Seminar, we discuss the epidemiology, causes, and symptoms of hypothyroidism; summarise evidence on diagnosis, long-term risk, treatment, and management; and highlight future directions for research.* https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)30703-1/fulltext *CeH most frequently occurs as a sporadic form of hypothyroidism. It can affect patients of all ages and, despite*	thyroid disease which needs to be confirmed by thyroid function tests. It is acknowledged that a trial of treatment could influence diagnosis for some patients but evidence for the clinical and cost-effectiveness of this approach was not looked for to allow for a recommendation to be made and the committee agrees it is unlikely to be cost-effective. Thank you for the references you highlight. Our recommendations do not contradict this information. Please note that the aim of the present recommendations is to provide guidance on what constitutes best clinical practice in the diagnosis and management of the majority of patients with thyroid disease and could not cover topics including central hypothyroidism and other sporadic forms of hypothyroidism.

				the recent discovery of X-linked forms of CeH, there is no evidence of a sex predominance. The prevalence of CeH was estimated to range from 1: 16,000 to about 1: 100,000 in the general adult or neonatal populations [4, 8-10]. Such variable prevalence probably depends upon several factors, including ethnicity but also differences in sensitivity of the diagnostic strategies. *2018 European Thyroid Association (ETA) Guidelines on the Diagnosis and Management of Central Hypothyroidism Persani L. Brabant G. Dattani M. Bonomi M. Feldt-Rasmussen U. Fliers E. Gruters A. Maiter D.i · Schoenmakers N. van Trotsenburg A.S.P.*	
Thyroid Patient Advocacy	Evidence Review C	9	12	Clinical efficacy is assured because if TFT tests do not 'reveal' hypothyroidism then the patient is not considered to have hypothyroidism. This is a perfect circular argument. TFTs miss out people with personal set points that sit outside the population reference range, people with poor conversion, people with thyroid hormone resistance, altered hypothalamic/pituitary axis as well as anyone with central hypothyroidism of any kind.	Thank you for your comment. Please note that the aim of the present recommendations is to provide guidance on what constitutes best clinical practice in the diagnosis and management of the majority of patients with thyroid disease. They cannot cover every possible scenario such as the diagnosis of people with thyroid hormone resistance and they do not replace clinical judgment in the diagnosis and management of individual patients according to their specific characteristics and needs. The committee is confident that the recommended approach to confirming thyroid dysfunction through TFTs reflects best practice and would be applicable to the vast majority of patients. The diagnosis of central hypothyroidism is outside the scope of the guideline.
Thyroid Patient Advocacy	Evidence Review C	9	22	Because it is actually quite difficult to get diagnosed with central hypothyroidism because of the use of TSH! If the standard test is the TSH when a patients TSH comes back 'normal' hypothyroidism is excluded so how does that person go on to get a diagnosis of hypothyroidism?	Thank you for your comment. Please note that the diagnosis of central hypothyroidism is outside the scope of the guideline. The circumstances under which TSH, FT4 and FT3 should be measured have been specified in the recommendations which the committee is confident reflect best practice.

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Thyroid Patient Advocacy	Evidence Review C	9	31 - 35	It is the relationship of TSH, FT4 and FT3 that reveals what is going on therefore all 3 need to be tested. This study demonstrates that in the L-T4-treated patients the dosage of L-T4 that was required to restore a normal serum TSH was accompanied by higher serum free T4 and lower serum free T3 values https://link.springer.com/article/10.1007/BF03343972 See also TPAUK's reply to lines 8-9 on page 5 of this Evidence Review [C].	Thank you for your comment. The committee has agreed that if there is suspicion of secondary thyroid dysfunction, the measurement of FT4 would be appropriate if TSH is above the reference range while both FT4 and FT3 would be necessary if TSH is below the reference range. The committee is confident that an abnormal FT4 is unlikely if TSH is normal. Where TSH, FT4 and FT3 need to be measured has been specified in the recommendations for Tests when thyroid dysfunction is suspected (1.2.7 to 1.2.9)
Thyroid Patient Advocacy	Evidence Review C	9	35 - 38	Many laboratories refuse to do FT3 even when requested by a doctor and will only do FT4 when TSH is out of range. Which again returns to the question, how does a patient get diagnosed with any form of central hypothyroidism?	Thank you for your comment. There was consensus that FT4 would be appropriate if TSH is above the reference range while FT3 would be necessary if TSH is below the reference range. The recommendations made capture the conditions under which FT4 and FT3 should be measured and the committee is confident these reflect the most appropriate approach to the diagnosis of primary hypothyroidism. The diagnosis of central hypothyroidism is outside the scope of the guideline.
Thyroid Patient Advocacy	Evidence Review C	9	38 - 43	to assess for conversion problems	Thank you for your comment; it is unclear what this refers to.
Thyroid Patient Advocacy	Evidence Review D	1	1	This document is labelled differently in the main NICE index [D] Tests for confirmed primary hypothyroidism	Thank you for your comment. This has been amended. The cover page now reads: 'Tests for people with confirmed primary hypothyroidism'
Thyroid Patient Advocacy	Evidence Review D	1	6 - 8	There are some people with auto immune hypo who do not exhibit antibodies. Definitive confirmation of auto immune hypo is by scan or biopsy. Auto antibodies are therefore a proxy.	Thank you for your comment. The committee agrees that ultrasound scanning (US) may be considered in a small minority of people with suspected autoimmune thyroid disease and negative antibodies; nevertheless, they are confident that antibody testing is the main and most useful approach to confirm autoimmunity as a cause of thyroid disease for the majority of patients.

					Since treatment decisions will be dependent on thyroid function, US scanning was considered unnecessary and biopsy was not considered appropriate.
Thyroid Patient Advocacy	Evidence Review D	1	11	The use of the expression 'overt hypothyroidism' implies a biochemical diagnosis rather than one made on symptoms and should not be used to exclude patients with symptoms. Antibody testing is useful when first testing for thyroid disease because significant symptoms may be present before TFTs reveal 'overt hypothyroidism'! See comments on Evidence Review [C] for TPAUk's criticisms of TFTs.	Thank you for your comment. This section is simply a chapter introduction; it is not part of the recommendations and does not preclude people with symptoms from being investigated.
Thyroid Patient Advocacy	Evidence Review D	1	18	In Table 1 the population section should say 'People being investigated for hypothyroidism or confirmed as having biochemical hypothyroidism via TSH +/- thyroid hormone results'	Thank you for your comment. This question is focused on the efficacy of antibody testing after confirmation of diagnosis of hypothyroidism. Therefore, participants in any relevant studies would need to have their hypothyroid status confirmed at the outset.
Thyroid Patient Advocacy	Evidence Review D	6	3	Again no relevant clinical studies were selected so what are recommendations based on? Was this basis subject to such a high level of scrutiny as inclusion in the current guidelines? Where is their evidence to support what they are saying and the evidence on which to base the Guidelines?	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence report. In areas where no clinical evidence was identified, the committee members used their collective experience to make consensus recommendations. The committee noted that in some areas not making a recommendation would leave a gap and, in such cases, expert guidance was better than none at all. This was applicable here and the committee is confident that recommendations made reflect best clinical practice in the investigation of people with confirmed primary hypothyroidism.

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Thyroid Patient Advocacy	Evidence Review D	6	9	No relevant health economic studies were found.	Thank you for your comment. The committee has used their judgment and experience to make recommendations that are cost effective in the absence of economic evidence.
Thyroid Patient Advocacy	Evidence Review D	6	18	Costs for Tg antibody testing should be included here.	Thank you for your comment. This has now been added to the unit cost table. The cost was obtained from one NHS hospital and was estimated to be £15.57.
Thyroid Patient Advocacy	Evidence Review D	7	11	This should say 'TPO and Tg antibody testing may be beneficial in early investigation of hypothyroidism' because it is possible to have negative TPO antibodies yet Tg antibody titres in the thousands.	Thank you for your suggestion. In absence of evidence of the clinical and cost-effectiveness of antibody testing for people with confirmed primary hypothyroidism, the committee made consensus-based recommendations using their clinical expertise. TPO antibodies have been considered particularly important in people with primary hypothyroidism by the committee, who discussed their usefulness and recommended testing for them. This section aims to capture the committee's discussion that took place and led to the recommendation and therefore Tg antibody testing has not been referred to here.
Thyroid Patient Advocacy	Evidence Review D	7	11 - 21	Antibody testing to determine whether a disease is auto immune is also helpful to both the patient and doctor from the point of view of knowing that the patient will be more prone to other auto immune diseases. https://www.thyroid.org/patient-thy...r-patients/vol-3-issue-4/vol-3-issue-4-p-7-8/	Thank you for your comment. We hope the recommendations made for antibody testing will help improve outcomes for patients with thyroid disease.
Thyroid Patient Advocacy	Evidence Review D	7	20	Antibody testing is extremely useful when a patient has symptoms but is apparently biochemically euthyroid or with biochemically sub clinical	Thank you for your comment and for contributing to the consultation process. The point you raise is what is being acknowledged in this section.
Thyroid Patient Advocacy	Evidence Review D	7	23 - 24	Ongoing antibody testing can indicate recurring auto immune attacks and explain subsequent instability of hormone levels. *Koulouri O, Gurnell M, Levy MJ How to interpret thyroid*	Thank you for your comment and for providing this reference. Not being a systematic review, this article does not meet the protocol inclusion criteria set for studies to be considered during decision making. The committee thought based on their clinical expertise that

				function tests, Clin Med (Lond). 2013 Jun; 13(3): 282–286. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5922674/	apart from measuring antibodies once to examine the underlying cause of hypothyroidism, repeated testing would not further contribute to the information provided by hormone testing.
Thyroid Patient Advocacy	Evidence Review D	7	25 - 26	Hypothyroidism is for life so temporary withdrawal of hormone support is tantamount to cruelty! The whole idea of withdrawing someone's medicine to 'see if they still have hypothyroidism' is outrageous but surprisingly common. People become very ill, lose jobs and livelihoods when this happens. It is akin to saying 'you have a somatoform disorder'. In what other lifelong illnesses is this practiced?	Thank you for your comment. The committee has not recommended the temporary withdrawal of hormone treatment; since the aim of the recommendations is to provide guidance for clinicians to follow towards best clinical practice and cannot replace clinical judgment. This section simply states what can occasionally occur in the clinical setting particularly during the transition from child to adult services, to highlight where repeating antibody testing can be helpful.
Thyroid Patient Advocacy	Evidence Review D	7	34	This should say 'TPO and Tg testing…'. Although it may be more common to have Tg antibodies when TPO antibodies are already positive it is definitely possible to have positive Tg antibodies without positive TPO antibodies.	Thank you for your suggestion. In absence of evidence of the clinical and cost-effectiveness of antibody testing for people with confirmed primary hypothyroidism, the committee made consensus-based recommendations using their clinical expertise. TPO-Ab antibodies have been considered particularly important in people with primary hypothyroidism by the committee, who discussed their usefulness and recommended testing for them. This section aims to capture the committee's discussion that took place and led to the recommendation and therefore Tg antibody testing has not been referred to here.
Thyroid Patient Advocacy	Evidence Review D	7	34 - 36	Comments here are similar to those given for lines 23-24. A person should have a right to know the cause of their disease especially as having one auto immune condition predisposes you to others. This is very dismissive of a patient. If symptoms don't resolve or hormone levels seem unstable it can be informative to test antibody levels.	Thank you for your comment. The committee's view, based on its combined clinical expertise, is that, apart from measuring antibodies once to examine the underlying cause of hypothyroidism, repeated testing would not further contribute to the information provided by hormone testing.

				https://www.thyroid.org/patient-thy...r-patients/vol-3-issue-4/vol-3-issue-4-p-7-8/	
Thyroid Patient Advocacy	Evidence Review D	9	2	Oddly a reference paper to the clinical utility of Tr antibodies was included although the utility was not discussed in this section. Either they should be included here or a separate section should be added.	Thank you for your comment. This study was referenced because it was on the excluded studies list. The reason for exclusion is given in Appendix G.
Thyroid Patient Advocacy	Evidence Review E	14	3	3 In Table 5 it actually shows positive outcome for NDT on all counts. The committee have chosen to interpret this as no evidence that it works. A more reasonable conclusion based on one paper that really is equivocal is that the best that can be said is that more research is needed. This is not enough evidence to stop prescribing something that 49% of recipients in the trial and many people on the ground finds works for them. NDT is currently prescribable on the NHS.	Thank you for your comment. Although there was a difference between groups this was not a clinically important effect as it was not sufficiently large to meet the standardised cut-offs for assessing clinical importance (1/2 median SD of the control group). Evidence from a single study with a limited number of participants and follow-up relevant to two outcomes of low to moderate quality was not sufficient to support the use of natural thyroid extract over T4. The committee agreed that the potential long-term adverse events of Natural thyroid extract are not known, noting that it is currently unlicensed in the UK and therefore not prescribable on the NHS. They therefore agreed that it should not be offered as treatment.
Thyroid Patient Advocacy	Evidence Review E	15	10	Natural Thyroid Extract is not always Natural Desiccated Thyroid as explained in answer to line 7 of page 6 of this document. Natural Desiccated thyroid (NDT) is a licensed prescription medicine available in tablets known as grains that contain specified amounts of T4 and T3. The term natural thyroid extract is usually used for dried thyroid gland and is a supplement. TPAUK is concerned that the authors of the report simply do not understand the difference.	Thank you for your comment. Natural thyroid extract which includes natural desiccated thyroid is not licensed in the UK on the NHS and its long term adverse effects are unknown.
Thyroid Patient Advocacy	Evidence Review E	16	20	The fact that nearly half the subjects preferred NDT was ignored.	Thank you for your comment. Patient preference was not included in the pre-specified protocol outcomes and was therefore not extracted from the studies. The committee chose to focus their search on outcomes

					based on validated measures like quality of life and symptom scores.
Thyroid Patient Advocacy	Evidence Review E	17	5 - 6	Note that the study looking at Natural Thyroid Extract (actually branded NDT was used in the study) had the highest quality of evidence across comparisons.	Thank you for your comment. The quality of all studies has been acknowledged and taken into account in decision making.
Thyroid Patient Advocacy	Evidence Review E	17	17	Evidence is not included to show that TSH suppression in a treated hypothyroid person with FT4 and FT3 within population reference ranges and in the absence of hyperthyroid symptoms is harmful.	Thank you for your comment. The use of harm here reflects a direction of effect. It is not possible for the guideline to conduct evidence reviews to support every aspect of the discussions informing recommendation making. The consensus of the committee was that TSH suppression as an outcome was a negative occurrence and therefore if there was an effect of sufficient magnitude on this outcome, it would be considered an important harm.
Thyroid Patient Advocacy	Evidence Review E	17	20	This is contradicted by the information presented in appendix K which states that *'A number of randomised controlled trials (RCTs) of T4-T3 combination therapy vs T4 monotherapy suggest there is no benefit of the combination therapy in the general population of people with hypothyroidism. However, most of these studies had small sample size, used variable and often non-physiological doses of T3, and had a short duration of follow-up. Furthermore, in some of the blinded randomised controlled trials, patients preferred the combination therapy over T4 monotherapy. Therefore, it remains to be tested in well conducted large RCTs whether T3 given in a more physiological dose and formulation (for example, sustained release formulation) improves outcomes specifically in the population of people who do not respond well to T4 alone'.*	Thank you for your comment, Kindly bear in mind that the clinical benefit stated on page 16 has emerged from the meta-analysis of findings from RCTs conducted within this review and is particularly related to two quality of life outcomes, while Appendix K refers to the overall conclusions drawn by individual studies.
Thyroid Patient Advocacy	Evidence Review E	18	13	The fact that levothyroxine is cheap is somewhat irrelevant for those patients in whom it does not work.	Thank you for your comment. The recommendations aim to provide guidance on the management of the majority of patients with the condition according to what

					constitutes best clinical practice and do not replace clinical judgment in the management of individual patients according to their specific characteristics and needs.
Thyroid Patient Advocacy	Evidence Review E	18	15	The anticipated cost of liothyronine does not take into account the fact that the price is subject to a CMA investigation at the moment or that the equivalent products cost very little on mainland Europe.	Thank you for your comment. The guideline is based on current UK list prices rather than future prices; a cross reference to the CMA investigation has been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). The NICE surveillance process (more information in the Guidelines Manual) will pick up on any price change and consider if the guideline needs updating.
Thyroid Patient Advocacy	Evidence Review E	18	16 - 18	This statement is inconsistent with those made in Appendix K and needs to be qualified with this information from Appendix K *'A number of randomised controlled trials (RCTs) of T4-T3 combination therapy vs T4 monotherapy suggest there is no benefit of the combination therapy in the general population of people with hypothyroidism. However, most of these studies had small sample size, used variable and often non-physiological doses of T3, and had a short duration of follow-up. Furthermore, in some of the blinded randomised controlled trials, patients preferred the combination therapy over T4 monotherapy. Therefore, it remains to be tested in well conducted large RCTs whether T3 given in a more physiological dose and formulation (for example, sustained release formulation) improves outcomes specifically in the population of people who do not respond well to T4 alone'.* Essentially what is being said in Appendix K is that there were lots of problems with the RCTs being considered as evidence	Thank you for your comment. The statement you refer to reflects the current review findings which are based on the meta-analysis of RCTs and is relevant to individual outcomes. The information in the Appendix is a statement about what the evidence base available to date shows overall and its purpose is to provide some background information relevant to the research recommendation. The limitations of the RCTs included in the review have been carefully considered by the committee who has agreed that the evidence available does not support the effectiveness of the addition of T3 to T4 monotherapy or of natural thyroid extract. The committee was also aware of evidence suggesting T4-T3 combination therapy could be harmful as it may suppress the production of TSH and agreed that it should not be routinely offered. Nevertheless, the committee acknowledges the potential benefit that the addition of T3 could bring to people not responding sufficiently to T4 monotherapy and have therefore

				therefore it seems logical to conclude that the situation should be left as it is with T3 and NDT being available for trial in those cases where patients do not recover on T4 monotherapy and that this advice will be reassessed in the light of new evidence.	prioritised a research recommendation in this area, which is what is summarised in Appendix K. Since natural thyroid extract is not currently licensed in the UK the committee has not made a recommendation for research.
Thyroid Patient Advocacy	Evidence Review E	18	32	NDT may be more expensive currently but it is not possible to assess the cost benefit of treatment due to the lack of health economic studies. Also if NDT were more widely prescribed then unit costs could fall due to bulk buying and favourable contract negotiation.	Thank you for your comment. Considering the lack of evidence to support the clinical efficacy and safety of natural thyroid extract, with its long-term adverse events being uncertain, the committee agreed it is unlikely to be cost-effective. The committee also noted that natural thyroid extract is not licensed in the UK.
Thyroid Patient Advocacy	Evidence Review E	18	33	This statement again contradicts what is said in appendix K. *'Furthermore, in some of the blinded randomised controlled trials, patients preferred the combination therapy over T4 monotherapy.' Appendix K* One of these was the RCT comparing NDT with T4 monotherapy *With regard to drug preference, 34 patients (49%) preferred DTE, 13 (19%) preferred L-T4, and 23 (33%) had no preference; the preference for DTE over L-T4 was statistically significant (P<0.002)*. Patient preference was statistically significantly in favour of NDT despite the untitrated doses. The committee appears to have had a bias against NDT and have been more negative about it than the evidence would	Thank you for your comment. Patient preference was not included in the outcomes pre-specified in the review protocol (Appendix A) and the study results you raise were therefore not extracted to be considered in the clinical and cost-effectiveness of the interventions. The committee chose prospectively to focus on outcomes measured by validated scaled (e.g. quality of life, symptom scores). Please note that review protocols based on which studies are selected and outcomes are extracted, are agreed with the committee prior to systematic searching to eliminate any potential bias in the selection of the evidence that comes to be included in each evidence review. The committee agreed that natural thyroid extract should not be offered based on the lack of sufficient evidence to support its effectiveness, its long-term adverse effects being uncertain. The study that you are referencing showed no clinically important benefit of NDT in terms of depression or symptom scores.

				indicate and have subjected NDT to a higher level of scrutiny than either levothyroxine or T4/T3 combinations.	
Thyroid Patient Advocacy	Evidence Review E	18	35	Safety data is as available for NDT as it is for Levothyroxine. It was used successfully for many years before the development of levothyroxine. There is plenty of anecdotal evidence which is what should be informing potential trials. The active ingredients in NDT are very stable so that the tablets have a long shelf life unlike levothyroxine where the instability means that overage has to be practiced and the tablets blister packed are short-dated. *Levothyroxine Tablet products A Review of Clinical and Quality Considerations, MRHA, Jan 2013,* https://assets.publishing.service.g...te_Levothyroxine_sodium_FINAL_04_Jan_2013.pdf In addition levothyroxine has never been subject to the level of scrutiny applied to NDT and T4/T3 combinations since it was introduced. None of the RCTs considered suitable for inclusion in this evidence review had a healthy control group against which levothyroxine could be compared.	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. RCTs are included based on protocol criteria that have been agreed with the committee prior to systematic searching to eliminate any potential bias in the selection of the evidence that comes to be included in the evidence review. No studies meeting protocol criteria compared levothyroxine with control. Since RCTs were currently identified for T4/T3 and natural thyroid extract, the committee considered that lower quality evidence was more likely to be unreliable and would not further assist in making recommendations. The evidence showed no benefit of natural thyroid extract over levothyroxine and the committee noted that the proportion of T3 to T4 is higher in natural thyroid extract than what is produced in the human body, causing uncertainty in regards to its adverse events. Considering these points and that natural thyroid extracts is not licensed in the UK, the committee agreed it should not be offered.
Thyroid Patient Advocacy	Evidence Review E	18	43 - 45	Where is the evidence for this? There is evidence that symptoms in hypothyroid people may be linked to the low T3 levels found in people who are treated with levothyroxine when compared to a healthy population, and that that adjusting the	Thank you for your comment. This is based on the committee's collective clinical expertise. Please note that recommendation 1.4.1 has been amended to suggest dose adjustments based on symptoms, even when TSH

				T4 dose upwards sometimes raises T3 enough to reduce symptoms. The implication from this would be that raising T3 would help reduce symptoms. *Larisch R, Midgley JEM, Dietrich JW, Hoermann R. Symptomatic Relief is Related to Serum Free Triiodothyronine Concentrations during Follow-up in Levothyroxine-Treated Patients with Differentiated Thyroid Cancer. Exp Clin Endocrinol Diabetes. 2018 Sep;126(9):546-552. doi: 10.1055/s-0043-125064. Epub 2018 Feb 2.* and *In this large population study, hypothyroid patients taking Levothyroxine who had a normal TSH level showed lower serum T3 and higher T4 levels, and consequently lower T3:T4 ratios than matched healthy individuals without thyroid problems. In addition, there were differences noted between the levothyroxine– treated and healthy matched subjects in BMI, cholesterol levels, medications used as well as reported caloric intake, physical activity, and the feeling of poor health. These findings suggest that a normal TSH level may not be sufficient as a single criterion used to find the right levothyroxine dose for each patient* *Peterson SJ et al. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? J Clin Endocrinol Metab. October 4, 2016*	is within the reference range, to achieve optimal well-being.
Thyroid Patient Advocacy	Evidence Review E	18	45 - 47	The 'vague' symptoms might not respond to levothyroxine dose changes because they may actually be linked to T3 levels and T3 levels are lower in people treated with levothyroxine than in healthy subjects. *Larisch R, Midgley JEM, Dietrich JW, Hoermann R.*	Thank you for your comment and this reference. Since this is a non-randomised study it is not considered as rigorous as randomised controlled trials and in line with the pre-specified review protocol criteria, its findings could not be taken into account in decision making within the context of the present review, This study does

				Symptomatic Relief is Related to Serum Free Triiodothyronine Concentrations during Follow-up in Levothyroxine-Treated Patients with Differentiated Thyroid Cancer. Exp Clin Endocrinol Diabetes. 2018 Sep;126(9):546-552. doi: 10.1055/s-0043-125064. Epub 2018 Feb 2.	provide evidence of an association of symptoms with FT3 levels but due to its observational nature, causality cannot be inferred and it may be the case that other factors, not adjusted for in the multivariable analysis that took place played a role. Nevertheless, the committee acknowledges the issue you raise that some people may still feel unwell with levothyroxine. The guideline has made a research recommendation to highlight the need for appropriate trials for the subgroup of people who do not respond to levothyroxine alone.
Thyroid Patient Advocacy	Evidence Review E	19	2 - 4	The committee 'could not make specific recommendations to titrate more subtly than to the reference range based on the evidence available' Surely the recommendation should be to titrate the dose to remove symptoms?	Thank you for your comment. Recommendation 1.4.1 has been amended to suggest dose adjustments based on symptoms, even when TSH is within the reference range, to achieve optimal well-being. This sentence has been removed.
Thyroid Patient Advocacy	Evidence Review E	27	3 in Table 7	3 In Table 7 VIII RCTS only. RCTs were the only evidence considered acceptable however there is evidence that RCTs are not an appropriate study tool for treatments for hypothyroidism. *Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: have they achieved their objectives? J Thyr Res. 2018;2018:3239197.* Also both anecdotal and epidemiological evidence needs to be considered because this is what informs RCTs. The over rigorous selection of studies has meant that much useful evidence has been excluded.	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. Currently RCT evidence was available and the committee considered that lower quality evidence was likely to be unreliable and that it would not assist in making recommendations. This is not sufficient evidence to support the insufficiency of RCTs.
Thyroid Patient Advocacy	Evidence Review E	5	1	In view of what is said in lines 10 and 11 the title here needs to be Management of Primary Hypothyroidism. However as all hypothyroidism is currently managed the same way it would be logical to include it here.	Thank you for your comment. We could not cover all aspects of thyroid disease and consequently focussed this review here to the management of primary hypothyroidism. With that in mind the committee did not

					discuss whether the same management could apply to all hypothyroidism, so we have not made recommendations related to this.
Thyroid Patient Advocacy	Evidence Review E	5	8	Actually, hypothyroidism occurs when there is insufficient thyroid hormone reaching the tissues/cells.	Thank you for your comment. This is intended as a brief introduction to the topic area and is not meant to be comprehensive. We have made some edits to this section in response to some of the comments made by stakeholders.
Thyroid Patient Advocacy	Evidence Review E	5	9	This ignores conversion problems and thyroid hormone resistance, problems that are acknowledged to exist and that result in the exactly the same symptoms and respond to exactly the same treatments.	Thank you for your comment. This is intended as a brief introduction to the topic area and is not meant to be comprehensive. We have made some changes to this section in response to comments made by stakeholders.
Thyroid Patient Advocacy	Evidence Review E	5	11	In which case the title of the whole document needs to reflect this very clearly despite it being massively illogical to single out primary hypothyroidism for this one section since all forms of hypothyroidism is treated the same way no matter what its aetiology. It also begs the question how does anyone with another form of hypothyroidism get diagnosed.	Thank you for your comment. We have amended the guideline context section to make it clear that the guideline only covers primary thyroid disease.
Thyroid Patient Advocacy	Evidence Review E	5	12	The committee needs to provide a reference here as some authorities put the incidence at more like 5%.	Thank you for your comment. This is intended as a brief introduction to the topic area and is not meant to be comprehensive. We have made some changes to this section in response to comments made by stakeholders.
Thyroid Patient Advocacy	Evidence Review E	5	14	The symptoms never resolve with standard treatment for a significant number (10-15%) of people. Apparent biochemical correction refers to getting people somewhere in the population reference ranges not getting them to their own individual set point. The committee acknowledges elsewhere for example that hypothyroidism that remains undiagnosed for a long time can result in dysfunction of the HP axis. This causes a lower TSH in response to a given dose of replacement hormone thus a poor conversion of T4 to T3 and a poor response to treatment with T4 monotherapy.	Thank you for your comment. Please note that the issue you raise has been acknowledged and recommendation 1.4.1 has been amended to suggest further adjustments to treatment in cases where symptoms persist when TSH levels are within the reference range.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
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Thyroid Patient Advocacy	Evidence Review E	5	15	Just because it is current practice does not make it right. There are large flaws in the use of population reference ranges to determine hypothyroidism (see TPAUK's criticisms of Evidence Review [C] Thyroid Function Tests) when actually individuals have set points that very personal and vary widely from person to person. *Using the observed historical narrower therapeutic range for an individual patient we note that the treatment targets may overlap for patients in a group. If that is true the general assumption that maintaining TSH anywhere within its broad reference limits to routinely achieve a satisfactory outcome for each and every patient may be ill advised. We have refuted the applicability of treatment targets based on the consideration of the reference ranges in the healthy population, by demonstrating dissociations between FT3 and FT4, and FT3 and TSH in LT4-treated athyreotic patients, and documenting altered equilibria between the hormones on LT4, compared to the healthy state [27, 56]. Others have arrived at similar conclusions [57]. In laboratory diagnostics, the high individuality of TSH and thyroid hormones has long been recognised since the pioneering work of Andersen and colleagues [58]* *Time for a reassessment of the treatment of hypothyroidism John E. M. Midgley, Anthony D. Toft , Rolf Larisch , Johannes W. Dietrich and Rudolf Hoermann, BMC Endocrine Disorders (2019) 19:37*	Thank you for your comment and for highlighting this information. The guideline did not specifically review evidence relating to diagnostic criteria for thyroid disease as the reference standard for diagnosis is thyroid function tests and so no alternative can perform better by accuracy measures. Therefore, the committee overall agreed it was most appropriate to address this aspect of the scope by considering which specific tests had most benefit. NICE recommendations are not intended to cover every possible aspect of a disease area and the committee agreed that clinical signs and symptoms are an important part of diagnosis. The issue you raise in regards to individual TSH optimal set points and that treatment targets may vary for patients as proposed in the article you cite, have been considered by the committee who have agreed this is likely to primarily impact monitoring of patients rather than the diagnosis of primary hypothyroidism. In light of this the recommendation 1.4.1 has been amended to suggest further adjustments to treatment in cases where symptoms persist when TSH levels are within the reference range, to allow for individual TSH targets and optimal well-being to be achieved.
Thyroid Patient Advocacy	Evidence Review E	5	16	Current practice also involves referral to an endocrinologist for a trial of treatment with a T4/T3 combination or NDT if T4 monotherapy proves to be unsuccessful. This needs to be included here because this is the current status quo so that this is the position that should remain if the evidence presented in	Thank you for your comment. This is intended as a brief introduction to the topic area and is not meant to be comprehensive. We have made some changes to this section and included mention of all the treatments included in the review protocol including T3 and NDT.

				this review does not clearly indicate another position. Missing this out here implies a bias towards not using T3 or NDT.	
Thyroid Patient Advocacy	Evidence Review E	5	16 - 17	'with the aim of achieving T4 and TSH in the normal range'. Firstly it is not a normal range it is a 95% population reference range. These are not the same and using the words 'normal range' implies something that is not determined by a population reference range and is very misleading. Note what is said in Evidence Review [F] on page 13 at line 10. Secondly the aim surely is to make the patient well and symptom-free. There is bias here in that it is implied that returning hormone levels to somewhere within a population reference range is synonymous with being well, when clearly it is not. That the aim is to remove symptoms and make the patient well needs to be mentioned strongly here and should be considered more important than returning TFTs to somewhere in a 95% population reference range.	Thank you for your comment. This has been amended to 'reference range'. The issue you raise has been discussed by the committee and recommendation 1.4.1 has been amended to suggest further adjustments to treatment in cases where symptoms persist when TSH levels are within the reference range, to allow for individual TSH targets and optimal well-being to be achieved.
Thyroid Patient Advocacy	Evidence Review E	5	17 - 18	Clearly here if a person remains well and on a stable dose they are not those that will need treatment with T3 or NDT yet these are the very subjects that are used in the trials chosen to illustrate that T3 or NDT do not work or is not necessary.	Thank you for your comment. The guideline has made a research recommendation to highlight the need for appropriate trials for this potential subgroup.
Thyroid Patient Advocacy	Evidence Review E	5	19 - 20	The whole basis of using these sort of biochemical population ranges is suspect as it is not possible to develop a reference range for a disease that is solely diagnosed using blood tests. No evidence that the ranges used by laboratories are developed accurately. Where the upper levels of the range should lie is subject to much argument and currently a patient is not considered to by hypothyroid when their TSH rises above the population reference range but only when they reach an arbitrary figure of 10 unless their FT4 and/or FT3 lie below the current laboratory population reference range. Little emphasis is put on	Thank you for your comment. This section serves as a chapter introduction. The importance of symptoms has been acknowledged by the committee and is reflected in the recommendations made that suggest repeating tests of thyroid function if symptoms worsen or new symptoms develop (1.2.9). Please note that central hypothyroidism and the administration of antidepressants are outside the scope of this guideline.

				symptoms at this point and in practice if blood hormone levels are within the population reference ranges then the possibility of hypothyroidism being the cause of symptoms will be dismissed and other causes sought. No thought is given to the possibility of central hypothyroidism or to individual set pints for thyroid hormones carrying from the population reference ranges. A trial of a therapeutic dose of thyroid hormone could also be used as a diagnostic tool. Antidepressants are handed out based on symptoms alone despite hypothyroidism being a leading cause of depression and anxiety.	
Thyroid Patient Advocacy	Evidence Review E	5	24	In table 1 in the section 'Population' 'people with primary hypothyroidism' How are these to be defined/diagnosed?	Thank you for your comment. This was not specified in the protocol in advance. In the studies identified, confirmation of diagnosis of primary hypothyroidism came from either measures of TSH, FT4 and FT3, occasionally TPO antibody testing, receiving treatment for hypothyroidism (e.g. with levothyroxine)/ LT4 replacement or not stated.
Thyroid Patient Advocacy	Evidence Review E	6	11 - 16	The use of subjects with various different causes of primary hypothyroidism makes the results of the studies less compelling. The various studies also used differing biochemical cut-offs for defining hypothyroidism and/or subclinical hypothyroidism. One study titrated dose on FT3 measurement which rendered the patients in the treatment group hypothyroid! This was not mentioned in the consideration of evidence. Most of the studies started with subjects who has been stable on Levothyroxine and these are not likely to belong to the subgroup who do not get well on Levothyroxine thus the subject population is not the one that should be studied.	Thank you for your comment. Considerations relative to the population included in this review were discussed by the committee who reviewed the evidence with caution and used their clinical expertise to make recommendations that reflect best clinical practice. The guideline has made a research recommendation to highlight the need for appropriate trials in the group of people who do not respond well to levothyroxine alone.
Thyroid Patient Advocacy	Evidence Review E	6	Table 1	Table 1 In Table 1 'Study design' This ignores evidence that RCTs are actually not really suitable for a number of reasons for investigating treatments for hypothyroidism. *Hoermann R,*	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an

				Midgley JEM, Larisch R, Dietrich JW. Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: have they achieved their objectives? J Thyr Res. 2018;2018:3239197.	intervention. Looking at RCTs ensures recommendations are based on the best available evidence. We do agree that RCTs come with limitations and may occasionally be of limited applicability to the current clinical practice setting. Within evidence reviews, RCTs are quality assessed rigorously. Their limitations are highlighted and impact the extent to which the committee's decision making is based on their findings.
Thyroid Patient Advocacy	Evidence Review E	6	3	Only 9 studies were included despite the many that are available. The criteria for studies was set so high that much useful information was excluded. RCTs are not the appropriate test method for thyroid diseases *Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: have they achieved their objectives? J Thyr Res. 2018;2018:3239197.* TPAUK also needs to be sure that the default position that ends up being recommended by the NICE draft guidelines is also subject to the same kind of scrutiny. *….no formal clinical trials have been performed to evaluate the current standard treatment against other treatment modalities such as the original use of natural desiccated thyroid extract (NDT) before that decision was made.* ***Hoermann R, Midgley J E M, Larisch R and Dietrich J W Lessons from Randomised Clinical Trials for Triiodothyronine Treatment of Hypothyroidism: Have They Achieved Their Objectives?*** *Journal of Thyroid Research* *Volume 2018, Article ID 3239197, 9 pages*	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. The criteria set for studies are to ensure that the best available evidence is identified to support the committee's decision making. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. Where RCT evidence was been available, the consideration of lower quality studies was not considered to further assist in decision making and where evidence meeting pre-specified standards has been limited, the committee have collectively used their clinical experience. Within the context of evidence reviews, RCTs are quality assessed rigorously and their limitations are highlighted and impact the extent to which the committee's decision making is based on their findings. It is not clear how a healthy control group would provide further information beyond the direct comparison of levothyroxine and combination therapy. The guideline has made a research recommendation to highlight the

				A control group was not used in any of the RCTs used as evidence here. *However, a healthy control group was lacking in virtually all combination trials. Neither dose adequacy for LT4 nor LT3/LT4 has been ascertained in the T3/T4 trials. It remains therefore unclear how much either treatment option was able to raise QoL outcomes, compared to a healthy population.* ***Hoermann R, Midgley J E M, Larisch R and Dietrich J W Lessons from Randomised Clinical Trials for Triiodothyronine Treatment of Hypothyroidism: Have They Achieved Their Objectives?*** *Journal of Thyroid Research* *Volume 2018, Article ID 3239197, 9 pages*	need for appropriate trials for the subgroup of people who do not respond to levothyroxine alone.
Thyroid Patient Advocacy	Evidence Review E	6	7	The terminology is difficult here. The term natural thyroid extract is not the exactly the same as Natural desiccated thyroid which is a prescription medicine whose quality is controlled (US Pharmacopaeia). Whilst all available NDTs are natural thyroid extracts, not all natural thyroid extracts are NDT as NDT refers to the licensed prescription medicines containing regulated doses of the active ingredients T4 and T3.	Thank you for your comment. This text is intended to be brief and introductory but much more detail on the exact components on the intervention is available in the appendix evidence tables.
Thyroid Patient Advocacy	Evidence Review E	6	17	A 3 month trial is not long enough for patients to get better.	Thank you for your comment. The committee acknowledge that three months constitute a short follow-up period and the potential implications of this have been discussed and taken into account in decision making.
Thyroid Patient Advocacy	Evidence Review E	7	9 - 12	3 Table 3 combining all the outcomes in this way is invalid because the methods were so different.	Thank you for your comment. The guideline has combined outcomes only when they have been measured on the same scale.
Thyroid Patient Advocacy	Evidence Review E	7	Table 2	Table 2	Thank you for your comment. Study limitations including previous treatment, limited follow-up and issues with

				Table 2 most studies use people previously receiving stable doses of T4 so the subjects are unlikely to be target population who might benefit from added T3 or NDT. Many potential non-subjective measurements of hypothyroidism were not included in the assessments for example cholesterol levels. Appelhof 2005 2 study arms usual dose -25 + enough T3 to make ratio of 10:1 or 5:1. Previously stable. Only 15 week study. Clyde 2003 calculated dose usual minus 50 +15 mcg T3. Previously stable. 4 month treatment. All patients were given one specific brand of Levothyroxine whether or not it was their usual brand. People taking 325mg/d of iron were excluded. Titration was by TSH to somewhere in the population reference range. Hoang 2013 Natural thyroid extract dose based on calculation from usual T4 dose. 4 month treatment cross over design Nygaard 2009 crossover study of 3 months on each treatment not very long when you consider it takes 6 weeks for T4 to stabilise! Previously stable and euthyroid. Roos 2005 high T4 starting dose or titrated dose. 12 month treatment Saravanan 2005 T4+T3 calculated dose with maximum of 10Ug T3. Previously stable. Only 3 months. Titrated dose by maintaining T3 levels which allowed TSH to rise and FT4 to fall in the group treated with T4/T3 combination. Not surprisingly found no differences although by conventional assessments they had made the intervention group more hypothyroid. They	dosing have been acknowledged by the committee and taken into account in decision making. Study reported outcomes meeting the review protocol only are included and quality assessed in light of the study limitations. Other measures, including cholesterol levels, that were not part of the protocol inclusion criteria that were agreed in advance have not been included. This is the standard approach taken in systematic reviews of evidence in order to focus decision making on prospectively agreed upon critical and important outcomes and minimise risk of bias. The subjective conclusions drawn by the included studies' authors are not part of the committee's decision making process.

				made assumptions on what were hyper or hypo thyroid symptoms in drop out cases. They mentioned that T3 levels were in the lower parts of the range at baselines. In sub group analysis those with the highest T3 at baseline *Division of free T3 values into quartiles revealed that patients with baseline free T3 in the highest quartile, approximately equivalent to the upper half of the reference range [>0.275 ng/dl (>4.27 pmol/liter), reference range, 0.18–0.457 ng/dl (2.8–7.1 pmol/liter)], responded best to the intervention* *Early studies suggested that TSH levels are more sensitive to T4 than T3 levels (29). Here, we confirm that this relationship holds true even with TSH levels in the laboratory reference range.* *In addition, TSH levels rose in response to a fall in T4 levels in the intervention group, even in the face of unchanged or probably higher T3 levels. This sensitivity of the pituitary/hypothalamic feedback to serum T4 and T3 explains how replacement with T4 alone can frequently achieve normal TSH levels with a combination of low T3 and high T4 levels as observed previously in smaller studies (9–11) and as seen in this study (Table 1). In addition, over a 9-month period, a significant fall in the T3 to T4 ratio was seen with no associated change in TSH (Fig. 4).* *In conclusion, data from this large community-based study do not provide conclusive evidence of specific benefit from partial substitution of T4 by T3 in patients on T4replacement.* TPAUK is really not sure how they come to this conclusion from the above statements!	

				Larisch R, Midgley JEM, Dietrich JW, Hoermann R. Symptomatic relief is related to serum free triiodothyronine concentrations during follow-up in levothyroxine-treated patients with differentiated thyroid cancer. Exp Clin Endocrinol Diabetes. 2018;126:546–52 Sawka 2003. Previously stable so wrong target group. T3 maximum of 25mcg adjusted for normal TSH. Only 15 weeks treatment Siegmund 2004 they assume that study subjects are still symptomatic when paper does not state this. Use 14:1 ratio and calculation of what people might need – not possible. 3 months treatment. Mostly surgery or RAI Valizadeh 2014 calculated dose not titrated only 4 months treatment.	
Thyroid Patient Advocacy	Evidence Review E	80	11	This should not say optimum dose because clearly if they still feel ill and have symptoms then the dose is not optimal for them. Better that it should say 'a dose that returns their hormone levels to within the population reference range'	Thank you for your comment. We agree and have edit this as suggested.
Thyroid Patient Advocacy	Evidence Review E	80	13	The inadequacies of the RCTs selected is admitted here. Therefore, although they may not show positive response to T4/T3 combination or NDT neither do they show a negative response therefore the situation should not be used to recommend that T4/T3 combination or NDT is not available for use in this sub group of patients. Why is this not explicitly stated in the main body of the text?	Thank you for your comment. All RCTs identified that met the criteria pre-specified in the review protocol were included in the review. In absence of sufficient evidence to support the effectiveness of the addition of T3 to T4 monotherapy, as well as its significantly higher cost, or of natural thyroid extract, the committee has also taken their clinical expertise into account while making recommendations, The committee was aware of evidence suggesting T4-T3 combination therapy could be harmful as it may suppress the production of TSH and agreed that it should not be routinely offered. With the long-term adverse events of natural thyroid extract

					also being uncertain and with it being unlicensed in the UK the committee agreed it should not be offered. The information you refer to aims to provide a rationale for the research recommendation and comes from the committee's clinical expertise rather than from the included studies or the committee's discussion of them, which is what is included in the main body of the review. Following NICE guidelines standard processes and evidence review templates, information relevant to research recommendations is provided in Appendix.
Thyroid Patient Advocacy	Evidence Review E	80	17	Why is this not included in the main body of the text but confined to an Appendix? Patients preferred the combination of T4/T3 or NDT.	Thank you for your comment. Please note that patient preference was not included in the pre-specified outcomes of the evidence review protocol and was therefore not looked for in the included studies or extracted in the main body of the review. Nevertheless, the committee was aware that patients may often prefer combination therapy and have taken this into consideration in prioritising a research recommendation in this area. Natural thyroid extract is currently unlicensed in the UK and therefore cannot be included in the research recommendations.
Thyroid Patient Advocacy	Evidence Review E	80	28	'*Whilst current national and international guidelines do not recommend routine use of T4-T3 combination in hypothyroidism, some of these guidelines suggest a trial of the combination therapy in some patients.* 'As no evidence shows that combinations therapies do or don't work the status quo should remain while high quality studies are performed . This would ensure continuity of care for the subset of patients who do not recover on T4 monotherapy.	Thank you for your comment. In light of evidence suggesting that despite being significantly more expensive, the addition of liothyronine does not offer any additional health benefit compared to levothyroxine monotherapy and evidence suggesting it could be harmful as it may supress the production of TSH, the committee agreed it should not be routinely offered.
Thyroid Patient Advocacy	Evidence Review E	80	38	*PICO question* needs to be *'Intervention(s): combinations of T4 and T3 (sustained release) and Natural Desiccated Thyroid (NDT)'* as NDT was one of the trial treatments that was preferred by participants in one study and is a sustained	Thank you for your comment. The committee decided to make a recommendation for future research to examine the effectiveness of T4 and T3 combination therapy compared to T4 monotherapy. Natural thyroid extract is

				release product. Mention should be made of realistic doses here too. In *Importance to patients or populations* the last sentence *'reducing the economic burden to the NHS. If the combination.…'* needs to be removed as this is not relevant to the patients or populations and is biased. Liothyronine is not costly in other European countries and is subject to a C&MA case in the UK at the moment. In *National Priorities 'A RCT would support national evidence based approach to the treatment of hypothyroidism'* – consideration needs to be given to the research that shows that RCTs may not be an appropriate tool for use in the treatment of hypothyroidism. *Time for a reassessment of the treatment of hypothyroidism Midgley et al. BMC Endocrine Disorders (2019) 19:37 https://doi.org/10.1186/s12902-019-0365-4* In *Current evidence base* – although the studies may *'have failed to show clear evidence of the benefit of the combination therapy'* they have also failed to show a clear lack of benefit. In *Study design ' Randomised controlled trial with corresponding health economic analysis'*. Again consideration needs to be given to the research that shows that RCTs may not be an appropriate tool for use in the treatment of hypothyroidism. *Time for a reassessment of the treatment of hypothyroidism Midgley et al. BMC Endocrine Disorders (2019) 19:37 https://doi.org/10.1186/s12902-019-0365-4*	not currently licensed in the UK and therefore cannot be included in the recommendations for future research. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. We are aware of differences in the cost of liothyronine across different countries; however this guideline is applicable to the UK setting.

				In *Feasibility* second sentence implies that T4/T3 combination previously used or NDT are unsuitable with no apparent evidence. Both T4/T3 and NDT are used successfully by patients. NDT is a sustained release preparation.	
Thyroid Patient Advocacy	Evidence Review E	82	General	In *Importance 'The guidelines are unable to provide clear recommendations for T4-T3 combination therapy for people with hypothyroidism due to a lack of sufficient evidence'*. Clearly this is also true in reverse that the guidelines are unable to provide clear recommendations against T4-T3 combinations either so that there should be no recommendation against their use at this time.	Thank you for your comment. This sentence has been amended to clarify the uncertainty is in the specific population who have not responded well to levothyroxine.
Thyroid Patient Advocacy	Evidence Review F	11	2 and 23	No relevant economic statements were identified which rather undermines the whole document because we cannot be clear about the long-term economic benefits because we cannot weigh the costs of monitoring against the costs of the disease if it is poorly monitored to the NHS and to the patient. The committee did state that (page 15 line 19)early detection of uncontrolled thyroid disease should improve treatment, survival time and QoL…	Thank you for your comment. In the absence of economic evidence, unit costs are presented to the committee to aid in decision making along the clinical evidence. The only available evidence in this review related to the comparison of aiming for a low-normal TSH target or a high-normal TSH target and no clinically important difference between these options for quality of life was found. Therefore, it is difficult to find the cost saving or impact between the tests as the clinical benefits are unclear. The recommendations are based on expert consensus.
Thyroid Patient Advocacy	Evidence Review F	11	25	Statements F1 is random and unsupported. What relevance does it have here?	Thank you for your comment. This was a formatting error and has been amended.
Thyroid Patient Advocacy	Evidence Review F	11	28	Statement F2 is random and unsupported. What relevance does it have here?	Thank you for your comment. This was a formatting error and has been amended.
Thyroid Patient Advocacy	Evidence Review F	12	4 - 7	This is muddled due to inclusion of all the different problems in one here. It would benefit from separating out at least into hypothyroidism and thyrotoxicosis.	Thank you for your comment. The committee agreed that the critical outcomes should be the same for all thyroid disease. Had we found evidence related to each condition then these would have been discussed separately here.

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Thyroid Patient Advocacy	Evidence Review F	12	11	Why is TSH suppression important? References needed. TSH suppression in T4 treated people with FT4 and FT3 within the population reference ranges is not thought to carry the same risk as TSH suppression caused by thyrotoxicosis.	Thank you for your comment. While TSH suppression caused by thyrotoxicosis may have differing effects to that caused by treatment, the committee agreed based on their experience and awareness of the evidence in the subject area that it remained an important outcome to consider.
Thyroid Patient Advocacy	Evidence Review F	12	23	No clinical evidence was identified.	Thank you for your comment. The committee agree that it is disappointing there is no evidence to guide recommendations in this area.
Thyroid Patient Advocacy	Evidence Review F	12	30 - 32	The committee made recommendations but based on no evidence.	Thank you for your comment. In areas where no clinical evidence was identified, the committee members used their collective experience to make consensus recommendations.
Thyroid Patient Advocacy	Evidence Review F	12	33	Order of presentation is changed again here which is confusing. Earlier it was hypothyroidism then thyrotoxicosis!	Thank you for your comment. We have made this more consistent.
Thyroid Patient Advocacy	Evidence Review F	12	34	Monitoring Trabs needs to be mentioned here.	Thank you for your comment. The committee agreed that testing antibody levels would not further assist in monitoring patients. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The committee and scoping exercise did not identify using TRAbs to predict remission on antithyroid drugs as a priority area, therefore no review was done of this evidence and the committee could not make specific recommendations on this topic.
Thyroid Patient Advocacy	Evidence Review F	13	10	*The committee noted that reference ranges are ranges and that for each individual person there will be variability as to what exact TSH targets are most appropriate for them.* This sentence needs to be borne in mind and repeated throughout all the evidence reviews!!	Thank you for your comment. The implications of this have been discussed by the committee and recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being.
Thyroid Patient Advocacy	Evidence Review F	13	17	This should say 'FT4 and FT3' rather than 'FT4 or FT3'	Thank you for your suggestion. This has been amended.

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Thyroid Patient Advocacy	Evidence Review F	13	18	An impact on resources might be a good investment if it led to improved health of hypothyroid patients.	Thank you for your comment. If there was convincing evidence or consensus of a likely benefit of sufficient magnitude to warrant the investment, the committee would incorporate this in their recommendations.
Thyroid Patient Advocacy	Evidence Review F	13	21	It should be possible to monitor FT3 in primary care if necessary since low FT3 is more closely linked with symptoms (*Larisch R, Midgley JEM, Dietrich JW and Hoermann R, Symptomatic Relief is Related to Serum Free Triiodothyronine Concentrations during Follow-up in Levothyroxine-Treated Patients with Differentiated Thyroid Cancer. Exp Clin Endocrinol Diabetes. 2018 Sep;126(9):546-552.*) and it is informative to be able order TSH, FT4 and FT3 as the relationship between these parameters can be instructive.	Thank you for your comment. The committee agreed that measuring FT4 should be considered in addition to TSH for monitoring of people who continue to have symptoms of hypothyroidism, but that FT3 would not inform monitoring further. The study you reference is specifically in patients following thyroid cancer treatment and therefore does not meet the inclusion criteria for the review.
Thyroid Patient Advocacy	Evidence Review F	13	23 - 25	dose should be titrated to symptoms (which are most likely to equate to T3 levels) not to some arbitrary level or population reference range.	Thank you for your comment. The committee acknowledges that individuals may differ in the TSH targets that are most appropriate for them and recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being.
Thyroid Patient Advocacy	Evidence Review F	13	26	This is a bias in assuming that the patient is not adhering to treatment. It should say that *'FT4 can be a marker of adherence or absorption problems'.*	Thank you for your comment. The committee does not assume that patients do not adhere to treatment but raise that they are aware this may be the case for certain people, in which case FT4 would be informative. This sentence is specifically describing the situation for people who struggle with compliance.
Thyroid Patient Advocacy	Evidence Review F	13	28	subclinical disease is only subclinical if it remains symptom free. Again, we need to include a reference to symptoms here as, particularly with hypothyroidism, there has been a transition away from using symptoms to relying only on blood test for diagnosis. This risks leaving a potentially substantial number of people undiagnosed.	Thank you for your comment. The definition of subclinical disease does not relate to the presence or absence of symptoms; please see the glossary for further details.

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Thyroid Patient Advocacy	Evidence Review F	14	16	*…current practice TFTs including Trabs should be repeated…* Also is dose of treatment not titrated when using anti thyroid medications?	Thank you for your comment. This section discusses the benefits and harms of the evidence included in the review. Monitoring with TRABs was not included in this review.
Thyroid Patient Advocacy	Evidence Review F	14	17 - 18	Relying solely on a TSH test assumes that the pituitary hypothalamic axis has not been reset by exposure to high levels of thyroid hormones. TSH is an unreliable proxy.	Thank you for your comment. The committee agree that TSH alone will only become suitable as a monitoring option in thyrotoxicosis after acute changes following treatment have settled; this is reflected in the recommendations.
Thyroid Patient Advocacy	Evidence Review F	14	21	Why is RAI being recommended as first line of treatment for thyrotoxicosis surely a patient should be allowed to try for remission using anti thyroid drugs first unless the belong to the small and very specific groups of people for whom remission is unlikely (although even then should the patient not be involved with this decision)? Replacing one disease with another, lifelong condition that has great dissatisfaction with its treatment does not seem like a choice that should be made on the cost to the NHS and ease of use by doctors.	Thank you for your comment. The committee discussed this in great detail and a recommendation linking to the shared decision making in NICE's guideline on Patient Experience in adult NHS service, has been added (rec 1.6.7) to highlight the importance of patient choice. In addition, a further recommendation has been added, please see recommendation 1.6.8 which offers anti-thyroid drugs to patients to stabilise their condition before (and if necessary) after treatment. Please also refer to chapter I, for the full explanation of how the committee come to recommend RAI as first line treatment.
Thyroid Patient Advocacy	Evidence Review F	14	22	Hypothyroidism is not a side effect it is a lifelong disease at least as unpleasant and life changing as thyrotoxicosis, with its own risks and consequences. It is not currently well managed. Presenting it as a side effect in this way is a bias!	Thank you. We have amended the wording for greater clarification, this now reads as 'This is because RAI was being recommended as first line treatment for thyrotoxicosis which can render them hypothyroid'.
Thyroid Patient Advocacy	Evidence Review F	14	24	See comment under line 22. Hypothyroidism should not be referred to as a side effect!	Thank you. We have amended the wording for greater clarification (from side effect to render them hypothyroid).
Thyroid Patient Advocacy	Evidence Review F	14	26	See comments for lines 22 and 24 above	Thank you. We have amended the wording for greater clarification (from side effect to render them hypothyroid).

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Thyroid Patient Advocacy	Evidence Review F	14	27	Thought should be given to the proportion of hypothyroid people who are dissatisfied with their treatment. There is some evidence that those without any remaining thyroid fare even worse on Levothyroxine than the general population of hypothyroid people.	Thank you for your comment. The committee did consider the impact of hypothyroidism when making decisions about treatment.
Thyroid Patient Advocacy	Evidence Review F	14	32	RAI may be more cost effective for the NHS but has massively underestimated consequences for the individual in that it is likely to render them hypothyroid so with another life changing disease. RAI should not be first line treatment for thyrotoxicosis except in those cases where remission using antithyroid drugs, or surgery is not possible. Why is block and replace not covered here?	Thank you for your comment. The committee discussed this in great detail and a recommendation linking to the shared decision making in NICE's guideline on Patient Experience in adult NHS service, has been added (rec 1.6.7) to highlight the importance of patient choice. In addition, a further recommendation has been added, please see recommendation 1.6.8 which offers anti-thyroid drugs to patients to stabilise their condition before (and if necessary) after treatment. The economic evidence showed that radioactive iodine offered a better balance of benefits and costs than surgery (total thyroidectomy) and was more cost effective than antithyroid drugs. The economic evaluation captured the key adverse events such as hypothyroidism. The evidence suggests that RAI leads to more people ending up in hypothyroid state as opposed to euthyroid, but the committee was aware of some evidence (not the focus of this review) that long-term cardiovascular outcomes for people who achieve hypothyroidism after radioactive iodine are better than for those who are euthyroid. The committee noted that current guidance by other groups is to aim for hypothyroidism when using radioactive iodine. Please also refer to chapter I, for the full explanation of how the committee come to recommend RAI as first line treatment. Block and replace treatment was considered for the treatment of thyrotoxicosis where the monitoring should vary depending on the treatment received i.e.

					titrated vs block and replace. This is also considered in chapter J.
Thyroid Patient Advocacy	Evidence Review F	14	36 - 38	The committee should emphasise the importance of offering replacement thyroid hormones after a total thyroidectomy not because it will reduce the need for monitoring but because the person without a thyroid will die if they do not take replacement hormones. There is evidence that those without thyroids do not do so well on levothyroxine alone as they are missing the 20% of T3 that is produced by the thyroid gland itself.	Thank you. We have amended the wording for greater clarification. This now reads 'Surgery – the group emphasised the importance of offering levothyroxine to people who have had total thyroidectomy, to replace the thyroxine that was produced by the thyroid gland which in turn will reduce the need for monitoring.'
Thyroid Patient Advocacy	Evidence Review F	14	39	People with a subtotal thyroidectomy also need to be monitored as there is a risk of developing hypothyroidism and monitoring could help with detection , hence earlier treatment and better quality of life in addition to reductions costs due to untreated hypothyroidism.	Thank you. We have amended the wording for greater clarification. This now reads 'Furthermore, People who have had subtotal thyroidectomy are at risk of thyrotoxicosis recurring or developing hypothyroidism and monitoring could help with early detection, hence earlier treatment improving quality of life in addition to reducing costs of complication associated with untreated thyrotoxicosis and hypothyroidism and mortality.'
Thyroid Patient Advocacy	Evidence Review F	14	43	Trab monitoring should be included here as declining antibody levels help detects likelihood of remission	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The committee and scoping exercise did not identify using TRAbs to predict remission on antithyroid drugs as a priority area, therefore no review was done of this evidence and the committee could not make specific recommendations on this topic.
Thyroid Patient Advocacy	Evidence Review F	15	5	A population reference range is not a normal range. In this section there is no reference to symptoms only to maintaining TSH within a population reference range. Having TSH within a population reference range does not equate to having no symptoms and being well. There is evidence now that symptoms are related to FT3 levels and that when treated with Levothyroxine FT3 levels are lower than in a healthy	Thank you for your comment. In light of the point you raise recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being.

				population for a given TSH or FT4. Even one of the RCTs (Saravan et al, 2005) included in Evidence Review [E] showed that if FT3 levels were maintained symptoms did not increase even though TSH levels rose and FT4 fell.	
Thyroid Patient Advocacy	Evidence Review F	15	6	This is inconsistent with what was said at line 10 page 13 Evidence Review [F]. *The committee noted that reference ranges are ranges and that for each individual person 11 there will be variability as to what exact TSH targets are most appropriate for them.*	Thank you for your comment. This line describes the identified evidence which supports a default position of aiming for within the reference range as a starting point. The recommendations have been amended to make the committee's stance on titration within the reference range (i.e. dose adjustment may be appropriate in response to symptoms) clearer.
Thyroid Patient Advocacy	Evidence Review F	15	11	Currently testing takes place 5-6 weeks after a dose change to allow time for the hormone levels to stabilise.	Thank you for your comment.
Thyroid Patient Advocacy	Evidence Review F	15	12	Replace *'normalise'* with *'to get TSH into population reference range'.*	Thank you for your suggestion. This has been amended.
Thyroid Patient Advocacy	Evidence Review F	15	17	This sentence would be less biased if it said *'The committee noted that practitioners should only test FT4 (and here is should add 'and FT3') if the patient continues to experience symptoms.*	Thank you for your suggestion. The sentence has been edited. There was agreement among the committee that FT3 measurements are not helpful in the management of either subclinical or overt hypothyroidism.
Thyroid Patient Advocacy	Evidence Review F	15	44	In people with symptoms and subclinical hypothyroidism consideration should be given to testing TPO and Tg antibodies and FT3 levels as both these parameters can offer an explanation for symptoms. Symptomatic patients could also be offered a trial of a therapeutic dose of thyroid hormones which would then need monitoring.	Thank you for your comment. The points you raise have been carefully considered by the committee who has updated the recommendations on managing people with subclinical hypothyroidism to include the measurement of TPO antibodies (recommendation 1.5.1). The committee agrees with you and has considered that a trial of levothyroxine would be appropriate for symptomatic adults under 65 whose TSH is above the reference range but under 10 mIU/L, which as you raise should then be monitored (recommendation 1.5.4).
Thyroid Patient Advocacy	Evidence Review F	4	1	The categorisation here is illogical, surely it would be better to keep subclinical hypothyroidism linked to hypothyroidism and subclincal thyrotoxicosis linked to thyrotoxicosis. Also in 1.1 the review question is 'How should non-malignant thyroid	Thank you for your comment. The titles of this section have been changed.

				enlargement, hypothyroidism, thyrotoxicosis and subclinical thyroid dysfunction be monitored? Yet in the Introduction 1.2 we have Hypothyroidism, Thyrotoxicosis, Subclinical thyroid function and Nodule monitoring.	
Thyroid Patient Advocacy	Evidence Review F	6	7	Where is this 2% figure for prevalence of hypothyroidism derived from? A reference is needed There are other perfectly valid estimates that put the prevalence much higher. This is important because the difference between the two estimates is over a million of people in the UK alone. In 1.2.2 below it mentions primary and central thyrotoxicosis. To be consistent at least primary and central hypothyroidism need to be mentioned here too, and preferably poor T4 to T3 conversion and thyroid hormone resistance as well. Recent research shows that thyroid hormone resistance can be inheritable. ***Pakkila F et al. Maternal Thyroid Dysfunction During Pregnancy and Thyroid Function of Her Child in Adolescence*** *J Clin Endocrinol Metab. 2013 Mar; 98(3): 965–972.* *Anselmo et al, Reduced Sensitivity to Thyroid Hormone as a Transgenerational Epigenetic Marker Transmitted Along the Human Male Line, Thyroid Vol. 29, No.6* https://doi.org/10.1089/thy.2019.0080	Thank you for your comment and for providing this information. This figure is based on the committee's clinical expertise and on numbers quoted by other organisations. Please note that this section serves as a chapter introduction and that central hypothyroidism is outside the scope of this guideline, which aims to provide general guidance relevant to the majority of patients and cannot cover every scenario such as poor T4 to T3 conversion and thyroid hormone resistance.
Thyroid Patient Advocacy	Evidence Review F	6	13	Standardisation should not be to the lowest common denominator as this will leave many patients much worse off, so guidelines need to be flexible enough to allow all patients to get optimal treatment for their individual case.	Thank you for your comment. The committee agrees with the point you raise. Please note that the aim of the recommendations is to provide guidance for clinicians on what constitutes best clinical practice and does not replace their clinical judgment in the management of

					patients according to their individual characteristics and needs.
Thyroid Patient Advocacy	Evidence Review F	6	15	But these patient groups will go on expressing dissatisfaction if the guidelines are so restrictive as to stop flexibility of approach in both primary and secondary care.	Thank you for your comment. The aim of the recommendations is to provide guidance for clinicians on what constitutes best clinical practice and does not replace their clinical judgment in the management of patients according to their individual characteristics and needs.
Thyroid Patient Advocacy	Evidence Review F	6	29	Current practice should include monitoring of Trab levels in patients with Graves' disease because declining levels of Tr antibodies can give information on how likely the patient will be to achieve remission.	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The committee and scoping exercise did not identify using TRAbs to predict remission on antithyroid drugs as a priority area, therefore no review was done of this evidence and the committee could not make specific recommendations on this topic.
Thyroid Patient Advocacy	Evidence Review F	6	36	Patients who have been rendered hypothyroid after surgery or RAI seem to be one of the groups that do better with NDT.	Thank you for your comment. With natural thyroid extract being unlicensed in the UK, with a lack of sufficient evidence to support its effectiveness over levothyroxine and with its long-term adverse events being uncertain the committee agreed it should not be offered as treatment for hypothyroidism.
Thyroid Patient Advocacy	Evidence Review F	6	38	These need to be divided up in to SCH and STX	Thank you for your suggestion. This was not considered necessary.
Thyroid Patient Advocacy	Evidence Review F	6	41	Again there is absolutely no reference to symptoms here. A disease ceases to be subclinical if the patient is suffering symptoms. Diagnosis by blood test is one of the things most complained about by patient groups especially for those with SCH. Population reference ranges do not allow for a disease that is currently entirely diagnosed by blood tests cannot be reliable.	Thank you for your comment. The committee is confident of their definition of subclinical hypothyroidism and has considered the importance of symptoms. Please see recommendation 1.5.4 suggesting a therapeutic trial for people with SCH who have symptoms and a TSH above the reference range but lower than 10 mIU/L. The committee agrees that blood tests provide the most accurate method of diagnosis of thyroid disease.

Thyroid disease

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Thyroid Patient Advocacy	Evidence Review F	7	6	A trial of a therapeutic level of thyroid hormone in those patients with apparent SCH who are suffering symptoms should be considered.	Thank you for your comment. This has been considered by the committee. Please see recommendation 1.5.4
Thyroid Patient Advocacy	Evidence Review F	7	16	Some patients with nodules suffer from symptoms of hypothyroidism despite having hormone levels within the population reference ranges.	Thank you for your comment. If people have nodules and hypothyroidism, their hypothyroidism should be treated.
Thyroid Patient Advocacy	Evidence Review F	7	21	Consideration should be given to patients with nodules who suffer symptoms of hypothyroidism.	Thank you for your comment. If people have nodules and hypothyroidism, their hypothyroidism should be treated.
Thyroid Patient Advocacy	Evidence Review F	9	2 in Table 2	2 In Table 2 Samuels et al. Although this was a RCT it contained no control group of healthy subjects so treatment arms were compared to each other but not to how a healthy person would be. Patients were all stable on Levothyroxine before study so might be expected to respond well to the treatment. And in fact FT3 levels remained stable despite lower levels of FT4 in two of the treatment groups because TSH rose. Rising TSH not only stimulates production by the thyroid gland but also increases rate of conversion of FT4 to FT3. However, without the presence of a healthy untreated control it is not possible to say whether FT3 levels are equivalent to that found in healthy subjects and evidence elsewhere shows conclusively that FT3 is lower in T4 treated patients than in healthy controls. We also have no idea how healthy controls would have done in all the tests to measure QoL, mood and cognition. Thus, we could be comparing three kinds of bad and does not actually reveal whether TSH is useful for monitoring hypothyroidism or subclinical hypothyroidism.	Thank you for your comment. A RCT involving a comparison with a control group of healthy subjects was not identified. As per all evidence reviews, the limitations of the included study were reviewed by the committee who was able to employ their clinical expertise in decision making. This study was considered informative in comparing the two strategies included.
Thyroid Patient Advocacy	Evidence Review G	15	3	No relevant economic studies were identified	Thank you for your comment. The committee have used their judgment and experience to make recommendations that are cost effective in the absence of economic evidence.

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Thyroid Patient Advocacy	Evidence Review G	16	37	Levothyroxine versus placebo in adults – These studies were flawed in that the treatments did not include a healthy control.	Thank you for your comment. The included studies have limitations, and this is acknowledged. However, it is not clear how a healthy control group would truly have assisted decision making over a well conducted RCT comparing levothyroxine with placebo.
Thyroid Patient Advocacy	Evidence Review G	17	15	Where is the evidence for 'current UK practice (100ug/d). 100ug/d is a starting dose which is then titrated.	Thank you for your comment. This has been clarified.
Thyroid Patient Advocacy	Evidence Review G	17	21 - 25	*It was raised that an overreliance on TSH levels in decision making about treatment that is 22 most often the case in clinical practice may be problematic, and that other factors, including 23 patients' symptomatology are to influence their need for treatment. The committee felt that a 24 trial period of treatment of 6 months would be appropriate for symptomatic patients with TSH 25 lower than the 10 cut-off.* Surely this underlies the whole set of documents and needs to be repeated in every section to do with the diagnosis and treatment of hypothyroidism and SCH.	Thank you for your comment. The same principles have not been considered to apply to the diagnosis and management of people with hypothyroidism. The importance of symptoms was however, revisited by the committee and recommendation 1.4.1 relevant to hypothyroidism has been amended to suggest adjusting the dose of treatment if symptoms persist to achieve optimal well-being.
Thyroid Patient Advocacy	Evidence Review G	17	24	This should say *'The committee felt that a trial period of treatment titrated to a therapeutic dose that removed symptoms… '* It is fundamentally important that the dose is titrated to see if symptoms abate (or at least lessen bearing in mind that it is a 6 month trial). Dose response is not linear in that symptoms may not lessen or abate until an optimal dose has been reached.	Thank you for your comment. This is reflected in the recommendations where dose of levothyroxine is titrated if no change in symptoms. However, it is not appropriate to recommend treating to a dose that removes symptoms as it is possible symptoms are not thyroid related and therefore not amenable to treatment.
Thyroid Patient Advocacy	Evidence Review G	17	28 - 29	*There was agreement that whether or not TSH returns to normal is a factor indicating the success of treatment but that symptoms are also important.* And this. As has been drawn attention to in earlier parts of the document there are many things that can confound the proper	Thank you for your comment. The committee agree and this is reflected in the recommendations.

				response of the TSH which means that it cannot be used uncritically as an indicator of health.	
Thyroid Patient Advocacy	Evidence Review G	17	35	The study was flawed in that it did not include a healthy control.	Thank you for your comment. The included studies have limitations, and this is acknowledged. However, it is not clear how a healthy control group would truly have assisted decision making over a well conducted RCT comparing levothyroxine with placebo.
Thyroid Patient Advocacy	Evidence Review G	18	5	These studies did not compare the treated subjects with healthy adults, so no measure of how successful levothyroxine is in relieving the symptoms of hypothyroidism are assessable.	Thank you for your comment. We do not believe that comparison with healthy subjects would be the best way of assessing effectiveness. In particular it would be difficult to control for confounding.
Thyroid Patient Advocacy	Evidence Review G	18	7 - 9	This sentence does not make sense. *Overall, better targeting whom gets treatment 8 compared to what is currently done, people getting treatment according to their TSH levels, 9 is likely to be cost saving.* And also appears to contradict what is said on page 17 lines 21-25 and 28-29.	Thank you. We have amended the wording for greater clarification. This now reads 'Overall, treating symptomatic patients compared to treating patients according to their TSH levels only, is likely to be cost saving.'
Thyroid Patient Advocacy	Evidence Review G	18	14 - 16	Why is the assumption made that 100mcg of Levothyroxine is an appropriate or suitable dose for reach individual? Doses need to be titrated to remove symptoms. 100mcg might be a suitable dose from which to start titration in many individuals but a rough calculation can be made from weight (is it 1.6mcg/kg?)	Thank you for your comment. Doses may well be adjusted after initiation as for treatment of clinical hypothyroidism; this starting dose is noted for costing purposes.
Thyroid Patient Advocacy	Evidence Review G	18	18 - 20	The committee goes against what is said in lines 21-25 and 28-29 of page 17 where it was noted that too much reliance was placed on TSH levels and not enough on symptoms.	Thank you for your comment. The importance of symptoms in the treatment of people with subclinical hypothyroidism is acknowledged by the committee and has now been reflected in the recommendations (1.5.2 to 1.5.10). However just because symptoms are also relevant does not mean that TSH level is irrelevant.

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Thyroid Patient Advocacy	Evidence Review G	5	5	SCH is a construct of dubious relevance. Understanding the relationship between TSH, FT4 and FT3 explains what is happening when the TSH rises. TSH stimulates both production of hormones from the thyroid gland and the conversion of T4 to T3 so should rise when hormone levels fall in order to maintain the hormones at the set point for the individual. If this happens successfully, they the person should not suffer symptoms however when symptoms occur it indicates that the process is unable to respond sufficiently to individual needs wherever the hormones are in the population reference range. The situation ceases to be subclinical if the patient is suffering symptoms. Symptoms need to be paramount. TPO and Tg antibodies are relevant here too. It is a 95% population reference range and should not be referred to as a normal range. The validity of this range is debatable as covered in earlier sections.	Thank you for your comment. The committee is confident of their definition of subclinical hypothyroidism and acknowledge the relevance of antibodies for subclinical hypothyroidism. The recommendations on measuring antibodies in people with confirmed primary hypothyroidism (1.3.1) have now been applied to people with subclinical hypothyroidism (see new recommendation 1.5.1). 'Normal range' has now been amended to 'reference range' in the evidence review.
Thyroid Patient Advocacy	Evidence Review G	5	15 - 16	If there is uncertainty as to whether people with 'SCH' will benefit from increasing their circulating thyroid hormones with replacement therapy, then a trial of thyroid hormone titrated to a therapeutic dose would offer a logical resolution.	Thank you for your comment. The aim of this review was to explore the effectiveness of treatment for people with sub-clinical hypothyroidism and resolve this uncertainty. A 6-month trial of levothyroxine was considered appropriate for adults with a TSH above the reference range who experience symptoms, and this is reflected in the recommendations. Doses may well be adjusted after initiation as for treatment of clinical hypothyroidism. This is reflected in the recommendations where dose of levothyroxine is titrated if no change in symptoms.
Thyroid Patient Advocacy	Evidence Review G	5	17	Before blood tests were used hypothyroidism was diagnosed successfully on symptoms.	Thank you for your comment. The committee acknowledges that symptoms are to be taken into account in the diagnosis and treatment and the wording

					of the recommendation on treatment for subclinical hypothyroidism (1.5.2) has been amended to reflect this.
Thyroid Patient Advocacy	Evidence Review G	5	23	Table 1 population no such thing as a context specific normal range exists. It is possibly a context specific 95% population reference range!	Thank you for your comment. The term 'normal' range has been amended to 'reference range'.
Thyroid Patient Advocacy	Evidence Review G	6	8	All 6 RCTs compared T4 with placebo. There needs to have been a healthy control to see what you are actually hoping to return subjects to. There is an implicit assumption that T4 is good in these studies.	Thank you for your comment. Comparison with a healthy control group was not considered to further assist the investigation of this review questions and the review population was a-priori set to be people diagnosed with subclinical hypothyroidism. RCTs comparing T4 with placebo are the most informative study design for determining whether or not T4 has a benefit, there is no assumption that it is beneficial.
Thyroid Patient Advocacy	Evidence Review G	65	9	A reference is needed for the statement that 1% of people less than 70 years of age suffering from SCH.	Thank you for your comment. This is based on the committee's clinical expertise.
Thyroid Patient Advocacy	Evidence Review G	65	10	A reference needed for the large observational study mentioned here.	Thank you for your comment. This is based on the committee's clinical expertise and its aim is to provide a brief introduction to the research recommendation.
Thyroid Patient Advocacy	Evidence Review G	65	22	*What remains unknown is whether symptomatic individuals with SCH aged regular replacement doses of thyroid hormones.* Change levothyroxine to thyroid hormones here as we don't actually know if levothyroxine returns people to good health.	Thank you for your comment. The committee has agreed that a recommendation for future research on the clinical and cost-effectiveness of levothyroxine in particular for the populations specified should be prioritised
Thyroid Patient Advocacy	Evidence Review G	65	27	*PICO question :* *Intervention ~1.0mcg/Kg/day; short duration –(?1 yr) for QoL 5 years for major cardiac events (MACE).* How has this dose of Levothyroxine been chosen? Why is it lower than the 1.6mcg/kg/day usually used for roughly estimating dose for hypothyroidism? There is no evidence that a full replacement dose is not needed in SCH. Also after the initial dose the dose is titrated to remove symptoms. An untitrated dose risks being under (or over) treatment.	Thank you for your comment. The details in this PICO as it stands are based on the committee's experience and consensus, supplemented with what evidence was identified in the review. The aim of the research question is to assess the effectiveness of levothyroxine in adults aged 50 to 70 years with persistent subclinical hypothyroidism. The committee believe that starting levothyroxine at a lower dose in milder hypothyroidism and not the full

				Comparison: placebo The comparison should also include healthy control to see if Levothyroxine returns hypothyroid sufferers to real QoL *Study Design : A*gain why is a lower dose chosen and where is the recommendation that dose needs to be titrated to raise T3 levels.	1.6mcg/kg dose would be of benefit to people with subclinical hypothyroidism. However, in the absence of evidence they have made a research recommendation in the hope of answering this question. The committee believe that FT3 measurements are not helpful in the management of either subclinical or overt hypothyroidism. Comparing the intervention to healthy controls would not answer the question on whether the specified dose is the correct one for people with subclinical hypothyroidism. Therefore, the population needs to be the same in both the intervention group and the control group. With research questions, the committee proposes their thoughts on the PICO. If NIHR decides to proceed with this research recommendation, the details of the trial including the appropriateness of all factors, including the intervention doses will be carefully re-discussed.
Thyroid Patient Advocacy	Evidence Review G	65 - 66	27	At the end of the table started at line 27 on page 65 labelled *Importance: The guidelines are unable to provide clear recommendations for levothyroxine treatment for symptomatic people with SCH due to a lack of sufficient evidence.* By the same lack of sufficient evidence the guidelines also cannot recommend that people are not treated due to lack of evidence.	Thank you for your comment. The circumstances under which people with subclinical hypothyroidism should be offered treatment have been specified in the recommendations (1.5.2 to 1.5.6) and the committee is confident they reflect best clinical practice. The committee agree that with further information the recommendations both on when to treat and when not to treat could be strengthened.
Thyroid Patient Advocacy	Evidence Review G	67	27	There is bias here in the paragraph labelled *Importance* (at the end of the table) which is not supported by the rest of the document. TPAUK makes the strong suggestion that the following sentence is deleted as it is unnecessary.	Thank you for your suggestion. The committee overall consider this to be an area worthy of further research but agree it is a low importance research recommendation based on the lack of available evidence suggesting even conventionally effective treatments (e.g. levothyroxine).

				'However existing evidence suggests that treatment of SCH in general with conventional treatments like Levothyroxine, does not result in clinically important benefits for most people.'	The sentence you flag makes this point. These are however relative statements and the committee would still welcome further research in this area.
Thyroid Patient Advocacy	Evidence Review G	7	2 in Table 2	2 In Table 2 Kong 2002 ascorbic acid is vitamin C and could have an effect in its own right. Post treatment TSH differed between placebo and treatment groups. Very small only 23 women in treatment group(50-100mcg) and 17 in placebo. No explanation for how treatment dose was chosen Meier 2001 Najafi 2015 Razvi 2007 Only 3 months. Reuters 2012 How can placebo dose be adjusted by TSH levels? Placebo dose would just go on increasing. Stott 2017 50mcg or 25mcg if body weight <50kg or known coronary heart disease titrated to TSH level but mean TSH was only 3.63 mIU and mean dose 50mcg in treatment group. Definition of SCH TSH up to 19.99 if FT4 in population reference range.	Information in Table 2 has been extracted as reported in the studies. Limitations and issues associated with the studies, including follow-up, sample size and dosing have impacted their quality assessment and have been taken into account in decision making.
Thyroid Patient Advocacy	Evidence Review H	10	9	Table 2: Summary of studies included in the evidence review Sulman 1990 Only abstract was available. The efficacy of the current TRAB test cannot be judged according to data from 1990	Thank you for your comment. The evidence is selected based on pre-specified inclusion criteria that can be found in Appendix A of each evidence review. These criteria have been set in order to ensure the best available evidence is identified. In this situation the committee did not consider cut-offs based on the age of evidence to be appropriate but did take into account the recency of studies in their decision making.

					The extent to which decision making is then based on the evidence presented in the review depends on the quality assessment of the evidence and the committee's clinical expertise and knowledge.
Thyroid Patient Advocacy	Evidence Review H	10	9	Table 2: Summary of studies included in the evidence review Syme 2011 Again only an abstract was available for review. The abstract, however, does seem to support the utility of TRAB testing for determining if Grave's disease is present	Thank you for your comment.
Thyroid Patient Advocacy	Evidence Review H	10	9	Table 2: Summary of studies included in the evidence review Theodoraki 2011 "The assay studied specifically identifies patients with Graves' disease. It is a reliable tool in the initial clinical assessment to determine the aetiology of hyperthyroidism and has the potential for cost-savings"	Thank you for your comment.
Thyroid Patient Advocacy	Evidence Review H	11	General	After assessing a large number of documents relating to tests for people with confirmed thyrotoxicosis it must be incredibly frustrating to then discover that the few documents that did initially "pass muster" are further assessed as being potentially biased and of questionable quality. Creating guidelines under such conditions must be incredibly difficult, and one must speculate that other documents of moderate quality with some small risk of bias may have been rejected at the initial cull, or overlooked altogether. It's possible that with such a small pool of documents remaining to be considered, the committee's own bias may come into play. Unfortunately in the present milieu this appears to come down to finance; and cost cutting is not necessarily correlated with an improvement of health on a societal level. It's an unenviable task that you have. There is a glimmer of light though. The only bit of evidence	Thank you for your comment and understanding of the challenges of guideline development. NICE guidelines do not routinely reference or adopt large sections of other guidelines. The evidence reviewed for the guidelines you highlight is broadly similar to that reviewed as part of the NICE guideline although different groups follow different precise methodologies. The committee agree that their recommendations are appropriate based on the evidence that is currently available. Cost effectiveness is an important part of NICE guidelines, but it is critical to remember this takes into account the efficacy of any proposed option as well as its costs.

				identified herein with moderate quality evidence seems to be third generation TRAB testing. Fortunately this is reasonably cheap, is a really good indicator of the presence of Grave's disease, is somewhat helpful in guessing the likelihood of remission, can be utilised in a serial manner to monitor immune sytem response to treatment, and is a very active area of research. A possible way forward for the committee, given the mostly poor quality of the evidence identified, is to 'outsource' the whole hyperthyroid section of these guidelines. Instead of making educated guesses based on a handful of studies, these guidelines could refer practitioners to existing international guidelines; For Grave's disease in particular: 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018 Aug; 7(4): 167–186. George J. Kahaly, Luigi Bartalena, Lazlo Hegedüs, Laurence Leenhardt, Kris Poppe, and Simon H. Pearce. Available at : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140607/ And for hyperthyroidism and thyrotoxicosis in general: 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosisis. Thyroid Vol. 26, No. 10. Douglas S. Ross, Henry B. Burch, David S. Cooper, M. Carol Greenlee, Peter Laurberg, Ana Luiza Maia, Scott A. Rivkees, Mary Samuels, Julie Ann Sosa, Marius N. Stan, and Martin A. Walter. Available at: https://www.liebertpub.com/doi/full/10.1089/thy.2016.0229	

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Thyroid Patient Advocacy	Evidence Review H	14	General	According to both the 2016 American thyroid association guidelines for the treatment of hyperthyroid disorders and the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism, TRAB (also called TSH-R-Ab) is cost effective in the diagnosis of Grave's disease. " Most immunoassays today use a competitive-binding assay and measure what are referred to as TSH-R binding inhibitory immunoglobulins (TBII). Binding assays only report the presence or absence of TSH-R-Ab and their concentrations, but do not indicate their functional activity" (Kahaly et al, p.7) "the highly sensitive cell-based bioassays [25, 26, 27, 28, 29, 30, 31, 32, 33] exclusively differentiate between the TSH-R-stimulating Ab (TSAb) and TSH-R-blocking Ab [34, 35]. Also, TSAb is a highly sensitive and predictive biomarker for the extrathyroidal manifestations of GD [36, 37, 38, 39, 40, 41, 42] as well as a useful predictive measure of fetal or neonatal hyperthyroidism" (ibid) Where doubt remains about diagnosis "Typical US patterns combined with positive TSH-R-Ab obviate the need for scintigraphy in the vast majority of cases. However, thyroid scintigraphy may be useful in the assessment of patients prior to radioactive iodine (RAI) treatment, especially when facing coexistent multinodular goiter [6]." (Kahaly et al, p9)	Thank you for your comment. The committee agree that TRAbs should be the first method of investigation to diagnose Graves' disease with a consideration for technetium scanning if TRAbs are negative. This is reflected in the recommendations.
Thyroid Patient Advocacy	Evidence Review H	14	General	Of the studies identified by the committee, according to the committee's own assessment, all were potentially subject to some level of bias and the best rating that was achieved was 'moderate' and this was in regards to TRAB testing.	Thank you for your comment. This is accurate.

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Thyroid Patient Advocacy	Evidence Review H	14	3	"No relevant health economic studies were identified" therefore speculation around the relative costs, over time, of the various treatment options cannot be fully delineated	Thank you for your comment. It is correct that due to the lack of economic evidence for this review question it is not possible to work out the cost-effectiveness of using different tests in the diagnosis of Graves' disease and therefore the recommendations are based on the expertise opinion of the committee members, clinical evidence and current practice.
Thyroid Patient Advocacy	Evidence Review H	14	12	Table 5 clearly shows that TRAB measurement is the most economic method for detecting Grave's disease. Serial testing is far cheaper than technetium scanning and there are some valid reasons for taking this approach with some patients	Thank you for your comments. Table 5 shows the unit costs of different tests; however, we cannot say by costs alone if it is the most cost effective method as other factors need to be taken into account, i.e. accuracy of test (is re-testing required), downstream costs etc. This question was not prioritised for new cost effectiveness analysis because the population is small and the cost of antibody testing is low compared to ultrasound
Thyroid Patient Advocacy	Evidence Review H	14	12	It is unclear from the information presented in this table whether a unit cost for power doppler scans was obtained? And what is the unit cost for combining greyscale and power-doppler ultrasound?	Thank you for your comment. Costs were obtained for index tests included in the PICO table for this review (Anti-TPO testing, TRAb testing, Ultrasound scan, Isotope scan). The committee agreed that the cost of the colour Doppler adds no real cost to the US as it is simply a button that is pressed on almost any US machine.
Thyroid Patient Advocacy	Evidence Review H	15	General	It is noted that the sensitivity and specificity of the third generation TRAB test is increased when the threshold is set at around <1.8, which seems to be the currently recognised threshold used in clinical practice. Patients with TRAB results below this threshold would perhaps be considered as subclinical, depending of course on levels of FT3, FT4 and TSH. These patients would perhaps benefit from close monitoring; including retesting of TRAB if necessary.	Thank you for your comment. The level of detail of precise TRAb test results and appropriate follow-up was beyond the granularity with which the committee was able to approach this evidence review. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders.
Thyroid Patient Advocacy	Evidence Review H	15	General	Really unimpressive sensitivity and specificity from the included studies relating to ultrasounds. Evidence quality is likewise mostly low. However the European guidelines suggest there may be some reliable studies on the use of ultrasound to	Thank you for your comment. The evidence reviewed for the guidelines you highlight is broadly similar to that reviewed as part of the NICE guideline although different groups follow different precise methodologies. The

				assist in the differential diagnosis of Grave's disease as recommendation 3 states: "US examination, comprising conventional grey scale analysis and color-flow or power Doppler examination is recommended as the imaging procedure to support the diagnosis of Graves' hyperthyroidism. 1, ØØØØ"	conclusions drawn from the available evidence base reflect differing guideline methodologies particularly with regards to costs and the experience and consensus of the committee.
Thyroid Patient Advocacy	Evidence Review H	15	27	Low quality evidence from a small study, this particular study would be best relegated to the 'further studies needed bin' as it's small size makes it more of a pilot study. TSI (thyroid stimulating immunoglobulin) is a bioassay that detects only the functionally stimulating TRAB. It is useful in some situations, but cannot be directly compared to TRAB (a competition assay) as they are completely different types of laboratory tests	Thank you for your comment. The committee agree that this study is small but as it met the protocol for inclusion it was taken into account alongside all other available evidence and the committee's experience in making recommendations.
Thyroid Patient Advocacy	Evidence Review H	15	27	TSI has it's uses, but TRAB is perhaps a better option for determining whether a patient has Grave's disease	Thank you for your comment. The committee agree and this is reflected in the recommendations.
Thyroid Patient Advocacy	Evidence Review H	15	30	Low quality evidence from a small study, why is this even included for consideration?	Thank you for your comment. The committee agree that this study is small but as it met the protocol for inclusion it was taken into account alongside all other available evidence and the committee's experience in making recommendations.
Thyroid Patient Advocacy	Evidence Review H	15	31	Really impressive sensitivity and specificity which sadly must be disregarded due to study size and the assessed risk of bias.	Thank you for your comment. The committee agree that this study is small but as it met the protocol for inclusion it was taken into account alongside all other available evidence and the committee's experience in making recommendations.
Thyroid Patient Advocacy	Evidence Review H	17	27	Patients must be informed that the technetium scan utilises radioactive material and be offered an ultrasound instead if they wish to avoid exposure.	Thank you for your comment. The committee agree that informed consent is an important part of any medical investigation but detail on every aspect of consent for each investigation in the guideline is beyond the granularity with which the committee was able to approach this review. We have added to the text in the discussion, but NICE guidelines are not meant to be

					exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders.
Thyroid Patient Advocacy	Evidence Review H	18	23	It may be useful at some point to define what is meant by a negative TRAB test, for instance a TRAB result above zero but below the reference point indicates that there are probably TSH receptors in the serum, but that these may not currently be at a level that either stimulates or inhibits thyroid hormone production (depending on which functional type of TRAB is predominant). In such a situation, since the result is not truly negative, a technetium scan might be considered overkill and would certainly be more expensive than repeat TRAB testing at a later date; or if rising or falling thyroid hormone levels indicate that antibody levels may have increased. A truly negative TRAB result in the presence of raised FT3 and/or FT4, alongside suppressed TSH may warrant some form of scan to determine aetiology. The evidence reviewed by the committee does not, unfortunately, enlighten one as to which sort of scan is truly effective. In the interests of minimising exposure to radioactive materials, and perhaps keeping costs down a comprehensive ultrasound exam, grayscale and power-doppler might be the best option here - however the unit costing provided in table 5 is not clear on how much such a combined test would cost the NHS	Thank you for your comment. The level of detail of precise TRAb test results and appropriate follow-up was beyond the granularity with which the committee was able to approach this evidence review. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The committee agreed that the cost of the grayscale and colour Doppler (which is a button that is pressed on almost any US machine) adds no real cost to the US.
Thyroid Patient Advocacy	Evidence Review H	18	29	Of course, patients who are not feeling well want answers, and this is a tricky area to address. Doctors will be aware that many patients self-fund private testing, some will find ways to treat themselves based on results thus obtained. This situation is obviously not ideal for anyone, with the possible exception of the laboratories running the tests. Perhaps there could be be a middle ground. Either doctors being able to request self paid tests as requested by the patient, or accepting and considering private results obtained by the patient. It seems there may be a	Thank you for your comment. The interplay between public and private sector investigation is a complex issue that applies in many circumstances and is not within the scope of this particular guideline.

				possible financial benefit if self-funded tests are carried out within the public hospital system. There is the further advantage here that such testing may indeed provide valuable data to both the patient and the doctor.	
Thyroid Patient Advocacy	Evidence Review H	18	30	Again, it is worth pointing out that a negative result and a subclinical result for TRAB are not the same thing	Thank you for this comment. The committee was aware of this when making the recommendations.
Thyroid Patient Advocacy	Evidence Review H	7	General	Please consult the following guidelines, these have been meticulously compiled by bodies much like the current review committee and between them offer pretty comprehensive advice for practitioners in regard to the detection, monitoring and treatment of hyperthyroid disorders. Recommendations offered by both of these guidelines have been based on a stringent review of available evidence, and the authors have gone a step further by specifying the level of evidence for each recommendation in the text of the guideline itself (of course this may be your intention for your final document) 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosisis. Thyroid Vol. 26, No. 10. Douglas S. Ross, Henry B. Burch, David S. Cooper, M. Carol Greenlee, Peter Laurberg, Ana Luiza Maia, Scott A. Rivkees, Mary Samuels, Julie Ann Sosa, Marius N. Stan, and Martin A. Walter. Available at: https://www.liebertpub.com/doi/full/10.1089/thy.2016.0229 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018 Aug; 7(4): 167–186. George J. Kahaly, Luigi Bartalena, Lazlo Hegedüs, Laurence Leenhardt, Kris Poppe, and Simon H. Pearce. Available at : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140607/ It may be feasible to remove the sections relating to	Thank you for your comment and for these references. NICE guidelines do not routinely reference or adopt large sections of other guidelines but are developed with specific reference to the English health service and costs. The evidence reviewed for the guidelines you highlight is broadly similar to that reviewed as part of the NICE guideline development although different groups follow different precise methodologies.

				hyperthyroidism from this draft altogether and instead link out to these existing guidelines	
Thyroid Patient Advocacy	Evidence Review H	8	2	Table 2: Summary of studies included in the evidence review Baskaran Diagnosis of Pediatric Hyperthyroidism: Technetium 99 Uptake Versus Thyroid Stimulating Immunoglobulins. Charumathi Baskaran, Madhusmita Misra, and Lynne L. Levitsky) states that "However, not all children with GD have increased TSI." This is an American retrospective paediatric study using TSI (thyroid stimulating immunoglobulin) not total TRAB or TSH-R-AB as it is sometimes called (TSH receptor antibodies). TSI tests detects only stimulating TSH receptor antibodies, the widely recognised cause of the hyperactive phase of Grave's disease (Kahaly et al., p.7) . The inhibitory (i.e. blocking) or 'neutral' TRABs are not detected by the TSI test, but these are still indicative of Grave's disease (ibid). "A more recent study evaluated the relationship between second-generation thyrotropin receptor antibody (TRAb) assays and 99mTc uptake in patients with untreated autoimmune hyperthyroidism, and found a significant association between antibody levels and 99mTc uptake (14). This study, performed primarily in adults, assessed TRAb levels but not their biological activity measured with cyclic-AMP production." (Baskaran et al) Second generation TRAB tests are not as accurate as third generation tests, and yet these still compared well to technetium scanning, and are much cheaper (Baskaran et al). Significant savings can be made by avoiding, where possible, the use of technetium scans for diagnostic purposes. This has the added advantage of not exposing patients to radioactive	Thank you for your comment. The committee acknowledge the precise details (e.g. use of TSI) of this study and used this as well as all other available evidence and their experience to make their recommendations. The study suggests that technetium scanning is accurate compared to the composite reference standard used.

				materials (ibid), decreasing the amount of radioactive materials that health workers may be exposed to, and decreasing the amount of radioactive waste that medical facilities must then dispose of. Overall this retrospective review, focusing as it does on stimulating TRABs (TSI), does not effectively compare the utility of technetium scanning to the TRAB tests generally available to the UK practitioner, and cannot be considered as evidence for an increased use of technetium scanning.	
Thyroid Patient Advocacy	Evidence Review H	9	2	Table 2: Summary of studies included in the evidence review Lee 2016 Abstract only - using ultrasound to detect thyroid nodules in a paediatric population, it is difficult to assess this evidence without access to the full text	Thank you for your comment. We have provided citation details for the full reference should you wish to obtain a copy.
Thyroid Patient Advocacy	Evidence Review H	9	2	Table 2: Summary of studies included in the evidence review Paunkovic 2006 First off it must be noted that only the abstract for this paper was available for review. Secondly, it should be recognised that TRAB testing has improved dramatically since 2006; and thirdly the knowledge base around the functionality of different types of TRAB has increased significantly since 2006. How this effects the interpretation of the paper's contents is unclear. One must assume that since in the Paunkovic study the "initial diagnosis was based on clinical findings (patient record, hypermetabolic state, goiter palpation) and laboratory testing (fT4 and TSH)" (Paunkovic & Paunkovik) that T3 toxocosis was not routinely looked for in 2006. Please consider that in "overt hyperthyroidism, both serum free T4 and T3 concentrations are elevated, and serum TSH is suppressed; however, in milder hyperthyroidism, serum total T4 and free T4	Thank you for your comment. The committee agree that TSH monitoring should be done with caution during early phases of treatment for hyperthyroidism and this is reflected in the recommendations.

				levels can be normal, only serum free T3 may be elevated, with an undetectable serum TSH" (Kahaly et al, p.6) As per the committee's comments in regards to this study in Table 2, TSH can certainly be a good test for the initial detection of Grave's disease, although extreme caution must be observed in its use during treatment of the condition (Kahaly et al. P. 11).	
Thyroid Patient Advocacy	Evidence Review H	9	2	Table 2: Summary of studies included in the evidence review Pishdad "Sonograhphy is safe as it doesn't use ionizing radiation and does not cause tissue damage" (Pishdad et al). A reminder that scans and treatments utilising radiation are not without risk and should be avoided where possible. This paper "compares gray scale sonography with clinical and lab data which are the gold standards in the diagnosis of Graves' disease and Hashimoto's thyroiditis" (Pishdad et al); what this study does not do is add in more comprehensive Colour Doppler flow ultrasound scan, which improves the ability of the radiologist to differentiate between the different thyroid aetiologies. A possible resource for you consideration: Role of color Doppler in differentiation of Graves' disease and thyroiditis in thyrotoxicosis. Ragab Hani Donkol, Aml Mohamed Nada, and Sami Boughattas, which concludes that "Color Doppler flow of the inferior thyroid artery can be used in the differential diagnosis of thyrotoxicosis, especially when there is a contraindication of thyroid scintigraphy by radioactive material in some patients." Please also see recommendation 3 on page 10 of the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism:	Thank you for your comment. The committee looked for evidence comparing the accuracy ultrasound, anti-TPO, TRAb and isotope scanning for testing in hyperthyroidism. The Donkol study you reference did not meet our criteria for the evidence review specified due to the nature of the reference standard used (no involvement of TRAbs).

				"US examination, comprising conventional grey scale analysis and color-flow or power Doppler examination is recommended as the imaging procedure to support the diagnosis of Graves' hyperthyroidism. 1, ØØØØ" and note the strength of the evidence associated with this recommendation.	
Thyroid Patient Advocacy	Evidence Review H	General	General	While TPAUK recognises that the financial burden on health systems of chronic diseases is increasing, we would like to emphasise that failing to address how well a patient with a thyroid disorder feels ultimately adds to that burden by increased visits to general practitioners and emergency departments. Treating chronic illness should not be a case of "shut up and put up". Appropriate testing and follow up are unfortunately not likely to be cheaper in the short term but making an extra effort and taking the extra time to help a patient become stable and feel well will pay off in the long run. Since there is no known cure for any autoimmune disease (including Hashimoto's and Grave's disease), efforts to help a patient to understand and manage their own condition should ultimately take some of the strain off the currently beleaguered health care system.	Thank you for your comment. The principles you underline are very much taken into account in NICE guideline development.
Thyroid Patient Advocacy	Evidence Review H	General	General	REFERENCES NOT ALREADY LISTED Douglas S. Ross, Henry B. Burch, David S. Cooper, M. Carol Greenlee, Peter Laurberg, Ana Luiza Maia, Scott A. Rivkees, Mary Samuels, Julie Ann Sosa, Marius N. Stan, and Martin A. Walter. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis. Thyroid Vol. 26, No. 10. Available at: https://www.liebertpub.com/doi/full/10.1089/thy.2016.0229 George J. Kahaly , Luigi Bartalena, Lazlo Hegedüs, Laurence Leenhardt, Kris Poppe, and Simon H. Pearce.	Thank you for this additional information. The references you include (1 & 2) are either other guidelines which are not routinely included in NICE guidelines as NICE conducts its own independent evidence reviews or did not meet the inclusion criteria of any of our protocols (3).

				2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018 Aug; 7(4): 167–186. Available at : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140607/ Ragab Hani Donkol, Aml Mohamed Nada, and Sami Boughattas. Role of color Doppler in differentiation of Graves' disease and thyroiditis in thyrotoxicosis. World J Radiol. 2013 Apr 28; 5(4): 178–183. Available at : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3647210/	
Thyroid Patient Advocacy	Evidence Review I	15	General	From the studies considered and the quality assessment of the evidence, it is quite clear that not much is actually clear. We are actually no further forward in that those things already known with reasonable certainty have been reaffirmed: relapse of hyperthyroidism is more likely after a set course of antithyroid drugs, ophthalmology is more likely after radioactive treatment and hypothyroidism is reasonably likely after RAi and almost certain after total thyroidectomy,. There is not enough evidence here for a change in policy.	Thank you for your comment. The committee agreed that on the basis of the available clinical and cost effectiveness evidence there was sufficient justification for the recommendations as they stand, although they have been amended slightly following stakeholder feedback.
Thyroid Patient Advocacy	Evidence Review I	16	2	With only one study identified as relevant, it is hard to judge whether the conclusions are sound. Further studies are needed to confirm the conclusions reached. International studies, which will not necessarily be relevant in a British context most often seem to reach the conclusion that the costs over time for RAI and antithyroid drug therapy are very similar. Unit prices for items may differ. Healthcare costs may be privately funded, goverment funded or partially government funded. One would expect, however, that within a particular country there is parity in the funding structure, so that although individual items may cost more or less than in other	Thank you for your comment. Only one study was found that met the inclusion criteria. Studies would be included from OECD countries with similar healthcare systems if they were relevant to the question. Studies from non-OECD countries and the USA were excluded because they were deemed not applicable in the context of decision making in the UK. NICE guidelines are written from an NHS and PSS perspective and therefore only NHS costs should be included. The study included in this review was a UK NHS perspective study, which was assessed as directly applicable with minor limitations.

				countries the proportions are likely to remain the same. So, for one country to claim that either RAI or ATD treatment is cheaper begs the question: what is being done differently? And is patient care being sacrificed in the interests of saving money?	We do not agree that patient care is being sacrificed. Whenever a treatment is recommended this inevitably means that there is less money to spend on other NHS patients. By only recommending cost effective treatments, we ensure that the sacrifice of these other patients does not exceed the benefits to the target patient group.
Thyroid Patient Advocacy	Evidence Review I	17	General	Is it not necessary to do a quality assessment when only one study has been identified?	Thank you for your comment. All potentially includable economic evidence is assessed on the basis of both the methodological quality and applicability. This study was found to be directly applicable. The limitations reported in Table 7 were assessed to be minor. Please refer to the health economics evidence table in this chapter for further information.
Thyroid Patient Advocacy	Evidence Review I	18	General	In regard to lines 24 to 26, the cons could outweigh the pros from a patient perspective	Thank you for your comment. These lines are a narrative summary of the evidence as identified that does not describe the magnitude of effects. The health economic evidence estimated an overall benefit. The committee's interpretation of the evidence is in the discussion section (2.7).
Thyroid Patient Advocacy	Evidence Review I	18	22	Apart from the statement (which still needs to be ratified by further reviews) that RAI is the cheapest option for the treatment of Graves the only real advantage is that if administered in sufficient doses is that hypothyroidism is attained. If you had attained hypothyroidism for yourselves you may be less inclined to call this an advantage.	Thank you for your comment. The committee carefully considered the implications of each treatment including thyroid state and overall agreed that the evidence justified the recommendations as they stand, although they have been modified slightly following stakeholder feedback.
Thyroid Patient Advocacy	Evidence Review I	18	27	No evidence was identified for other outcomes, but according to the selected papers there remains doubt on rates of subsequent cancers and all cause mortality. More clarity is needed here before a doctor can say in good conscience that these are not possible consequences of RAI treatment	Thank you for your comment. This line reflects the conclusions of the review of RCTs comparing the 3 main modalities of treatment. The additional review specifically of the effects of radioactive iodine on cancer explores your point further.

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Thyroid Patient Advocacy	Evidence Review I	19	2	Further clarity in regards to the roles played by different thyroid parameters in osteoporosis (including antibodies) is needed. It is a complex problem that is all too often reduced to being dependent on TSH alone.	Thank you for this information. Osteoporosis was one of the important outcomes considered in the evidence review. Where evidence was available the influence of different thyroid parameters were considered and this was not just limited to the effects of TSH concentrations.
Thyroid Patient Advocacy	Evidence Review I	19	4	Surgery is also often, but not always, associated with a decrease in TSH receptor antibodies and could thus be considered as offering a cure for hyperthyroidism, albeit at the expense of creating a new disorder (Wiersinga, p. 1).	Thank you for this information.
Thyroid Patient Advocacy	Evidence Review I	19	14	Euthyroidism and the avoidance of hypothyroidism can be an important goal for some patients, and patient choice is implicit in 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism (Kahaly et al) and explicit in the 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis, which states that "These guidelines are not intended to replace clinical judgment, individual decision making, or the wishes of the patient or family. Rather, each recommendation should be evaluated in light of these elements so that optimal patient care is delivered" (Douglas et al) Please see Patient values that may impact choice of therapy in section [C] of the 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis (Douglas et al)	Thank you for your comment. Patient choice is important in NICE recommendations and a similar disclaimer can be found at the beginning of each evidence review. However overall the committee agreed that the identified evidence was sufficient to warrant recommendations that prioritised radioactive iodine as the first definitive treatment of choice. Should a person refuse radioactive iodine treatment, other options can be considered.
Thyroid Patient Advocacy	Evidence Review I	19	21	However, the authors added that "Finally, the choice of cost-effectiveness threshold (i.e. how much one is willing to pay for one extra QALY) is potentially important, particularly in the English analysis. NICE guidance recommends a cost-effectiveness threshold of £20 000 to £30 000 per QALY gained (12). If the threshold was rigidly set at £20 000 per	Thank you for your comment. The NICE methods manuals state that: "Above a most plausible ICER of £20,000 per QALY gained, judgments about the acceptability of the technology as an effective use of NHS resources will specifically take account of the following factors:

				QALY gained, ATD may not be cost-effective in England, because in the base case and in most one-way sensitivity analyses, the ICER estimates sit between £20 000 and £30 000 per QALY gained. NICE guidance suggests that a threshold of £30 000 per QALY gained may be used where there is some uncertainty around the true ICER and HRQoL capture. As there is uncertainty in both these in our study, we believe that our pre-specified threshold of £30 000 per QALY gained is reasonable" meaning that ATDs are considered a cost effective alternative to RAI in that analysis In addition, as the study points out, it "was performed from the perspective of the government contribution to the healthcare sectors in each country and thus ignores any costs borne by patients (e.g. out-of-pocket medication costs), their preferred choice of therapy and any anxiety that may be experienced (e.g. as a result of possible future cancer risk from RAI)" and, one might add, the anxiety caused by the thought that a doctor, who may or may not assess a patients clinical symptoms correctly, being in charge of deciding how much and what type of thyroid hormone will be prescribed.	1) The degree of certainty around the ICER. In particular, the Committee will be more cautious about recommending a technology when they are less certain about the ICERs presented. 2) Whether there are strong reasons to indicate that the assessment of the change in health-related quality of life has been inadequately captured, and may therefore misrepresent the health utility gained." We would argue that this means the committee is right to be cautious about recommending the drugs, since the incremental cost per QALY is uncertain and therefore could be much higher.
Thyroid Patient Advocacy	Evidence Review I	28	General	It is impossible to draw any conclusions from papers whose quality has been assessed as so low. Therefore the cancer and all cause mortality questions remain unanswered. On these grounds alone recommending RAI as the first-line treatment for Grave's disease seems somewhat precipitous and possibly even detrimental to public health	Thank you for your comment. The quality of these studies as per GRADE principally reflects their non-randomised nature in terms of study design. It is worth bearing in mind their substantial sample size and long follow-up periods. The committee overall considered this evidence of no increased risk of cancer at a clinically important level with radioactive iodine (compared with surgery or in a general population cohort) in the doses used for treating hyperthyroidism.
Thyroid Patient Advocacy	Evidence Review I	30	9	No reliable evidence was found for anything as the identified papers were all assessed as being low quality	Thank you for your comment. The quality of these studies as per GRADE principally reflects their non-randomised nature in terms of study design. It is worth

					bearing in mind their substantial sample size and long follow-up periods. The committee overall considered this evidence of no increased risk of cancer at a clinically important level with radioactive iodine (compared with surgery or in a general population cohort) in the doses used for treating hyperthyroidism.
Thyroid Patient Advocacy	Evidence Review I	31	14	Resolution of the hyperthyroid state without subsequent hypothyroidism is the main goal of many hyperthyroid patients as both states are extremely unpleasant and both carry significant health risks (and monetary costs). Sucessfully acheiving this aim is more or less attaining euthyroidism with the added caveat that an individual's ideal euthyroid state may be contained within the population reference intervals, but are unlikely to be as broad as these. You will be quite aware that early on (Kahaly, p. 11) , and for an extended period in some patients, the TSH may remained suppressed, making this a troublesome metric.	Thank you for your comment. The committee acknowledge that TSH levels may remain suppressed in some people and have reflected this in their recommendations on monitoring after treatment.
Thyroid Patient Advocacy	Evidence Review I	31	16	A patient who places "relatively higher value on the possibility of remission and the avoidance of lifelong thyroid hormone treatment, the avoidance of surgery, and exposure to radioactivity and a relatively lower value on the avoidance of ATD side effects (see Section [E]), and the possibility of disease recurrence." (Douglas et al, section C) may do so in the hope of avoiding an outside agency being responsible for the correct replacement of missing hormones. Not all doctors are made equal, and some may not be very good at this. A patient who chooses this course of action doe so often in the hope that the hypothalmus / pituitary / thyroid feedback loop will return to normal function allowing thyroid hormone to be produced in a biologically responsive and natural manner.	Thank you for your comment. The committee sought to reflect this aspect in the recommendations by considering either radioactive iodine or antithyroid drugs in those for whom antithyroid drugs are likely to achieve remission.
Thyroid Patient Advocacy	Evidence Review I	31	17	It's not possible to tell if the evidence mentioned here has been subjected to any scrutiny and since it is not the focus of the review should perhaps not be considered here	Thank you for your comment. This statement was included to provide the fullest detail on the committee's considerations in making recommendations. The

					committee did not make recommendations on the specific aims of treatment as they had not reviewed the full evidence base. However, it was important information to discuss in order for them to fully interpret the included studies for this question.
Thyroid Patient Advocacy	Evidence Review I	31	22	An observation rather than a comment, but one that may be worthy of consideration: Being dependent on a doctor to prescribe a needed drug is subtly different to being dependent on a doctor to correctly replace something that has effectively been taken away. There's an element of loss of control in both situations, but removal or destruction of the thyroid gland also removes hope of regaining that control.	Thank you for your comment. The committee consisted of both clinical and lay members, and their views are considered with equal weight during discussions and when developing recommendations. The committee of acknowledged the importance many people place on avoiding long term hypothyroidism.
Thyroid Patient Advocacy	Evidence Review I	32	General	"34Balanced against this evidence of no important harm of radioactive iodine, the committee 35 noted the underlying biological principles that any exposure to radiation is likely to increase 36 cancer risk to some degree. However the evidence in this review suggests that the risk 37 associated with the radiation involved in treatment of thyroid disease is not clinically 38 impactful." Given the assessed poor quality of the evidence, one would hope that you would err on the side of caution. Failing that, please ensure that patients ars aware that evidence is poor one way or another, please do not coerce them into making irreversible decisions whilst in a hyperthyroid state and please respect their personal choices about which treatment option suits them	Thank you for your comment. The committee agrees it is important for people to make informed decisions about their care and have included recommendations about the types of information that may allow people to make these decisions. The committee also agrees on the basis of the evidence available that there is sufficient justification to promote the use of radioactive iodine as the default first definitive treatment option. However, the committee have included a number of caveats where this may not be appropriate, including if antithyroid drugs are likely to achieve remission. Finally, a person always has the right to refuse treatment and at this point, other options may be considered.
Thyroid Patient Advocacy	Evidence Review I	32	General	"23 are likely to achieve remission with a course of antithyroid drug therefore unlikely to be 24 rendered hypothyroid, reducing the need for long-term hormone replacement therapy which	Thank you for your comment. The committee was not surprised to find that people do not like being a burden and the guideline seeks to find solutions that improve quality of life at reasonable cost. Health economics is

				25 in turn saves money and improves patients quality of life. " As a patient, the quality of life business is quite important; it might surprise you to know that many patients do not like being a burden, financially or otherwise and would like to find a balanced approach where regaining quality of life is not associated with escalating costs to the health care system	about finding the optimum balance between effects and costs and if something is more costly but leads to a large gain then this could still be a cost effective thing to do.
Thyroid Patient Advocacy	Evidence Review I	32	8	There is theoretically an improved response to antithyroid drugs if they are titrated correctly. See both the American and European guidelines for the treatment of hyperthyroid disorders (Kahaly et al and Douglas et al). This is difficult to substantiate as antithyroid drugs are most often adjusted according to TSH levels, which especially early on, is contrary to these guidelines. Treatment failure in such cases may be more to do with the titration regime than the effectiveness of the drug itself. It is also worth noting that many of the minor side effects of ATDs are dose dependent and may not arise at all if the guidelines are followed correctly	Thank you for your comment. The committee made their recommendations based on the evidence available in this review but agree there may be ways of optimising each major form of treatment and have made some specific recommendations about specific ways this could be done.
Thyroid Patient Advocacy	Evidence Review I	33	General	"Overall, the recommendation for the use of RAI as first line is a change to current practice, which is likely to have a substantial cost saving as shown by the economic evidence and agreed by the committee." You have referred to one paper dealing with costings, that by its own admission has several short-comings and recommended further reviews to substantiate it's claims. Most of the evidence comparing treatment methods was assessed as being poor, with a couple of exceptions and all of the papers investigating the safety of RAI were assessed as being low quality. It's not clear what this recommendation is based upon	Thank you for your comment. NICE guidelines are written from an NHS and PSS perspective and therefore healthcare costs included in any review would only include costs to the NHS. Only one study was found that met the inclusion criteria and included in this review which was based on a UK NHS perspective study and assessed as directly applicable with minor limitations. Whenever a treatment is recommended this inevitably means that there is less money to spend on other NHS patients. By only recommending cost effective treatments, we ensure that the sacrifice of these other patients does not exceed the benefits to the target patient group. Evidence is not assessed as poor as part of NICE evidence reviews. While a number of studies may have reported outcomes that contributed to GRADE

					ratings of low or very low quality, particularly for the cancer outcomes this reflected their non-randomised nature and the committee considered the substantial sample size and long term follow-up of these studies to be informative.
Thyroid Patient Advocacy	Evidence Review I	33	44	Research into TSH receptor antibodies is a pretty active field. There are quite a lot of papers available in PubMed that explore and expand upon the functional differences of the various types of TRAB (too many to list here), and there is some promise for the future in understanding Grave's disease better via gaining a better understanding of these antibodies. To this end testing of antibodies could provide minable data for future studies	Thank you for your comment. The committee considered antibody testing in separate reviews for both hypo and hyperthyroidism.
Thyroid Patient Advocacy	Evidence Review I	6	General	An important aspect not emphasized in the introduction is patient preference in regard to treatment, this is not nearly respected enough out there in the trenches; so, emphasising this in the guidelines will remind doctors of its importance 21 stopped. Patients will then be faced with the prospect of long term ATD therapy or choosing 22 radioactive iodine or surgery – both of which will usually result in hypothyroidism and a 23 requirement for life-long thyroid hormone replacemen	Thank you for your comment. This section is a brief introduction to the area and is not intended to be exhaustive. Further detail including on patient choice is included in the discussion and recommendations themselves.
Thyroid Patient Advocacy	Evidence Review I	6	21	Somewhat in line with the previous comment on patient preference not always being respected, patients who might prefer long-term drug therapy are often not told this is even an option. Even when a patient is aware, they may be made to feel bullied and pressured into definitive treatments. The upshot of this is that some reluctantly agree to the favoured treatment (with the potential for loss of faith in the medical establishment) and some are faced with the prospect of finding a new doctor. There may be financial implications inherent in both of these situations; the patient who has lost faith may	Thank you for your comment. The committee agree that informed decision making is a crucial part of the process of managing thyroid disease and have made recommendations on the types of information that people with thyroid disease should be provided with in order to achieve this.

				avoid consulting doctors until they have a new condition firmly established and expensive to treat; or they may be so unhappy with the unwanted treatment that they see symptoms everwhere, resulting in extra visits and extra costs. When a patient seeks a second, or third opinion there may be costs associated due to the time taken for a new physician aquainting themselves with the patient's individual situation. Much better all-around for the patient to be respected and allowed to feel part of the decision making process.	
Thyroid Patient Advocacy	Evidence Review I	General	General	REFERENCES: Douglas S. Ross, Henry B. Burch, David S. Cooper, M. Carol Greenlee, Peter Laurberg, Ana Luiza Maia, Scott A. Rivkees, Mary Samuels, Julie Ann Sosa, Marius N. Stan, and Martin A. Walter. 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosisis. Thyroid Vol. 26, No. 10. Available at: https://www.liebertpub.com/doi/full/10.1089/thy.2016.0229 George J. Kahaly , Luigi Bartalena, Lazlo Hegedüs, Laurence Leenhardt, Kris Poppe, and Simon H. Pearce. 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. Eur Thyroid J. 2018 Aug; 7(4): 167–186. Available at : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140607/ Wilmar M. Wiersinga. Graves' Disease: Can It Be Cured? Endocrinol Metab (Seoul). 2019 Mar; 34(1): 29–38. Available at : https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6435849/	Thank you for this additional information. The references you include (1 & 2) are either other guidelines or non-systematic reviews (3) which are not routinely included in NICE guidelines as NICE conducts its own independent systematic evidence reviews.

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Thyroid Patient Advocacy	Evidence Review J	17	27	Correct titration of antithyroid drugs will in most cases avoid iatrogenic hypothyroidism. Please refer to 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism (Kahaly Et al, p.11)	Thank you for your comment. This line in the review refers to the specific outcomes identified in the included studies.
Thyroid Patient Advocacy	Evidence Review J	19	General	Please refer to the 2018 European and the 2016 American guidelines, both of which provide recommendations for starting doses of antithyroid medication	Thank you for your comment. The aim of this review was not to make recommendations on the starting doses of antithyroid medication but specifically considered evidence for and against different drug options, treatment regimens and durations of treatment.
Thyroid Patient Advocacy	Evidence Review J	19	General	Duration of antithyroid drug treatment should be tailored according to the response of the patient. Shorter courses may result in remission for some patients, others may require longer than 18 months. Long term, low dose antithyroid drug therapy is a safe alternative for patients who prefer this approach as long as there are no serious counter-indications. Doctor preference for ablative therapy should not override patient choice.	Thank you for your comment. The precise duration of treatment will be dictated by the circumstances of each individual. However, the committee agreed on the basis of the evidence in this review and their experience that 12-18 months would be an appropriate target for the majority of people. The evidence in the review comparing radioactive iodine, drugs and surgery supported definitive treatment options as the starting point for long term treatment due to their benefits in avoiding persistence or relapsing hyperthyroidism.
Thyroid Patient Advocacy	Evidence Review J	19	45	Again, hypothyroidism can generally be avoided by the correct titration of antithyroid drugs. This necessitates physicians understanding that TSH is not by itself useful in determining thyroid status in a patient with Grave's disease	Thank you for your comment. This line reflects the observed outcomes in the studies included in this review.
Thyroid Patient Advocacy	Evidence Review J	20	21	Lack of benefit for treatment beyond 18 months is a cohort observation. Individual responses to extended treatment may indeed be beneficial (to that individual)	Thank you for your comment. This line reflects the observed outcomes in the studies included in this review. The precise duration of treatment will be dictated by the circumstances of each individual.
Thyroid Patient Advocacy	Evidence Review J	6	14	Several months is not a prolonged course, use of such a phrase might undermine the validity of long term antithyroid drug therapy	Thank you for your comment. This section is a brief introduction and the recommendations contain more specific information about the intended duration of treatment. We have changed “several months” to “usually a minimum of 12 months”.

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Thyroid Patient Advocacy	Evidence Review J	6	15	As in the previous comment, several months is not a "prolonged" course. Please note the "standard" course is 12 to 18 months - according to your own research and also to both the 2018 European and the 2016 American guidelines. Treatment with antithyroid drugs beyond 18 months could be described as prolonged	Thank you for your comment. This section is a brief introduction and the recommendations contain more specific information about the intended duration of treatment. We have changed “several months” to “usually a minimum of 12 months”.
Thyroid Patient Advocacy	Evidence Review J	6	15	Long term antithyroid drug therapy (i.e. beyond 18 months) can also be considered when remission has not yet been achieved if the patient prefers this approach	Thank you for your comment. This section is a brief introduction and the recommendations contain more specific information about the intended duration of treatment. We have changed “several months” to “usually a minimum of 12 months”.
Thyroid Patient Advocacy	Evidence Review J	6	15	Most minor reactions are dose dependent. "The dose of MMI should be targeted to the degree of thyroid dysfunction because too low a dose will not restore a euthyroid state in patients with severe disease (115) and an excessive dose can cause iatrogenic hypothyroidism in patients with mild disease (116). In addition, adverse drug reactions are more frequent with higher MMI doses. Thus, it is important to use an MMI dose that will achieve the clinical goal of normalization of thyroid function reasonably rapidly, while minimizing adverse drug effects." (Douglas et al) Even major (though rare) side effects have been reported as beingbto some degree dose dependent, making it extremely important to titrate ATDs correctly and to monitor patients "Agranulocytosis has been reported in about 0.3% of adult patients taking MMI or PTU (128,324,335). Data on the prevalence of agranulocytosis in children are unavailable, but it is estimated to be very low. In adults, agranulocytosis is dose dependent with MMI and rarely occurs at low doses (e.g., 5–10 mg/d) (128,324,335). When agranulocytosis develops, 95% of the time it occurs in the first 100 days of therapy (128,324,335). The overall rate of side effects from ATDs (both	Thank you for your comment. This section is a brief introduction and the recommendations contain more specific information about the adverse effects.

				major and minor) in children has been reported to be 6%–35% (332,334,336,337)." (Douglas et al, section [P3]) "MMI was associated in a dose-dependentmanner with an increased risk for hepatitis and cholestasis." (Kahaly et al, p. 15)	
Thyroid Patient Advocacy	Evidence Review K	11	15	It is probably quite important to maintain a pool of high volume thyroid surgeons, since side effects seem to decrease with the increased experience of the surgeon. Elsewhere in these documents it has been suggested that thyroidectomy is to be rarely offered, consideration should be given to what, if any effect this will have on the experience levels of surgeons. In the absence of a suitably experienced surgeon is a partial thyroidectomy safer for the patient?	Thank you for your comment. NICE guidelines do not routinely comment on the staffing models required to implement recommendations. Based on the general paucity of evidence comparing surgical options, there is unlikely to be evidence that a partial thyroidectomy is a safer option than total if surgery is done by a less experienced surgeon. However, experience level was not the focus of this review.
Thyroid Patient Advocacy	Evidence Review K	12	12	Patient choice should also be considered in regards to the type of surgery selected	Thank you for your comment. Patient choice is considered in all NICE recommendations. In this case the committee's consensus was sufficiently strong to make definitive recommendations for one intervention option.
Thyroid Patient Advocacy	Evidence Review K	5	13	More emphasis on patient choice would be appreciated	Thank you for your comment. This section is meant to be a brief introduction to the topic area and does not make recommendations. A link has been added to the NICE guideline on patient experience which includes recommendations on optimising shared decision-making.
Thyroid Patient Advocacy	Evidence Review K	General	General	Patient choice in regards to treatment method should be respected. In order for patients to make an informed choice they should be provided with sufficient information. With the definitive treatment modalities it should be explained to patients that without a functioning thyroid gland they will need to take replacement thyroid hormones for the rest of their lives as thyroid hormones are vital. The oft used expression "it's just one little pill a day" should be retired as it's rather patronising	Thank you for your comment. The recommendations on information for people with thyroid disease include information on the consequences of treatment and specifically likely thyroid state. The committee agree that people should be given appropriate information to support them to make informed choices.

				and not always that simple, the only advantage to patients in being told this is that it may be a good indication that a better doctor is needed - especially if that patient chooses one of the definitive treatment options. A bit more transparency would be helpful. Patients should be informed what tests will be undertaken to decide on replacement hormone dose, how often tests are run, who makes the dosage decision, what hormones can be prescribed, what happens if the patient has adverse effects to the replacement and what happens if symptoms do not resolve or get worse.	
Thyroid Patient Advocacy	Evidence Review L	16	19	Given the lack of good quality evidence strong recommendations for this method of treatment seem a bit precipitous	Thank you for your comment. The strength of the recommendations takes into account the full breadth of evidence on clinical and cost effectiveness as well as the additional review on radioactive iodine long term safety and the caveats within the recommendations for those in whom radioactive iodine may not be suitable.
Thyroid Patient Advocacy	Evidence Review L	17	25	It is noted that remaining euthyroid post-treatment as opposed to hypothyroid has quality of life and treatment burden benefits (avoiding the need for long term levothyroxine treatment). Fixed dose methods of treatment are specifically aimed at creating a hypothyroid state and could thus be interpreted as lowering a patient's quality of life. Becoming permanently hypothyroid means that a patient is forever dependent on an outside agency to provide vital hormones of the right type and at the right dose, there are no guarantees that this will be done correctly. Perhaps patients should be alerted to the possibility of this eventuality before they make an informed choice as to which treatment option they prefer	Thank you for your comment. The recommendations on information for people with thyroid disease include information on the consequences of treatment and specifically likely thyroid state. The guideline does not make recommendations about what long term thyroid state should be targeted with radioactive iodine, whether given as a fixed administered activity or calculated absorbed dose.
Thyroid Patient Advocacy	Evidence Review L	17	25	TPAUK are not aware of this evidence that suggests that long term cardiovascular outcomes are better for those who remain	Thank you for your comment. Some evidence related to this point is in publications by Franklyn et al 2005 in JAMA, Boelaert et al 2013 in JCEM. Note that

				hypothyroid and would appreciate being provided with a copy of this document for consideration	cardiovascular outcomes in those who are hypothyroid was not a specific review question for this guideline and therefore the studies themselves are not included within the guideline.
Thyroid Patient Advocacy	Evidence Review L	17	40	In regards to the regulatory perogatives around the use of radiation, one would assume from the comment here that using less is better? This would argue strongly against an increase in the number of patients being treated via this method	Thank you for your comment. The evidence identified in this review supports the recommendation to use radioactive iodine as a default first definitive treatment option. Principles around maintaining radiation doses as low as reasonably achievable do not override convincing evidence to support the use of radiation in general but are likely to inform dosing strategies.
Thyroid Patient Advocacy	Evidence Review L	17	42	Since a consensus could not be reached as to which method of RAI treatment should be used (calculated or fixed dose) and it seems unclear as to the different outcomes these two methods have for the patient, perhaps it may be wise to hold back on recommending RAI as first-line treatment for Grave's disease until such time that appropriate studies have been undertaken	Thank you for your comment. The view of the committee is that both approaches are likely to have a similar balance of risks and benefits to the person being treated and therefore that this is not a reason to delay recommendations to use radioactive iodine. While the committee could not reach consensus on which dosing strategy to recommend, this stemmed primarily from balancing considerations of resource impact against theoretical and debatable regulatory principles.
Thyroid Patient Advocacy	Evidence Review L	18	27	With such uncertainty and a lack of consensus about the clinical and cost benefits of either method of RAI treatment, recommending this treatment as first line therapy does not seem to outweigh the other methods for managing Grave's disease.	Thank you for your comment. The view of the committee is that both approaches are likely to have a similar balance of risks and benefits to the person being treated and therefore that this is not a reason to delay recommendations to use radioactive iodine. While the committee could not reach consensus on which dosing strategy to recommend, this stemmed primarily from balancing considerations of resource impact against theoretical and debatable regulatory principles.
Thyroid Patient Advocacy	Evidence Review M	5	17 - 18	New studies have shown that the risk of atrial fibrillation is more complicated than simply being linked to low TSH. In fact it seems to be linked to both high T3 and low T3. Similarly the link between osteoporosis and low TSH is not now thought to	Thank you for your comment. This section is meant to be give brief introduction to the topic giving the background to the condition. It is not meant to be

				be straightforward. *FT3 concentrations, unlike TSH, correlated with heart rate within a more narrowly defined euthyroid TSH range [46]. A recent meta-analysis confirms that TSH measurements alone are unable to detect cardiac vulnerability with sufficient sensitivity and specificity [47]. In a large prospective study of euthyroid patients with AF undergoing catheter ablation, variations in concentration of thyroid hormones, but not TSH, were associated with recurrence of arrhythmias [48]. Importantly, the risk association, while increasing linearly with FT4, was u-shaped for FT3; both high and low FT3 levels were associated with AF recurrence [48].* ***Lessons from Randomised Clinical Trials for Triiodothyronine Treatment of Hypothyroidism: Have They Achieved Their Objectives?*** *Hoermann R, Midgley JEM, Larisch R, Dietrich JW. Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: have they achieved their objectives? J Thyr Res. 2018;2018:3239197*	exhaustive so we have not gone into detailed discussions.
Thyroid Patient Advocacy	Evidence Review M	8	21	Rather than institute a treatment for which there is no evidence of success surely a logical step would be to increase monitoring to check for a decline into over hyperthyroidism. If this should occur then treatment options could be discussed.	Thank you for your comment. Should a person with subclinical thyrotoxicosis be clinically thyrotoxic then the recommendations for that group will apply. This area is about considering interventions in those who never/have not yet become clinically thyrotoxic.
Thyroid Patient Advocacy	Evidence Review M	8	31	There is a serious ethical problem with a trial that treats a patient with an intervention that is irreversible and will have irreversible effects for a problem for which the benefits of treatment are not yet established. Treatment with antithyroid drugs is at least reversible.	Thank you for your comment. The committee agree that research for irreversible treatments is challenging but important if these treatments are ever to be considered.
Thyroid Patient Advocacy	General	General	General	While TPAUK recognises that the financial burden on health systems of chronic diseases is increasing, we would like to	Thank you for your comment. The committee agrees on the importance of patient information and follow up to

				emphasise that failing to address how well a patient with a thyroid disorder feels ultimately adds to that burden by increased visits to general practitioners and emergency departments. Treating chronic illness should not be a case of "shut up and put up". Appropriate testing and follow up are unfortunately not likely to be cheaper in the short term, but making an extra effort and taking the extra time to help a patient become stable and feel well will pay off in the long run. Since there is no known cure for any autoimmune disease (including Hashimoto's and Grave's disease), efforts to help a patient to understand and manage their own condition should ultimately take some of the strain off the currently beleaguered health care system.	help people understand their condition. The guideline has made recommendations for information and recommendations for follow up and monitoring. There is also a section title “Information for the public” on the guideline web pages on NICE’s web site that provides more information and may link to patient information on other organisations’ web sites.
Thyroid Patient Advocacy	Guideline	10	10	Change to 'Aim to titrate the dose to resolve symptoms ideally maintaining the hormone levels within or close to the population reference ranges.' It is vitally important not to replace removal of symptoms with results from a blood test. FT3 levels are lower for a given TSH/FT4 when treated with levothyroxine than in a healthy person. The ration of FT3 to FT4 is lower too. New studies indicate that symptoms are more closely associated with FT3 levels than FT4 or TSH.	Thank you for your comment. We have amended the first recommendation (1.4.1) to state “Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing.”
Thyroid Patient Advocacy	Guideline	10	17	Change to 'For adults who are taking replacement thyroid hormones for primary hypothyroidism consider measuring hormone levels 6 weeks after a dose change and once levels have stabilised measure hormone levels once a year. Bear in mind advice at 1.4.2 for people who had high TSH levels on diagnosis.	Thank you for your comment. The committee agreed that 3 months was an appropriate time period for the majority of people.
Thyroid Patient Advocacy	Guideline	11	11	Change to 'Consider measuring FT4 and FT3 as well as TSH for adults, young people and children who continue to have symptoms after starting replacement thyroid hormones.'	Thank you for your comment. TSH and FT4 are recommended. No evidence was identified to recommend the use of FT3. The committee noted that FT3 measurements are not useful in

					managing hypothyroidism as T3 is a short acting hormone and measurements will be very different on different days.
Thyroid Patient Advocacy	Guideline	11	16	Symptoms need to be included here. Change to ' …. Take into account features that might suggest underlying thyroid disease such as symptoms previous surgery or raised levels of thyroid auto antibodies.'	Thank you for your comment. The recommendation has been amended to include symptoms.
Thyroid Patient Advocacy	Guideline	12	6	Change to 'if symptoms do not improve after starting replacement thyroid hormones, re-measure TSH, FT4 and FT3 and titrate dose.'	Thank you for your comment. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Thyroid Patient Advocacy	Guideline	12	11	Change to 'Consider replacement thyroid hormones …'	Thank you for your comment. The committee considered that only levothyroxine should be routinely recommended.
Thyroid Patient Advocacy	Guideline	12	23	Change to 'Consider replacement thyroid hormones…'	Thank you for your comment. The committee considered that only levothyroxine should be routinely recommended.
Thyroid Patient Advocacy	Guideline	13	6	Change to '…measuring TSH, FT4 and FT3.' As this would pick up problems of T4 to T3 conversion.	Thank you for your comment. The committee agreed TSH is the most appropriate test in this group. FT4 would have been tested in order to diagnose subclinical hypothyroidism and there would be little benefit in remeasuring it in these circumstances as it is unlikely to have changed. The committee also agreed there is no value in testing FT3 for people with subclinical hypothyroidism.
Thyroid Patient Advocacy	Guideline	13	8	Change to '…disease, such as symptoms, previous thyroid surgery or raised levels of thyroid auto antibodies,'	Thank you for your comment. These recommendations relate to what to do for people who are not receiving treatment or have had treatment stopped and therefore they are unlikely to have symptoms.

Thyroid disease

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Thyroid Patient Advocacy	Guideline	13	17	Change to' …disease. Such as symptoms, thyroid dysgenesis (an under-developed thyroid gland) or raised thyroid auto antibodies,	Thank you for your comment. These recommendations relate to what to do for children with untreated subclinical hypothyroidism and therefore they are unlikely to have symptoms.
Thyroid Patient Advocacy	Guideline	14	General	TPAUK would like to refer the draft NICE guideline committee to the following two references with regards to the recommendations in treating hyperthyroid conditions: 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosisis. Douglas S. Ross et al. Available at: https://www.liebertpub.com/doi/full/10.1089/thy.2016.0229 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. George J. Kahaly et al. Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6140607/#!po=22.0000 These two documents, considered separately or together, contain useful guidelines for the recommended treatment of hyperthyroid conditions and/or Grave's disease. Both have been researched, debated and agreed upon by experts in the area of thyrotoxicosis after thoroughly reviewing available medical literature.	Thank you for your comment. The committee was aware of these two guidelines when writing their recommendations. They made their recommendations based on the available evidence and consensus.
Thyroid Patient Advocacy	Guideline	14	General	Supporting evidence considered by the review board (Thyroid Ultrasonography in Differentiation between Graves' Disease and Hashimoto's Thyroiditis. P. Pishdad,1 G.R. Pishdad,2* S. Tavanaa,1 R. Pishdad,3 and R. Jalli1). "Sonograhphy is safe as it doesn't use ionizing radiation and does not cause tissue damage. It is also more affordable than the other imaging modalities. Since it is a noninvasive	Thank you for your comment. Technetium scanning was considered to be the best option when TRAb tests are negative and ultrasound was only useful if there is a palpable thyroid nodule. The committee would anticipate that clinicians get a person's full consent before going ahead with any diagnosis or treatment interventions.

				modality, patients are comfortable during the process. No specific preparation or discontinuation of medications is needed for this procedure [3]." This evidence that has been considered by the committee states that radioactive scintigraphy poses risks that should be comprehensively weighed up against a more benign and thorough ultrasound examination by a competent technician (including ultrasound using colour doppler flow). Several of the supporting documents used throughout this section of the draft recommendations mention the desirability of avoiding exposure to radiation where possible, TPAUK would like to add that a patient's fully informed consent is required for any diagnostic tests. Since the above reference document examines the use of "grey scale sonography" only, and a single radiologist whose competence and experience was not deliniated, decisions regarding the comparative usefulness of sonography vs scintiography should be postponed until more comprehensive studies have been undertaken. In the meantime the cheaper, safer option of ultrasound sonography should be utilised.	
Thyroid Patient Advocacy	Guideline	14	General	...A possible resource for you consideration: Role of color Doppler in differentiation of Graves' disease and thyroiditis in thyrotoxicosis. Ragab Hani Donkol, Aml Mohamed Nada, and Sami Boughattas "CONCLUSION: Color Doppler flow of the inferior thyroid artery can be used in the differential diagnosis of thyrotoxicosis, especially when there is a contraindication of thyroid scintigraphy by radioactive material in some patients." "a diffusely increased thyroid blood flow is pathognomonic of untreated Graves' disease and an abnormal color flow Doppler (CFD) pattern identifies the majority of Graves' patients with a normal thyroid ultrasound pattern." Again a single radiologist was used throughout this study,	Thank you for your comment. This small study of 26 people did not meet our criteria for the evidence review specified due to the nature of the reference standard used (no involvement of TRAbs).

				however it seems care was taken to select a very experienced radiologist.	
Thyroid Patient Advocacy	Guideline	14	General	In addition, arguing against increased use of radioactive scintiography: Supporting evidence considered by this review board (Does autoantibody-negative Graves' disease exist? A second evaluation of the clinical diagnosis. Paunkovic J1, Paunkovic N.) states that "Based on this work, TSH receptor autoantibody-negative GD is extremely rare."	Thank you for your comment. This reference is included in our review. On the balance of all evidence available and based on their experience, the committee considered the recommendation for scintigraphy where it is as appropriate.
Thyroid Patient Advocacy	Guideline	14	General	Supporting evidence considered by this review board (Diagnosis of Pediatric Hyperthyroidism: Technetium 99 Uptake Versus Thyroid Stimulating Immunoglobulins. Charumathi Baskaran, Madhusmita Misra, and Lynne L. Levitsky) states that "However, not all children with GD have increased TSI." This is an American retrospective pediatric study using TSI (thyroid stimulating immunoglobulin) not total TRAB (TSH receptor antibodies). TSI Test detects only stimulating TSH receptor antibodies the proximate cause of the hyperactive phase of Grave's disease (2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. George J. Kahaly et al. , p.7) . The inhibitory or 'neutral' TRABs are not detected by the TSI test, but these are still indicative of Grave's disease. Total TRAB tests may be more informative in these situations. TPAUK would like to ask the draft guidelines committee to familiarise themselves with the functionally different types of TRAB. Medline has many papers discussing these and the European guidelines for the Management of Graves' Hyperthyroidism references papers that may be useful for the committee to consider This paper also advises that Technetium scintiography, while preferable to I123 scans, still exposes patients to radioactivity: "Uptake studies with 123I or 99Tc (99mTc) provide accurate and rapid diagnosis but are expensive and involve radiation	Thank you for your comment. This study was included in the evidence review on the topic. The committee was aware of the functionally different types of TRAbs but based on the evidence available at this point did not consider it was appropriate to make recommendations differentiating between them.

				exposure" Addressing the cost of radioacive scanning, albeit from an American perspective and comparing to TSI rather than TRAB testing: "99mTc scan costs approximately two and a half times as much as a blood test for TSI. While 16% of our subjects might have required the 99mTc uptake test in addition to TSI for accurate diagnosis of GD, most children with GD would have been diagnosed with TSI alone. Without doubt, 99mTc uptake is an excellent diagnostic tool for diagnosis of hyperthyroidism. Nevertheless, the additional costs and radiation exposure of such uptake studies need to be factored into the choice of diagnostic tests during the process of decision making."	
Thyroid Patient Advocacy	Guideline	14	General	According to both the 2016 American thyroid association guidelines for the treatment of hyperthyroid disorders and the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism, TRAB (also called TSH-R-Ab) is cost effective in the diagnosis of Grave's disease. " Most immunoassays today use a competitive-binding assay and measure what are referred to as TSH-R binding inhibitory immunoglobulins (TBII). Binding assays only report the presence or absence of TSH-R-Ab and their concentrations, but do not indicate their functional activity" (2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism p.7) "the highly sensitive cell-based bioassays [25, 26, 27, 28, 29, 30, 31, 32, 33] exclusively differentiate between the TSH-R-stimulating Ab (TSAb) and TSH-R-blocking Ab [34, 35]. Also, TSAb is a highly sensitive and predictive biomarker for the extrathyroidal manifestations of GD [36, 37, 38, 39, 40, 41, 42] as well as a useful predictive measure of fetal or neonatal hyperthyroidism" (ibid)	Thank you for your comment. The committee take patient preference into account with all of their recommendations. All NICE guideline recommendations are intended to be taken into account in the context of each individual person's situation.

				TPAUK would also like to remind the review committee that such decision making should take patient preference into account	
Thyroid Patient Advocacy	Guideline	14	9	The European guidelines for the Management of Graves' Hyperthyroidism only recommended use of radioactive Scintigraphy in the case of hyperthyroid conditions coexisting with thyroid nodularity, or prior to RAI ablation. These are the considered recommendations in regards to diagnostic scanning: "Recommendations 3 US examination, comprising conventional grey scale analysis and color-flow or power Doppler examination is recommended as the imaging procedure to support the diagnosis of Graves' hyperthyroidism. 1, ØØØØ 4 Scintigraphy of the thyroid is suggested when thyroid nodularity coexists with hyperthyroidism, and prior to RAI therapy. 2, ØØØ○" ...Please note the strength of the evidence to support these recommendations and also the fact that such recommendations were agreed upon after much research and discussion by appropriate medical professionals	Thank you for your comment. The committee was aware of the European guidelines when writing their recommendations. They made their recommendations for this guideline based on the available evidence and consensus.
Thyroid Patient Advocacy	Guideline	14	10	Please see comment for line 9 (page 14)	Thank you for your comment. The committee was aware of these two guidelines when writing their recommendations. They made their recommendations based on the available evidence and consensus.
Thyroid Patient Advocacy	Guideline	14	11	Please see comment for line 9 (page 14)	Thank you for your comment. The committee was aware of these two guidelines when writing their recommendations. They made their recommendations based on the available evidence and consensus.
Thyroid Patient Advocacy	Guideline	14	17	Please see comment for line 9 (page 14)	Thank you for your comment.

					The committee was aware of these two guidelines when writing their recommendations. They made their recommendations based on the available evidence and consensus.
Thyroid Patient Advocacy	Guideline	14	18	Please see comment for line 9 (page 14)	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Thyroid Patient Advocacy	Guideline	14	19	Please see comment for line 9 (page 14)	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Thyroid Patient Advocacy	Guideline	14	20	Please see comment for line 9 (page 14)	Thank you for your comment. The recommendations are based on the available evidence and committee consensus. The committee agree that TRAbs alone may not confirm Graves' disease. Therefore, it recommends technetium scanning if TRAbs are negative and ultrasound if there is palpable thyroid nodule. No evidence was found for the other tests.
Thyroid Patient Advocacy	Guideline	15	General	As per the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism, TPAUK would like to remind the review committee that the first-line treatment should nearly always be antithyroid medication. Please refer to Recommendation 5 on page 13. "Patients with newly diagnosed Graves' hyperthyroidism should be treated with ATD. RAI therapy or thyroidectomy may be considered in patients who prefer this approach. 1, ØØØØ"	Thank you for your comment. The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore,the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the

					response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options. The committee also recommend antithyroid drugs while patients wait to be seen by a specialist and has added a recommendation to offer antithyroid drugs to stabilise hyperthyroidism for people waiting for treatment with radioactive iodine and surgery.
Thyroid Patient Advocacy	Guideline	15	7	It is worth noting that is very difficult to predict whether an individual will attain lasting remission from hyperthyroid Grave's disease "Patients with severe hyperthyroidism, large goiters, or persistent high titers of TSH-R-Ab are most likely to relapse when treatment stops, but the outcome is difficult to predict." (Kahaly et al. P.13). As you are no doubt aware this difficulty is acknowledged throughout the available medical literature; it is also an area in which the current research into the different functional types of TSH receptor antibodies (TRAB) may prove useful. The European guidelines suggest there is some value in " Monitoring the titers of functional stimulatory and blocking TSH-R-Ab during treatment help in predicting the outcome [58, 59]" since overall TRAB may remain elevated even after levels of the stimulating type of TRAB have fallen and hyperthyroidism has resolved. At minimum practitioners need to be made aware that there are currently three identified sub-types of TRAB: Stimulating, inhibitory and neutral and that these have different (functional) effects on the thyroid gland, hormone levels and the hypothalmus / pituitary / thyroid feedback loop. Please consult	Thank you for your comment. The committee discussed that it is indeed very difficult to identify those patients in whom antithyroid drugs are likely to induce a remission. Research recommendation 3 is aimed at trying to identify subgroups of patients with Graves' disease who are likely to have a good response to antithyroid drugs. The intricacies of different types of TRABs are likely to be discussed in a specialist setting but the evidence regarding this was not reviewed and the committee was unable to recommend discussion of this by all practitioners.

				medline for further information on the functional properties of TRAB. The European guidelines quoted above also reference some relevant papers.	
Thyroid Patient Advocacy	Guideline	15	8	Please see response to line 7, page 15 It is also worth, at this point, reminding the practitioner to provide the patient with appropriate written materials outlining the available treatment options, possible side effects and chances of reaching remission, or undergoing a relapse (as per table 1, which has hopefully been reconfigured and improved by now). This should assist the patient to make an informed decision abour their choice of treatment. Providing written materials is helpful where a patient is experiencing symptoms of thyrotoxicosis and may be less able to process and fully understand information that is supplied, since " In some instances, patients' hyperthyroid state will impair rational decision-making" (Vishnu et al, p.16)	Thank you for your comment. We agree that information-sharing is very important and have included a recommendation that written and verbal information should be provided.
Thyroid Patient Advocacy	Guideline	15	10	This should read "Offer antithyroid drugs as first-line treatment for adults with Graves' " This offers the possibility of remission and in some cases assists the patient to be better able to participate in decision making and management of the disorder (Vishnu et al, p.16). This also aligns with International guidelines for the treatment and management of Grave's disease, as always, patient preference should be respected.	The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore, committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options.
Thyroid Patient Advocacy	Guideline	15	11	With the previous edit this line becomes redundant, and as noted elsewhere it is very difficult to correctly assess whether remission is likely	Thank you for your comment. The committee believe the recommendation should stay as written and therefore this line is still important.

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Thyroid Patient Advocacy	Guideline	15	16	This should read "Offer antithyroid drugs as first-line treatment for adults with Graves'. Thyroidectomy or RAI should be considered if the patient prefers either of those approaches "	The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore,the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options. The committee also recommend antithyroid drugs while patients wait to be seen by a specialist, and has added a recommendation to offer antithyroid drugs to stabilise hyperthyroidism for people waiting for treatment with radioactive iodine and surgery.
Thyroid Patient Advocacy	Guideline	15	17	Please see comment for line 7, page 15 It is not yet possible to reliably predict which patients will attain remission from a hyperthyroid phase of Grave's disease	The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore,the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options.

					The committee also recommend antithyroid drugs while patients wait to be seen by a specialist, and has added a recommendation to offer antithyroid drugs to stabilise hyperthyroidism for people waiting for treatment with radioactive iodine and surgery.
Thyroid Patient Advocacy	Guideline	15	18	Please see comment for line 7, page 15	The guideline recommendations are based on the available evidence and committee consensus. The evidence suggested that radioactive iodine produced better long-term outcomes than antithyroid drugs. Therefore,the committee recommend radioactive iodine as a first-line definitive treatment but also noted important exceptions in the recommendations. The committee also agreed that the response to antithyroid drugs is better in some people than in others. For adults who are likely to have a particularly good response to antithyroid drugs (mild uncomplicated Graves' disease), radioactive iodine and antithyroid drugs could be considered as equally appropriate options. The committee also recommend antithyroid drugs while patients wait to be seen by a specialist, and has added a recommendation to offer antithyroid drugs to stabilise hyperthyroidism for people waiting for treatment with radioactive iodine and surgery.
Thyroid Patient Advocacy	Guideline	15	21	Please change to: " disease if radioactive iodine and surgery are unsuitable, or if the patient prefers this approach"	Thank you for your comment. The recommendations give the most appropriate treatment options to offer or consider for patients. Where there is a choice this is noted in the recommendation. The recommendations also advise what to offer when a treatment option is not appropriate. It is hoped that the discussion on risks and benefits with the person will establish which treatment they choose.

Thyroid disease

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Thyroid Patient Advocacy	Guideline	15	109	Change order of 1.6.8 and 1.6.9 so that antithyroid drugs are first line because they are reversable. Essentially use the same order as with children and young adults.	Thank you for your comment. The committee discussed this and believe this is the best order for the recommendations. Their aim is to emphasise that radioactive iodine is the best treatment option for people with Graves' disease and the characteristics listed in recommendation 1.6.8 (now recommendation 1.6.10). A new recommendation has also been added following stakeholder responses recommending antithyroid drugs are offered to control hyperthyroidism in people who are waiting for treatment with radioactive iodine or surgery.
Thyroid Patient Advocacy	Guideline	16	General	Please alter the order of these recommendations by moving section 1.6.14 into the first position. Treatment for toxic nodules seems to be controversial and a patient's hyperthyroidism should, where possible, be stabilised before they are offered definitive treatments. Nodules need to be investigated and monitored and sometimes a fine needle aspiration helps to determine the nature of any nodules.	
Thyroid Patient Advocacy	Guideline	16	General	While rates of thyroid cancer are thought to be reasonably low, there seems to be a strong indication in the various guidelines that RAI is counter-indicated in the presence of thyroid cancer. Caution is therefore advised in considering radioactive treatment	Thank you for your comment. This guideline excludes people with thyroid cancer. There is a separate thyroid cancer guideline currently in development (https://www.nice.org.uk/guidance/indevelopment/gid-ng10150).
Thyroid Patient Advocacy	Guideline	16	6	Please change to "Consider continued low dose or repeat antithyroid drug therapy, surgery or radioactive iodine depending upon patient preference" "Patients with newly diagnosed Graves' hyperthyroidism are usually medically treated for 12–18 months with methimazole (MMI) as the preferred drug. In children with GD, a 24- to 36-month course of MMI is recommended. Patients with persistently high TSH-R-Ab at 12–18 months can continue MMI treatment, repeating the TSH-R-Ab measurement after an additional 12 months, or opt for therapy with RAI or	Thank you for your comment. This recommendation applies to people with Graves' disease after they have had 12-18 months of treatment with antithyroid drugs as first line definitive treatment. No evidence was identified to suggest repeating antithyroid drugs and the committee agreed it was important to try and resolve the hyperthyroidism. Radioactive iodine or surgery were considered to be the next best treatments.

				thyroidectomy." (Kahaly et al, p.12) Please note that "in some countries, carbimazole, a precursor of MMI, is widely used. Carbimazole is rapidly converted to MMI in the serum (10 mg of carbimazole is metabolized to approximately 6 mg of MMI). They work in an identical fashion" (Douglas et al, section E1).	No evidence was identified relating to the utility of TRAbs measurements before stopping antithyroid drugs. Carbimazole is recommended as it is the licenced drug for the UK whereas methimazole is not.
Thyroid Patient Advocacy	Guideline	16	7	Please see comment for line 6, page 16	Thank you for your comment. This recommendation applies to people with Graves' disease after they have had 12-18 months of treatment with antithyroid drugs as first line definitive treatment. No evidence was identified to suggest repeating antithyroid drugs and the committee agreed it was important to try and resolve the hyperthyroidism. Radioactive iodine or surgery were considered to be the next best treatments. No evidence was identified relating to the utility of TRAbs measurements before stopping antithyroid drugs. Carbimazole is recommended as it is the licenced drug for the UK whereas methimazole is not.
Thyroid Patient Advocacy	Guideline	16	8	Please see comment for line 6, page 16	Thank you for your comment. This recommendation applies to people with Graves' disease after they have had 12-18 months of treatment with antithyroid drugs as first line definitive treatment. No evidence was identified to suggest repeating antithyroid drugs and the committee agreed it was important to try and resolve the hyperthyroidism. Radioactive iodine or surgery were considered to be the next best treatments. No evidence was identified relating to the utility of TRAbs measurements before stopping antithyroid drugs.

					Carbimazole is recommended as it is the licenced drug for the UK whereas methimazole is not.
Thyroid Patient Advocacy	Guideline	19	General	In regards to follow up to RAI treatment: please alter these recommendations so that they are in keeping with international standards of care, especially in regards to the utility of TSH measurements as TSH may still be under the influence of autoimmune activity or a confused feedback loop. Please note specifically that "Most patients eventually develop hypothyroidism following RAI, which is indicated by a free T4 below normal range. At this point, levothyroxine should be instituted. TSH levels may not rise immediately with the development of hypothyroidism and should not be used initially to determine the need for levothyroxine. When thyroid hormone replacement is initiated, the dose should be adjusted based on an assessment of free T4. " (Douglas et al, section D3)	Thank you for your comment. NICE guidelines are made independently of other organisations and recommendations are based on the evidence and committee consensus. The committee agreed to recommend measuring TSH as well as FT4 and FT3 until TSH is in the reference range. When TSH subsequently rises above the reference range (i.e.hypothyroidism develops) starting treatment with levothyroxine is recommended with appropriate monitoring.
Thyroid Patient Advocacy	Guideline	19	General	In regard to follow low up to total throidectomy: please alter these recommendations so that they are in keeping with international standards of care, especially in regard to the utility of TSH measurements as TSH may still be under the influence of autoimmune activity or a confused feedback loop. Please note specifically that "If TSH was suppressed preoperatively, free T4 and TSH should be measured 6–8 weeks postoperatively, since recovery of the pituitary–thyroid axis is occasionally delayed. The appropriate dosing of L-thyroxine will vary with patient body mass index (219), and the percentage of levothyroxine absorbed from the gut. Once stable and normal, TSH should be measured annually or more frequently if clinically indicated." (Douglas et al, section F3)	Thank you for your comment. NICE guidelines are made independently of other organisations and recommendations are based on the evidence and committee consensus. The committee agreed that following thyroidectomy levothyroxine should be offered and monitored using the recommendations for monitoring of patients with hypothyroidism. The recommendation on monitoring after surgery has been amended to read “Consider measuring TSH and FT4 at 2 and 6 months after surgery, and then TSH once a year for adults, children and young people who have had a hemithyroidectomy.”
Thyroid Patient Advocacy	Guideline	19	3	'…until TSH is within population reference range' Stopping the monitoring because TSH is within population reference range	Thank you for your comment. The recommendation does not suggest stopping monitoring TSH, it

				will not reveal those patients who go on to develop an underactive thyroid whose TSH would continue to climb out of the population reference range. Add 'Follow 1.7.3.'	recommends considering longer gaps between measurements.
Thyroid Patient Advocacy	Guideline	19	6	Change levothyroxine to 'thyroid hormone replacement therapy'	Thank you for your comment. Only evidence for levothyroxine was identified and therefore it is levothyroxine that is recommended not any thyroid hormone replacement therapy.
Thyroid Patient Advocacy	Guideline	19	26	Change to consider measuring thyroid hormones	Thank you for your comment. This has been amended to recommend measuring TSH and FT4 at 2 and 6 months post-surgery, then TSH annually. If TSH is below the reference range FT4 (if not already measured) and FT3 should also be measured.
Thyroid Patient Advocacy	Guideline	20	General	We are terribly sorry, but the cheaper TSH test is often misleading in Grave's disease. The exact cause for this is not currently fully elucidated. Both the 2018 European and 2018 American guidelines point out that TSH is not a reliable metric in early treatment of Grave's. Many of the growing number of studies into functional TSH receptor antibodies are undertaken at least in part because it is understood that in some patients TSH can remain unresponsive for a long time. Unless and until the hypothalmus / pituitary / thyroid feedback loop returns to somewhat normal function the TSH is of limited utility and should take a back seat when deciding on treatment. This will likely effect the cost of monitoring the patient, but seems unavoidable if one wants to avoid doing a less than stellar job. This applies mostly to patients who have selected antithyroid drug therapy, but as you can see from previous comments it also applies in the follow up to the other treatment methods for Grave's disease.	Thank you for your comment. These recommendations have been amended to recommend testing with cascading. By cascading we mean measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range
Thyroid Patient Advocacy	Guideline	20	General	Since drug therapy should be adjusted according to thyroid hormone levels, until the feedback loop is reestablished, testing TSH only is unlikely to result in favourable patient response.	Thank you for your comment. These recommendations have been amended to recommend testing with cascading. By cascading we mean measuring FT4 in the same sample if TSH is above the reference range and

					measuring FT4 and FT3 in the same sample if TSH is below the reference range
Thyroid Patient Advocacy	Guideline	20	General	Follow up of adult patients with Grave's disease should be similar to that recommended for children in section 1.7.12. Timing of the blood tests can perhaps be stretched out a little sooner in adults, resulting in some small savings there.	Thank you for your comment. The committee made specific recommendation on which tests to do at which time-point in the treatment and it was felt that this was slightly different for adults and children.
Thyroid Patient Advocacy	Guideline	20	4	Add Trab to this list as declining antibody titres are linked to the likelihood of remission.	Thank you for your comment. No evidence was identified for retesting TRAb levels and the committee felt unable to recommend that this be done routinely.
Thyroid Patient Advocacy	Guideline	21	7	Once a year testing of TSH in adults with subclinical disease may miss a progression into active Grave's disease. Initial six monthly testing might be more beneficial in this population.	Thank you for your comment. This recommendation has been amended to testing every 6 months.
Thyroid Patient Advocacy	Guideline	21	7	A suppressed TSH should be followed up by testing of FT3, FT4 and TSH receptor antibodies to confirm subclinical Grave's disease. It may be worth considering that subclinical Grave's disease may be a normal part of the process for a patient recovering from a hyperthyroid episode, keeping in mind once again the unusual behaviour of TSH in this condition. The patient's prior condition, if known could be useful here. If TRABs have never been tested this could be a useful time to run such a test. If Grave's disease is known to pre-exist, this may be a good time to offer self paid TRAB testing as patients may be willing to pay for such a test, if this is feasible and if the patient wishes to monitor their immune system function. Although at present doctors may not see the value of immune sytem monitoring, results from such tests may prove useful for future research purposes. Please note as far as TPAUK are aware testing for total TRAB is not currently available via private laboratory services	Thank you for your comment. This recommendation advised measuring TSH, and FT4 and FT3 when TSH is outside the reference range. The time period has been amended to testing every 6 months.
Thyroid Patient Advocacy	Guideline	21	12	Please consider changing this line to something along the lines of: "Consider increasing the time period between testing once	Thank you for your comment. This recommendation has been amended to testing every 6 months.

				TSH stabilizes (assuming a euthyroid condition) with a view to eventual once a year testing"	
Thyroid Patient Advocacy	Guideline	24	1 – 10	Hypothyroidism is not defined here although both hyperthyroidism and thyrotoxicosis are included. Ideally hypothyroidism should be defined as a lack of thyroid hormones in the cells and tissues.	Thank you for your comment. This has been added.
Thyroid Patient Advocacy	Guideline	24	16	levothyroxine-liothyronine combination therapies	Thank you for your comment. We are not sure what you mean by this comment. Levothyroxine and liothyronine combination treatment is part of this research question.
Thyroid Patient Advocacy	Guideline	25	General	Recommendation for research What are the effects of the different functional TSH receptor antibodies on thyroid hormone and TSH levels	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
Thyroid Patient Advocacy	Guideline	25	General	Recommendation for research What are the short and long term effects of the disposal of increased levels of radioactive iodine into sewage treatment plants servicing facilities that perform this treatment?	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
Thyroid Patient Advocacy	Guideline	25	General	Recommendation for additional research What are the overall costs to the governmental budget of the various treatment options for Grave's disease? Factoring in the proposed increase in waste products generated by radioactive iodine therapy, and increased monitoring of the health status of exposed health and sewage plant workers	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
Thyroid Patient Advocacy	Guideline	25	20	Replace with 'Thyroid hormone replacement therapy for subclinical hypothyroidism in people under 65'	Thank you for your comment. The focus of the research question the committee wants to address is the

					effectiveness of levothyroxine and not all thyroid hormone replacement therapy.
Thyroid Patient Advocacy	Guideline	25	21	Replace T4 with 'thyroid hormone replacement…'	Thank you for your comment. The focus of the research question the committee wants to address is the effectiveness of levothyroxine and not all thyroid hormone replacement therapy.
Thyroid Patient Advocacy	Guideline	25	29	Whilst TRAB levels help a physician make an educated guess about the likelihood of reaching remission, there is as yet no known way to accurately assess the chance of lasting remission	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The area you highlight was not a focus of the guideline.
Thyroid Patient Advocacy	Guideline	27	7	It should be understood that hypothyroidism should be diagnosed on signs and symptoms using clinical judgment and should be ruled out by blood tests alone but more that blood tests should add to the clinical picture. See criticisms in evidence review.	Thank you for your comment. The committee agree that clinical judgment is important but disagree that diagnosis should be based on signs and symptoms alone.
Thyroid Patient Advocacy	Guideline	27	18	Likewise, patients with a confirmed autoimmune thyroid disorder may justify for screening for other autoimmune disorders	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. Investigations for other conditions based on the presence of thyroid disease was not an area of focus for the guideline
Thyroid Patient Advocacy	Guideline	27	22	Patients suffering from depression and anxiety should be comprehensively screened for thyroid dysfunction prior to initiating antidepressant medication	Thank you for your comment. The committee have recommended considering testing for thyroid dysfunction in people with depression or unexplained anxiety.
Thyroid Patient Advocacy	Guideline	28	15	See criticisms of Evidence Review.	Thank you for your comment.
Thyroid Patient Advocacy	Guideline	28	25	If subsequent tests are only performed when the TSH is outside the 95% population reference range people with central hypothyroidism, dysregulated HP axis, positive auto immune antibodies or poor T4 to T3 conversion will be missed. See criticisms in evidence review [C].	Thank you for your comment. Different testing strategies are recommended for people in whom secondary thyroid disease is suspected.

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Thyroid Patient Advocacy	Guideline	29	3	Adults with secondary thyroid dysfunction are normal identified by testing TSH, FT4 and FT3 so how will a different approach be applied to them?	Thank you for your comment. The guideline contains separate recommendations for testing when secondary thyroid disease is suspected.
Thyroid Patient Advocacy	Guideline	29	11	See criticisms of Evidence Review [C]	Thank you for your comment. We have responded to those comments in turn.
Thyroid Patient Advocacy	Guideline	29	19	This needs to say 'TPA and Tg antibodies'	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Thyroid Patient Advocacy	Guideline	29	20	Measuring thyroid auto antibodies (both TPO and Tg) can be informative if symptoms still persist after treatment.	Thank you for your comment. The committee found no evidence to support monitoring auto antibodies after treatment and based on their experience, did not consider that there was sufficient benefit to warrant the resource impact or investigative burden.
Thyroid Patient Advocacy	Guideline	29	23	Needs to say 'TPO and Tg antibodies'	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line

					with current practice. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Thyroid Patient Advocacy	Guideline	29	27 - 28	See criticisms of Evidence Review [E]	Thank you for your comment. We have responded to those comments in turn.
Thyroid Patient Advocacy	Guideline	30	6 - 7	This should say 'Natural Desiccated Thyroid (NDT)'	Thank you for your comment. The committee chose to use natural thyroid extract in the guideline.
Thyroid Patient Advocacy	Guideline	30	15	No evidence was presented in Evidence Review [E] to show that a suppressed TSH was harmful in a patient treated with replacement thyroid hormones when FT4 and FT3 were within the 95% population reference ranges.	Thank you for your comment. TSH suppression was considered harmful by the committee based on their experience and on the large body of observational evidence that long term TSH suppression is associated with adverse cardiovascular and skeletal outcomes.
Thyroid Patient Advocacy	Guideline	30	20	The committee shows some bias in coming to this conclusion about Natural Desiccated Thyroid (NDT) in that the same considerations given toe the levothyroxine/liothyronine combination in lines 9-13 and 18-19 on page 30 should be given here. In fact the one study in the evidence review comparing levothyroxine to NDT showed a significant positive result for patient preference with nearly half the subjexts preferring NDT despite the untitrated dosing. Also in lines 1 and 2 on page 31 the committee felt that it wa unable to make recommendations on iodine or selenium because of the lack of evidence but showed bias against NDT when they were quite happy to make a recommendation that changes the status quo for NDT without any evidence. To be logical and consistent with both the evidence reviewed and the recommendations made for T4/T3 combinations this should be changed to 'However, the committee noted the one trial reviewed did show significant patient preference and anecdotal evidence suggests beneficial effects of treatment	Thank you for your comment. NDT is an unlicensed treatment in the UK and there was no evidence to suggest it was beneficial over a licensed alternative, as a consequence the committee agreed it was not necessary to recommend further research in this area. NICE cannot make research recommendations for an unlicensed product.

				with NDT in small subgroups of patients. Based on this evidence, the committee concluded that levothyroxine should be offered as first-line treatment for primary hypothyroidism and that NDT should not be routinely offered. However they noted the limited evidence in this area and made a recommendation for research to help inform future guidance.'	
Thyroid Patient Advocacy	Guideline	30	22 - 23	The committee did not note that NDT has been used safely for many years and continues to be used safely. The committee did not produce evidence or reasoning to show that the T4:T3 hormone ration in NDT might cause adverse effects.	Thank you for your comment. NDT is an unlicensed treatment in the UK and there was no evidence to suggest it was beneficial over a licensed alternative.
Thyroid Patient Advocacy	Guideline	30	23	Natural Desiccated Thyroid has been offered on the NHS for many years and was 'grandfathered' in that it has been in use successfully for so many years and that it was accepted as a licensed medicine. The branded medicines, including Armour and ERFA amongst others, are licensed prescription medicine in other countries including the USA and Canada. The hormone content of NDT is regulated and monitored in the same way as all prescription medicines. The committee offered no evidence for their blanket refusal to consider NDT for those cases where symptoms are not resolved with T4 monotherapy or levothyroxine/liothyronine combinations, and in fact ignored some findings of the one RCT that was considered. This leaves the many hypothyroid patients for whom NDT is the only medicine that makes them well with the only option to pay for private prescription or to buy NDT over the internet. At the very least, given the results of the reveiwed paper and the amount of anecdotal and epidemiological evidence that is available on NDT, the logical and unbiased conclusion for the committee to make woruld have been to suggest that NDT should be included in the recommendations for futehr research	Thank you for your comment. NDT is an unlicensed treatment in the UK and there was no evidence to suggest it was beneficial over a licensed alternative. NICE cannot make a research recommendation if a product is not licensed.

				into T4/T3 combinations, especially considering they felt that a closw release T4/T3 preparation would be usefully considered.	
Thyroid Patient Advocacy	Guideline	31	12	The evidence that this recommendation was based on was poor. TSH level does not equate to symptoms. Treatment should be monitored primarily by remaining symptom free.	Thank you for your comment. The committee agree that symptoms are important but TSH level is also important. The recommendations have been reworded to reflect this feedback.
Thyroid Patient Advocacy	Guideline	31	13 - 17	In contrast to what is said here the committee noted in Evidence Review [F] page 13 line10 '*The committee noted that reference ranges are ranges and that for each individual person there will be variability as to what exact TSH targets are most appropriate for them.'*	Thank you for your comment. The rationale has been edited to reflect this feedback and the following additional text added “Nevertheless, the committee acknowledged that some people may still have troublesome symptoms even with TSH levels in the reference range. Therefore, they recommended adjusting the dose of levothyroxine if symptoms persist to achieve optimal wellbeing for individual patients. The committee also agreed that it was important not to use doses high enough to cause TSH suppression or thyrotoxicosis.”
Thyroid Patient Advocacy	Guideline	32	9	See TPAUK comments on Evidence Review [F] Monitoring Thyroid Disease	Thank you for your comment.
Thyroid Patient Advocacy	Guideline	32	21	No evidence was presented to support the figure of 10mlU/L for TSH. Should this say 'In a patient without symptoms a TSH of 5-10mlU/L…'?	Thank you for your comment. This figure was based on the committee’s experience and consensus. It is meant to apply to everyone regardless of symptoms.
Thyroid Patient Advocacy	Guideline	33	9	Change to 'with replacement hormones if thyroid hormone levels are appropriate for age.'	Thank you for your comment. The focus of the research question the committee wants to address is the effectiveness of levothyroxine and not all thyroid hormone replacement therapy.
Thyroid Patient Advocacy	Guideline	33	18	See TPAUK's response to Evidence Review [G] Managing Subclinical Hypothyroidism	Thank you for your comment.
Thyroid Patient Advocacy	Guideline	33	27	Change to 'Trabs provide confirmation of clincal features that suggest Graves Disease and may help predict likelihood of remission being achieved'	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. Prediction of remission was not an area of focus for this guideline.

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Thyroid Patient Advocacy	Guideline	33	29	However, predicting chances of remission is not an exact science at this point and patient preference should still be respected regarding preferred treatment modality.	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. Prediction of remission was not an area of focus for this guideline.
Thyroid Patient Advocacy	Guideline	34	13	The 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism states that a "conventional grey scale analysis and color-flow or power Doppler examination is recommended as the imaging procedure to support the diagnosis of Graves' hyperthyroidism." (Kahaly et al, p.10)	Thank you for your comment. The committee made their recommendations based on the evidence identified in the review and their experience.
Thyroid Patient Advocacy	Guideline	34	17	The 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism recommends that "Scintigraphy of the thyroid is suggested when thyroid nodularity coexists with hyperthyroidism, and prior to RAI therapy" (Kahaly et al, p.10)	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The level of granularity you reference was not the degree the committee considered in this area.
Thyroid Patient Advocacy	Guideline	36	3	On the contrary RAI was judged by your good selves to represent a 'harm' to euthyroidism	Thank you for your comment. The committee agreed overall it was important to avoid hyperthyroidism persistence and that the balance of remaining euthyroid vs hypothyroid was debatable. The exact aim of treatment was not the focus of a specific evidence review.
Thyroid Patient Advocacy	Guideline	36	6	The assessed poor quality of the studies meant that no conclusions could be drawn either way about the risk of cancer or all cause mortality	Thank you for your comment. The committee disagree that no conclusions could be drawn; however they acknowledge that the evidence base has some limitations in its requisite reliance on non-randomised studies.
Thyroid Patient Advocacy	Guideline	36	10	It's hard to judge the balance of risks and benefits of RAI treatment given the papers considered during this process TPAUK strongly feel that not enough weight is given to patient preference, whilst aknowleging that a significant number of patients may prefer this approach anyway. An increase in the use and disposal of radioactive materials probably needs	Thank you for your comment. On the basis of full breadth of the clinical and cost effectiveness evidence the committee agreed it was appropriate to make recommendations that meant radioactive iodine would be offered over the other first line definitive treatment options (long term ATDs or surgery) to more people than

				further thought, a higher level of monitoring (including environmental) , and is an area for future studies. Overall we agree with the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism that " Patients with newly diagnosed Graves' hyperthyroidism should be treated with ATD. RAI therapy or thyroidectomy may be considered in patients who prefer this approach" Making treatment with ATDs the first-line treatment and the other options available if patients prefer either of those methods	is currently the case. However, they listed a number of situations in which either of the alternatives may be preferable and emphasised the importance of discussing this treatment with the patient in recommendation 1.6.7. If a person refuses radioactive iodine then other options can be considered.
Thyroid Patient Advocacy	Guideline	37	16	This cannot be determined on the basis of one study alone	Thank you for your comment. The guideline committee felt that the evidence base is strong enough to support the recommendations.
Thyroid Patient Advocacy	Guideline	39	12	Iatrogenic hypothyroidism can generally be avoided if antithyroid drugs are titrated according to thyroid hormone levels and it is remembered that TSH has limited utility in early Grave's disease.	Thank you for your comment.
Thyroid Patient Advocacy	Guideline	4	7	Thyroid disease can respond well to treatment.	Thank you for your comment. The committee has reviewed this and in their experience thyroid disease does usually respond well to treatment and therefore have left the statement as originally written.
Thyroid Patient Advocacy	Guideline	4	8	The goal of treatment is to remove symptoms (not manage them which implies a different thing) ideally to align thyroid function tests to within or close to the population reference range.	Thank you for your comment. We have changed ‘manage symptoms’ to ‘alleviate symptoms.
Thyroid Patient Advocacy	Guideline	4	18	Where is the evidence that supports this statement? The experience of many TPAUK subscribers would not necessarily support this and suffers can have symptoms that are permanently present as well as symptoms that come and go or change in intensity which disappear when treatment is optimal for the individual.	Thank you for your comment. We have amended this bullet point to read “Day-to-day changes in unexplained symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine.” We have also amended the previous bullet point to read “Symptoms may lag behind treatment changes for several weeks to months.”

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Thyroid Patient Advocacy	Guideline	41	8	TSH alone may be sufficient for monitoring once the pituitary-thyroid feedback loop has normalised, until that point it is more harmful than helpful since the temptation (and perhaps pressure?) to regard it as a useful metric is so great	Thank you for your comment, the timing of the monitoring recommendations is intended to reflect the point at which TSH alone becomes sufficiently useful to be the predominant biochemical marker used
Thyroid Patient Advocacy	Guideline	47	12	Change to 'Most people with a non-malignant enlarged thyroid gland, normal thyroid function and no symptoms need no treatment as it is symptoms that are important.	Thank you for your comment. The committee agreed that even people with mild symptoms may not need treatment and have therefore prefer to leave the text as written. This context section is not part of the recommendations and provides background information.
Thyroid Patient Advocacy	Guideline	47	18	Long-term consequences of hypothyroidism include cardiovascular disease, and increase in cardiac risk factors including hypercholestolaemia and myxoedema.	Thank you for your comment. This context section is not part of the recommendations and provides background information. It is not meant to be an exhaustive discussion of the conditions in question.
Thyroid Patient Advocacy	Guideline	5	11	This should read 'possible drug interactions of their replacement thyroid hormones, including interaction with over the counter medicines – again it should not be assumed that the replacement thyroid hormones will be levothyroxine.	Thank you for your comment. We have changed ‘levothyroxine’ to ‘thyroid hormone treatment’.
Thyroid Patient Advocacy	Guideline	5	13	How and when to take their thyroid medications – again it should not be assumed that the replacement thyroid hormones will be levothyroxine.	Thank you for your comment. The committee agreed the specific issue here was how and when to take levothyroxine.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 2, column 4 "Small chance of not needing thyroid medicines in the long term" please change to "Remission from Grave's disease via the use of antithyroid medication is difficult to predict, and relapse rates can be higher with this method of treatment necessitating repeat or long term drug therapy" Some bias evident in the draft text	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 "Likelihood of long-term hypothyroidism with need for levothyroxine" please change to "strong likelihood of permanent hypothyroidism with a consequent need for thyroid hormone replacement therapy"	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with

				TPAUK, with access to patient experiences over many years, would like to remind the authors of this draft proposal that a small but significant proportion of hypothyroid patients do not respond well to levothyroxine	thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 Please add "Patient must be informed that in the event of life-long a hypothyroid condition being attained, replacement hormone will be prescribed."	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 Please note: " A recent meta-analysis found no increase in the overall cancer risk after RAI treatment for hyperthyroidism; however, a trend towards increased risk of thyroid, stomach, and kidney cancer was seen, requiring further research" (2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosisis. Douglas S. Ross et al)	Thank you for your comment, the issue of a potential association between radioactive iodine use and cancer is explored in detail in the evidence review on radioactive iodine safety. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 Please add: "Increased likelihood of weight gain post-treatment" Please see 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. George J. Kahaly et al. Page 18	Thank you for your comment, the issue of a potential association between radioactive iodine use and cancer is explored in detail in the evidence review on radioactive iodine safety. The table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 "Need for short-term radiation protection (limited contact with other people for a few days after treatment)" please change to "need for patient to fully understand short-term radiation	Thank you for your comment, the issue of a potential association between radioactive iodine use and cancer is explored in detail in the evidence review on radioactive iodine safety. The table has been removed

				protection and the ability to implement post-treatment protocols"	from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 TPAUK foresee an increase in the financial burden to the country in the monitoring of effluent in sewage treatment plants connected to treatment centres using higher levels of radioactive iodine. While not seemingly patient specific, some patients may not want to contribute to the environmental load of radioactive waste. Furthermore it is currently unknown what, if any, impact this will have on the future health of sewage plant workers	Thank you for your comment. Regulations governing waste disposal are covered by the Environmental Permitting (England &Wales) Regulations 2016 (EPR2016) and are beyond the remit of this guideline. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 3 "Long-term hypothyroidism after total thyroidectomy and the need for life-long levothyroxine" please change to "Long-term hypothyroidism after total thyroidectomy and the need for life-long thyroid hormone replacement therapy" Again TPAUK would like to remind the authors of this draft proposal that a small but significant proportion of hypothyroid patients do not respond well to levothyroxine	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 2 Please add "Patient must be informed that in the event of life-long a hypothyroid condition being attained, replacement hormone will be prescribed in amounts and forms as determined by the medical practitioner"	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 4 "Low long-term cure rate (fewer than half of people)" Please change to "Low long-term remission rate". In order to use the term "cure rate" a definition of what precisely constitutes a cure	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the

				is necessary and this has by no means been agreed upon; some of the proposed definitions would argue that none of the generally accepted treatment options (Antithyroid medication, total thyroidectomy or RAI) offer a cure for Grave's disease. To use the term in relation to antithyroid drug treatment and not the other treatment modalities suggests bias.	recommendation on providing information to people with thyrotoxicosis. A bullet point has been included mentioning the need for thyroid hormone replacement if treatment leads to life-long hypothyroidism.
Thyroid Patient Advocacy	Guideline	6	General	Table 1, Row 3, column 4 "Rare but serious side effects such as: agranulocytosis (low white blood cells) with carbimazole and propylthiuracil; liver failure with propylthiuracil; and pancreatitis with carbimazole" Please consider moving this comment to the last position in this column since although the possibility of such side effects exist their occurrence is, as mentioned, quite rare. Placing this comment high up in the hierarchy gives the impression that these side effects are quite common	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	General	Please change the table structure so that column 2 (Radioactive iodine) and column 4 (antithyroid drugs) are reversed. COMMENTARY: please see the 2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism. George J. Kahaly et al Recommendation 5 on page 13. Antithyroid drugs should nearly always be used as the first-line therapy for the management of Grave's disease, even when the patient is to proceed to one of the other treatment options	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	Table 1	In Benefits/advantages (within table) the use of the word cure seems inappropriate here.	Thank you for your comment. This table has been removed from the guideline as we were unable to provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	6	Table 1	Table 1, Row 2, column 2 "Non-invasive treatment with an excellent cure rate of	Thank you for your comment. This table has been removed from the guideline as we were unable to

				overactive thyroid". Please change to "Non-surgical radioactive treatment which removes hyperthroidism in a significant proportion of patients". The use of the term "excellent cure rate" is misleading and indicates a strong bias	provide definitive numbers for risks. Some of the information has been transferred into the recommendation on providing information to people with thyrotoxicosis.
Thyroid Patient Advocacy	Guideline	7	10	This should be Diagnosing Thyroid Disease/Investigating Thyroid enlargement	Thank you for your comment. We think the title “Investigating suspected thyroid dysfunction or thyroid enlargement” most accurately reflects the recommendations and have left it as it is.
Thyroid Patient Advocacy	Guideline	7	13	Change to 'Consider tests for thyroid dysfunction in adults, young people and children to support to support diagnosis but bear in mind that symptoms are as important as blood test results. One symptom alone may not be indicative of thyroid disease.	Thank you for your comment. The aim of this set of recommendations is to indicate who need the thyroid function tests. Therefore, we have not added the statement about blood results to the wording of the recommendation.
Thyroid Patient Advocacy	Guideline	7	18 - 19	Family history of thyroid disease or auto immunity should be included along with type 1 diabetes or other auto immune disease and new-onset atrial fibrillation.	Thank you for your comment. We did not find evidence for family history as a clear indication of thyroid disease. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated. The guideline does include specific symptoms/conditions where we found evidence for an association.
Thyroid Patient Advocacy	Guideline	8	7	This is disingenuous as central hypothyroidism will only be revealed by testing TSH with FT4 and FT3. How will people with central hypothyroidism be diagnosed as they will always be told that their thyroid function is fine as their TSH is in range? Patients can have symptoms despite having hormone levels within population reference ranges when they have auto immune hypothyroidism.	Thank you for your comment. This recommendation refers to people with confirmed primary hypothyroidism. The guideline focuses on primary thyroid disease; although there is some consideration on appropriate testing for people when secondary thyroid disease is suspected in the recommendations prior to the one you highlight.
Thyroid Patient Advocacy	Guideline	8	10	As in line 7 above this will mean that nobody with central hypothyroidism or poor T4 to T3 conversion will get diagnosed.	Thank you for your comment. This recommendation refers to people with confirmed primary hypothyroidism.

					The guideline focuses on primary thyroid disease; although there is some consideration on appropriate testing for people when secondary thyroid disease is suspected in the recommendations prior to the one you highlight.
Thyroid Patient Advocacy	Guideline	8	16	How will pituitary dysfunction be suspected? It is usually suspected when TSH does not rise as it should when FT4 and FT3 are low.	Thank you for your comment. The committee agreed there would be other pointers towards pituitary disease. The guideline focussed on primary thyroid disease and not secondary. We have made this clear in the context section.
Thyroid Patient Advocacy	Guideline	8	21	Perhaps a repeat test would be the point at which to suggest testing FT4 and FT3, TPA and Tg antibodies as well as TSH if symptoms do not lessen with the 6 weeks.	Thank you for your comment. These recommendations only cover the initial thyroid function tests and not antibody testing.
Thyroid Patient Advocacy	Guideline	9	5	Consider measuring TPO and Tg antibodies. Both types of antibody can be present together or separately. Consider measuring antibodies if symptoms persist with treatment as high antibody titres seems to be associated with active disease.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Thyroid Patient Advocacy	Guideline	9	8	Considering measuring TPO and Tg antibodies.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with

					hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Thyroid Patient Advocacy	Guideline	9	14 - 16	There is not enough evidence to show that it doesn't work either so the option to try it should be left open for individual patients who find that levothyroxine alone does not resolve their symptoms.	Thank you for your comment. The committee makes the recommendations for NICE guidelines using the available evidence and consensus of the committee. Evidence was not found to support the use of liothyronine. The high list price also made it highly unlikely to make it cost-effective should the evidence exist. With this in mind the guideline recommends that liothyronine should not be routinely prescribed. This allows for healthcare professionals to use their discretion on using liothyronine for individual patients.
Thyroid Patient Advocacy	Guideline	9	17 - 19	This sentence shows bias and should be changed. The recommendation is substantially different from that for liothyronine in lines 14-16 page 9 whilst the very small amount of reviewed evidence leaves the committee in a similar position. The evidence that was reviewed showed that patients significantly preferred Natural Desiccated Thyroid (NDT). It is not acceptable to say that long term adverse effects are uncertain when this is not applied to levothyroxine or liothyronine. No effort was made to look for evidence of long-term impact and in fact NDT has fewer adverse effects than levothyroxine. It has a long history of safe and successful use. Change to 'Do not offer Naturual Desiccated Thyroid (NDT) routinely for primary hypothyroidism' as has been said for liothyronine because then it would be available for non-routine cases.	Thank you for your comment. The committee believe it is justified in including the statement about unknown adverse effects because of the high proportion of T3 to T4 in them. Licensed medications go through a rigorous process of testing before they are available to be prescribed.

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Thyroid Patient Advocacy	Supporting document Methods chapter	7	General	Central hypothyroidism was studiously avoided in the draft NICE guidelines for Thyroid Disease there needs to be a link to the guidelines on Central hypothyroidism.	Thank you for your comment. The focus of the guideline was on primary thyroid disease. Secondary thyroid disease was considered in the recommendations on initial testing. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders.
Thyroid Petition Scotland	Evidence Review A	General	General	Every comment made in my earlier submission as a stakeholder prior to the guidelines process beginning still stands. See document submitted last year. Nothing has changed and I am damned if I am going to write the whole lot again. The problems have been roundly ignored in those submissions by myself and various other thyroid groups.	Thank you for your comment. We are sorry to hear that you believe your comments to have been ignored. We believe we have covered what we said we would in response to your comments on the scope. The guideline reviewed the evidence for several of the areas you suggested and includes recommendations on information for patients, diagnostic tests, and natural thyroid extracts.
Thyroid Petition Scotland	Evidence Review C	General	General	The complete lack of evidence cited for the use of Thyroid Function Guidelines and the fact that the original guidelines by the Association of Clinical Biochemists have been archived ought to be a red flag that work ought to be done on obtaining evidence prior to basing an entire set of NICE guidelines on these.	Thank you for your comment. Different expert groups may use different methods for deriving evidence and composing clinical guidelines. The current guidance was produced in accordance with the NICE guidelines manual (2014). This outlines what to do in the absence of evidence including the guideline committee making consensus recommendations.
Thyroid UK	Comments form	Q1		1. Which areas will have the biggest impact on practice and be challenging to implement? We believe that GPs and endocrinologists will find it challenging to implement the non prescribing of liothyronine for their patients as they will have either seen a vast improvement in their patients' symptoms prior to this guidance and be very unhappy that they are not allowed to prescribe or a vast increase in their symptoms if they are denied liothyronine in the future.	Thank you for your comment. The guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine). However, the review did not find evidence of better outcomes compared with levothyroxine.

				Patients are becoming very impatient with doctors and CCGs who do not listen to them and we are concerned that being denied liothyronine will cause a huge lack of trust in clinicians causing a rift between clinicians and patients. This will cause even more patients to seek help from private doctors, which then means that the NHS does not have all the data that it needs on patients, or to self treat by purchasing from outside of the UK.	
Thyroid UK	Comments form	Q2		2. Would implementation of any of the draft recommendations have significant cost implications? If this guideline continues to state that liothyronine should not routinely be prescribed, it may bring cost savings in respect of the drug but there will be an increase in costs of patients visiting GPs and endocrinologists time and time again in an attempt to resolve all their symptoms. Patients will be referred to various specialists to try to get to the bottom of why they are still ill when liothyronine would improve matters. We already know that patients are contacting us because their symptoms have returned and they are having to go through appeal processes in order to try to get their liothyronine prescribed again. This is all such a waste of time and money both for the clinicians, the CCGs and especially the patients.	Thank you for your comment. The recommendation is based both on clinical effectiveness and cost effectiveness evidence taken together. On balance the committee felt that the clinical evidence was not strong enough to recommend the routine use of liothyronine. There was no clinically important difference between the two treatments in terms of general health-related quality of life and five different aspects of quality of life. The committee agreed that it is plausible in some people who are not responding to levothyroxine that combination therapy may be beneficial, but it is unclear who those patients are and due to the high costs of liothyronine it was agreed that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine). However, the review did not find evidence of better outcomes compared with levothyroxine. Furthermore, the committee made a high priority research recommendation.
Thyroid UK	Comments form	Q3		3. What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)	Thank you for your comment. The wording reflects the committee's opinion that liothyronine should not be routinely prescribed. A footnote has been added to the rationale and impact section for recommendation 1.3.4

				Changing the wording to similar wording from the RMOC guidance may go some way to allowing the patients who need liothyronine to have it prescribed.	on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).
Thyroid UK	Evidence Review A	15	15	**The committee's discussion of the evidence – General:** Unfortunately, well-being is not always restored in patients with hypothyroidism until the TSH is at or near the bottom of the range. Not all doctors agree with this though. In our experience, patients contact us because their TSH level is within the range but they still experience symptoms. Patients without thyroid disease often have TSH levels nearer the bottom of the range. Hypothyroid patients may become symptom free if their TSH was allowed to decrease via an increase in dosage. If FT4 and FT3 levels were also checked, (this is rare in our experience) this may flag up that the patients need an increase in their medication.	Thank you for your comment. The committee has acknowledged that TSH levels do not always coincide with well-being. The importance of restoring both as well as monitoring treatment has been captured in the recommendations for patient information. The committee acknowledged that targeting TSH towards the lower end of the reference range can be beneficial for some patients and recommendation 1.4.1 has been amended to suggest further adjustments to treatment in cases where symptoms persist when TSH levels are within the reference range. Cases where FT4 measurement would be useful in the follow-up and monitoring of people with confirmed thyroid disease have been specified in the recommendations. The clinical and cost-effectiveness evidence has not however supported the usefulness of FT3 measures. There has been consensus among the committee that TSH testing alone is sufficient in adults and TFT investigations would not further contribute to monitoring people being treated for thyroid disease for which TSH is in the reference range unless they continue to have symptoms.
Thyroid UK	Evidence Review A	15	19	**The committee's discussion of the evidence – General**: If FT4 and FT3 tests are undertaken as well as TSH and they are within the range, there may well be no reason for treatment if there are no symptoms. **Please see Item 4 above.**	Thank you for your comment. The clinical and cost-effectiveness evidence has not supported the usefulness of routine FT4 or FT3 testing for monitoring people with thyroid disease. There has been consensus among the committee that for people who are not experiencing

					symptoms, TSH alone is a sufficient preliminary investigation and that routine additional FT4/FT3 testing would not provide any additional benefit. The guideline recommends testing for FT4 if TSH is above the reference range, and FT4 and FT3 if the TSH is below the reference range.
Thyroid UK	Evidence Review A	15	27	**The committee's discussion of the evidence – General**: Thyroid UK is often approached by newly diagnosed people who are very concerned that they have not become well yet. It transpires that they have only been on treatment for three/four weeks. If patients were informed that it can take many months for their symptoms to alleviate completely, it would prevent them from worrying.	Thank you for your comment. This has been acknowledged by the committee who has specified that it may take time for treatment to have an impact on thyroid function and that people should be made aware of that to avoid frustration. This is also reflected in the recommendations in the general information to be given to people (1.1.2). Details on the committee's discussion of this can be found in 1.7 the committee's discussion of the evidence in Evidence review A.
Thyroid UK	Evidence Review A	3	Disclaimer	Although NICE have stated in their disclaimer, *"The recommendations in this guideline are not mandatory and the guideline does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and, where appropriate, their carer or guardian"* and NHS England state that, *"The proposed guidance would not remove the clinical discretion of the prescriber in deciding what is in accordance with their professional duties."* in our experience these disclaimers are completely ignored. We know that doctors are having their choice of treatment for a patient taken away from them even though both the doctor, whether it be an endocrinologist or a GP, and the patient are aware that one particular medication is more appropriate for them. At this moment patients are being forced to switch from T3 to levothyroxine against both their own wishes and those of their doctor. Patients are telling us that their doctors do not	Thank you for your comment. The recommendation about use of liothyronine advises against routine use and this does not replace clinical judgment in the management of individual patients. Evidence review E considers the issue of managing hypothyroidism further.

				want to switch them but that they have no choice because they are afraid of getting into trouble with their superiors or the General Medical Council. At a face to face meeting in London regarding the NHS England consultation in the prescribing of liothyronine, Dr Graham Jackson, Co-Chair of NHSCC; Chair, NHS Aylesbury Vale CCG, categorically stated that doctors could decide for themselves whether to prescribe T3 for a patient who had a clinical need. Unfortunately, local CCGs are ignoring this fact and looking solely at the cost of liothyronine. In respect of information for patients, it should be made extremely clear in this guidance that it is **not** mandatory and does **not** override the responsibility of healthcare professionals. It would be better if this was not hidden away in the NICE disclaimer. Doctors must be made aware that they can't be bullied by CCGs if they want to help their patients get or remain well.	
Thyroid UK	Evidence Review A	8	9	**TSH Targets and Symptoms:** We have had women approach us because they have been diagnosed with subclinical hypothyroidism (usually from a Well Woman appointment). Although they have had no symptoms, they have been prescribed levothyroxine and have become poorly with symptoms of thyrotoxicosis. They often continue with the medication because their doctor has told them they need it but have a very poor quality of life at this time. Patients such as these should be given information that this may happen and that if it does, they should stop taking the medication and visit their GP immediately.	Thank you for your comment. The section of the review you refer to is simply a summary of the findings emerging from the included studies. We acknowledge that the management of patients with subclinical hypothyroidism warrants special attention and it was included in the scope of the guideline. The appropriateness of starting treatment for patients with subclinical hypothyroidism as well as managing and monitoring henceforward has been addressed in the recommendations made specifically for these patients in section 1.5 of the recommendations.

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Thyroid UK	Evidence Review A	8	19	**Non specific nature of symptoms**: In our experience, patients do not read the PIL that comes with their levothyroxine and therefore if the doctor doesn't inform them of interactions or side effects, the patient can just attribute these to their condition and not to anything they are doing i.e. taking the tablets at the same time as eating breakfast. Biotin can cause abnormalities in thyroid function tests and information regarding biotin would be useful prior to starting medication. Some patients look for natural alternatives to thyroid hormone replacements but, depending on the cause of their hypothyroidism i.e. total thyroidectomy, patients need to be informed that herbs and supplements i.e. kelp cannot replace their medication effectively.	Thank you for your comment. The importance of providing people with information on the possible interactions and side effects of their medication was highlighted in evidence review A and has been captured in the recommendations. We did not look for evidence on natural products to be able to recommend against their use and the present guideline cannot determine patients' personal choice. We did however look for evidence for selenium and iodine supplementation, the absence of which has led the committee to make a recommendation for future research regarding their usefulness particularly for subclinical hypothyroidism considering patient expressed interest.
Thyroid UK	Evidence Review A	9	16	**Availability of information**: We are aware that doctors don't have much time to explain all aspects of thyroid disease to patients. Because thyroid disease mostly affects patients over 50, some patients are not experienced in using online forums and websites. Information leaflets for these patients are a good idea. At least ask the patient if they would like an information leaflet. The majority of patients who come to us have not been told they have Hashimoto's disease. Thyroid UK suggests that this information is given to the patient if thyroid antibody tests show this to be the case. It is useful for the patient to know that they have an autoimmune condition as they can then pass this information onto family members so that they are aware of the consequences to themselves.	Thank you for your comment. The section on availability of information reflects the themes identified in the evidence in the review. The committee agree that discussing the underlying condition is important and have included this in their recommendations on what information should be given to people. There will also be a section on 'Information for the public' on the guideline webpage which may link to other organisations' web sites.
Thyroid UK	Evidence Review A	9	32	**Risks of over or under treatment:** In our experience, hypothyroid patients sometimes take more medication than	Thank you for your comment. The reasons why patients often take more medication than prescribed cited in the

				they are prescribed to alleviate symptoms rather than weight loss. This is usually done because their GP will not allow an increase even though the patient still has symptoms. Patients are desperate to be well and do not see what else they can do. Information about other reasons for their symptoms i.e. vitamin deficiencies such as vitamin D, iron, vitamin B12 and selenium that have a role in the thyroid system may encourage patients to look into their lifestyle and check that they are eating a well-balanced diet. Vitamin B12 deficiency causes very similar symptoms to hypothyroidism.	line you refer to reflects the information reported in the included studies and these have included both weight loss and the alleviation of symptoms. The importance of adjusting the dose of treatment for people with primary hypothyroidism if symptoms persist, has been addressed in the recommendations relevant to follow-up and monitoring (1.4.1). Reasons for symptoms other than thyroid disease including potential vitamin deficiencies are outside the remit of the guideline.
Thyroid UK	Evidence Review A	n/a	n/a	**Additional comments:** We have been approached by patients needing information on whether they can access benefits whilst going through treatment. Also, they need information for their employers. It would be a good idea if their GP could give them information about this even if it is verbal information.	Thank you for your comment. Information on accessing benefits and information for employers of people with thyroid disease are beyond the remit and scope of this guideline.
Thyroid UK	Evidence Review B	18	4	**The outcomes that matter most**: Some thyroid disease guidance states that doctors should be testing for other conditions that could be causing the patients' symptoms. Some patients are diagnosed with depression before thyroid function tests are undertaken but treatment for depression is not successful. Thyroid UK agrees with the committee that thyroid testing should be undertaken if a patient has depression. However, in our experience patients are not tested for vitamin and mineral deficiencies such as iron, ferritin, vitamin B12, vitamin D and selenium. When patients self test (because their doctor is unwilling to test) they are often found to be deficient, especially in vitamin D which can cause symptoms in adults. Patients should be encouraged to request vitamin and mineral testing from their	Thank you for your comment. Vitamin and mineral deficiency testing and testing for exclusionary conditions is outside the remit of this guideline.

				doctor and if they self test, to ask for their results to be put into their records.	
Thyroid UK	Evidence Review B	19	7	**Cost effectiveness and resource use**: If patients attending Well Woman or Well Man clinics are tested for thyroid disease given levothyroxine even though they don't have any symptoms this could very well be a waste of NHS funds. As I said previously, some of these patients are given levothyroxine and it makes them ill. If there is no clinical suspicion for thyroid disease, perhaps these tests do not need to be done as it would be more cost effective. However, in patients with symptoms or other autoimmune conditions, it may be advisable to test for thyroid function.	Thank you for your comment. The committee agree that testing in the absence of symptoms or suspicion of thyroid disease is ill advised and this is reflected in the recommendations in section 1.2.
Thyroid UK	Evidence Review B	6	3	**Included studies**: It is disappointing that only 8 studies we included in this review. The fact that the quality of the research was mostly moderate to low due to serious risk of bias or serious imprecision is also disappointing. This shows that some good quality research needs to be undertaken in regard to testing for thyroid disease.	Thank you for your comment. Evidence reviews have been carried out in accordance with the NICE guideline method processes. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. Given the nature of the question of Review B, the committee felt it was appropriate to look at cross-sectional and cohort studies. The studies included are those that have met the protocol criteria that were pre-specified to prevent bias and ensure that only studies of the highest quality available that would provide relevant information are included in the evidence review. We acknowledge the need for high quality research regarding testing for thyroid disease, however the

					committee is only able to make a limited set of priority recommendations for future research and there were other areas considered of greater impact which were prioritised.
Thyroid UK	Evidence Review D	7	7	**The outcomes that matter most**: It is disappointing that there was no evidence identified for the outcomes in this review.	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence report. In areas where no such evidence was identified, the committee considered that performing a systematic review of studies of lower methodological quality would have taken a huge amount of resource and considering the likelihood of this evidence being unreliable, would not have assisted decision making. Therefore, committee members have used their collective experience to make consensus recommendations as they have noted that not making a recommendation would leave a gap and expert guidance would be better than none at all.
Thyroid UK	Evidence Review D	7	22	**Benefits and harms:** In our experience, patients prefer to be retested for TPO as this shows the progression of the autoimmune disease whether on levothyroxine or not. Patients with high levels of TPO prior to levothyroxine treatment have informed us that reducing gluten in their diet and/or stress in	Thank you for your comment. The committee agreed that retesting would not provide further information beyond TSH and FT4 testing. We recognise that various strategies for which evidence is lacking can be helpful for people. However, the committee is able to make a limited number of recommendations for future research

				has reduced their TPO levels. Further research into this area is very much needed.	and hence considers making those based on a careful consideration of factors including their importance for patients, their potential impact on the NHS and technical feasibility. Other areas where evidence was lacking such as the clinical and cost-effectiveness of levothyroxine and liothyronine combination therapy whose symptoms have not responded sufficiently to levothyroxine alone, were considered of greater importance and have hence been prioritised.
Thyroid UK	Evidence Review D	7	35	**Cost effectiveness and resource use**: In our experience, patients prefer to know the cause of their thyroid disease. If it is autoimmune this information is useful to their siblings and their children as they may be diagnosed sooner if they develop symptoms.	Thank you for your comment. The committee's view, based on their combined clinical expertise, is that, apart from measuring antibodies once to examine the underlying cause of hypothyroidism, repeated testing would not further contribute to the information provided by hormone testing.
Thyroid UK	Evidence Review E	15	10	**Unit costs:** Concordia (now Advanz Pharma) is being investigated by the Competitions and Marketing Authority. However, the Department of Health have a part to play in the huge rise in the cost of liothyronine. On the 26th June 2019, Oxera published a report, "The supply of generic medicines in the UK" prepared for The British Generic Manufacturers Association. This report shows that the NHS is reimbursing much higher amounts than the actual price of drugs. The report states, *"It shows that, for a large proportion of observations (around 63%), the reimbursement price was 40–100% higher than the manufacturer's actual selling price in the relevant year. It also illustrates, however, that for a sizeable proportion of observations the difference was much larger (up to around 190% higher—i.e. the reimbursement price was 2.9 times the manufacturer selling price in some cases)."*	Thank you for your comment. We have now updated all drug costs in the guideline to 2019 costs (BNF August 2019). We believe that the costs have not changed enough to change the conclusions. This NICE guideline is written from the UKNHS and PSS perspective, and therefore only takes account of UK list prices and does not account for prices outside the UK.

				In the July Drug Tariff, the reimbursement cost of liothyronine is about £184 per pack although we believe the actual cost is much less than this due to competition in the market. We will be urging the Department of Health to reduce the amount they are reimbursing in order to make liothyronine more cost effective. This will mean that the unit costs quoted by NICE and which were used in decision making by the committee will be out of date. If the cost of T3 were to reduce, more patients could benefit from its use. An alternative to the combined treatment of levothyroxine and liothyronine is natural thyroid extract. It is much cheaper to use than T3 and some patients fare much better on it.	
Thyroid UK	Evidence Review E	16	21	**Natural thyroid extract vs levothyroxine**: More research should be undertaken comparing natural thyroid extract and levothyroxine. Anecdotal evidence shows that a lot of patients do very well on natural thyroid extract as opposed to levothyroxine. There is no evidence of harm from the current brands. In fact, there is more evidence of harm with levothyroxine. We are very concerned and disappointed that the committee did not include this in their research recommendations.	Thank you for your comment. Based on their clinical expertise, with no evidence to support the use of natural thyroid extract and its long-term adverse events being uncertain, the committee agreed to recommend against its use. NICE cannot make a research recommendation if a product is not licensed.
Thyroid UK	Evidence Review E	17	20	**Benefits and harms – Combined levothyroxine and liothyronine vs levothyroxine alone**: The research regarding combined levothyroxine and liothyronine vs levothyroxine is not of good quality. Anecdotally, patients that we have had dealings with feel very much better on the combined medication. Levothyroxine is a pro hormone that some people do not convert properly to T3 due to a number of factors including genetic defects i.e. the DIO2 gene and nutrient deficiencies such as selenium deficiency.	Thank you for your comment. We recognise the included evidence was not of high quality. This has been discussed by the committee and taken into account in decision making. The issue you raise has been acknowledged by the committee who has decided to make a recommendation for future research regarding the potential effect of DIO2 polymorphism on the response to treatment with combined levothyroxine and liothyronine.

Thyroid UK	Evidence Review E	17	32	**1.7.1.3 Benefits and harms - Combined levothyroxine and liothyronine vs levothyroxine alone:** Most of the research used in this review was of very low or low quality. Our advisers have published research showing that the studies done regarding levothyroxine and liothyronine combined are not only of low quality but are not asking the right questions. In respect of the statement, "Without RCT evidence to support this hypothesis, the committee agreed it was not appropriate to recommend the use of liothyronine even in this subpopulation" our advisers state, I would like to inform you of the study, *"Lessons from randomised clinical trials for triiodothyronine treatment of hypothyroidism: Have they achieved their objectives.",* (J Thyroid Res. 2018;2018:3239197). The authors, Hoermann R, Midgley JEM, Larisch R, Dietrich JW., explain: *"Given the high individuality expressed by thyroid hormones, their interrelationships, and shifted comfort zones, the response to LT4 treatment produces a statistical amalgamation bias (Simpson's paradox), which has a key influence on interpretation. In addition to drug efficacy, as tested by RCTs, efficiency in clinical practice and safety profiles requires re-evaluation. Accordingly, results from RCTs remain ambiguous and should therefore not prevail over physiologically based counterarguments. In giving more weight to other forms of valid evidence which contradict key assumptions of historic trials, current treatment options should remain open and rely on personalised biochemical treatment targets.* *Optimal treatment choices should be guided by strict requirements of organizations such as the FDA, demanding treatment effects to be estimated under actual conditions of use. Various improvements in design and analysis are*	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. We acknowledge the included evidence was not of high quality. This has been discussed by the committee and taken into account in decision making. The article you provide does not justify making a change to NICE guideline method processes. We are pleased you are happy with the research recommendation and hope it will help establish a better understanding of the effectiveness of combined levothyroxine and liothyronine therapy in the future. The statements you reference are subjective and not entirely in line with the committee's viewpoint or standard NICE methodologies. Those statements do suggest that there is equal efficacy between LT4 and LT3/LT4, and given the substantial difference in costs of these approaches, there is therefore a reason not to use the more expensive approach (combination therapy).

				recommended for future randomised controlled T3/T4 combination trials." In their conclusion they state, "*Until better evidence becomes available, the reliance on dated RCTs should be questioned, giving more weight to other forms of valid evidence that have accumulated in recent years and contradict key assumptions from these trials. In addition, strict regulations by organizations such as the FDA demand treatment effects to be estimated under actual conditions of use. To achieve this, inherent shortcomings of RCTs, such as the expectancy bias caused by uncertainty about the treatment in RCTs, as opposed to treatment certainty under conditions of use, must be addressed."* Prof Rudolph Hoermann has told us, *"In other words, an RCT informs whether a drug is suitable, compared to alternatives, either no drug or another drug. In this respect, LT4 vs LT3/LT4 come out equal.* *Therefore, equal efficacy has been demonstrated in RCTs. There is no reason that T3/T4 cannot be used. If a drug is deemed usable, then its is about actual drug use. When to use that drug, not if that drug can be used. The practical use of a drug is evaluated in the real world, under "conditions of actual use". Practical recommendations of drug* ***use*** *have to assess both efficacy and conditions of actual use* *The consideration of RCTs as the sole class of evidence is biased and in blatant violation of legal requirements of the process of evaluating a drug established by a leading organisation in the world."*	

				We are pleased that the committee made a recommendation for better quality research to be undertaken and since the RCTs used for this review were mostly not of good quality we urge that any further research is done to a much better standard. Perhaps NICE could ensure that patients are involved in the design and control of this research as specified by INVOLVE - https://www.invo.org.uk/	
Thyroid UK	Evidence Review E	17	37	**Levothyroxine high starting dose vs levothyroxine titrated dose:** In our experience high doses for some patients may be unsuitable. Patients should be warned of possible side effects.	Thank you for your comment. The recommendations aim to provide guidance on what constitutes best clinical practice and do not replace clinical judgment in the management of individual patients according to their specific characteristics and needs.
Thyroid UK	Evidence Review E	18	4	**Natural thyroid extract vs levothyroxine**: Given that there was insufficient evidence, no TSH suppression and no clear harms to patients, it might be prudent to allow some GPs to prescribe this to some patients where clinically appropriate. We are aware of large numbers of patients who have been on natural thyroid extract for many years without harm and who have had this taken away from them recently making them ill again. Thyroid UK believes this to be unethical and that these patients should have this medication re-prescribed. At present this is much cheaper than liothyronine and would be most cost effective.	Thank you for your comment. Considering the lack of evidence to support the clinical efficacy and safety of natural thyroid extract, with its long-term adverse events being uncertain, the committee agreed it is unlikely to be cost-effective. The committee also noted that natural thyroid extract is not licensed in the UK.
Thyroid UK	Evidence Review E	18	21	**Cost effectiveness and resource use**: Given that the evidence for this review was poor and that anecdotally, there are a subgroup of patients who feel so much better on this medication, doctors should be informed that they can prescribe liothyronine where clinically appropriate and not be bullied into making patients have levothyroxine when they have symptoms that are unresolved.	Thank you for your comment. Based on the evidence identified and with the long-term adverse events of liothyronine being uncertain, the committee agreed that combination therapy should not be routinely offered. The committee recognises that a sub-group of patients whose symptoms do not respond sufficiently to levothyroxine monotherapy may benefit from combination therapy and has therefore prioritised a recommendation for future research in this area.

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Thyroid UK	Evidence Review E	19	3	**Other factors the Committee took into account**: Perhaps the guidance could state that titration within the reference range should be to the point where patients' symptoms have been resolved.	Thank you for your comment. The point you raise has been taken into account. Recommendation 1.4.1 has been amended to suggest dose adjustments based on symptoms.
Thyroid UK	Evidence Review E	5	8	You have described hypothyroidism as "Hypothyroidism occurs when there are insufficient circulating levels of thyroid hormones". In actual fact, levothyroxine is a pro-hormone. The only active hormone is T3 (tri-iodothyronine). If there are insufficient circulating levels of T3, then hypothyroidism occurs, which is why it is so important to check this level.	Thank you for your comment. This is intended as a brief introduction to the topic area and is not meant to be comprehensive. We have made some changes to this section in response to comments made by stakeholders.
Thyroid UK	Evidence Review E	5	15	**Introduction**: It is **not** usual to have TSH and FT4 testing done. In many areas of the UK, only the TSH is tested. This makes for a postcode lottery.	Thank you for your comment. The recommendations made by the committee have specified the circumstances under which TSH and FT4 should be measured (recommendations 1.2.7 to 1.2.9). We hope the current recommendations will help achieve consistency in clinical practice that is in line with the recommendations across the UK and improve outcomes for people with thyroid disease.
Thyroid UK	Evidence Review E	80	34	**Research recommendation**: In the study, "Variation in the biochemical response to L-thyroxine therapy and relationship with peripheral thyroid hormone conversion efficiency", the authors, John E M Midgley, Rolf Larisch , Johannes W Dietrich and Rudolf Hoermann conclude, *"The findings of the present study have several clinical implications. First, they recognize thyroid hormone conversion efficiency, as defined by the calculated global deiodinase activity or more simply the T3–T4 ratio, is an important determinant of L-T4 dose requirements and the biochemical response to treatment. Second, in view of a T4-related FT3–TSH disjoint, FT3 measurement should be adopted as an additional treatment target. Third, in cases where an FT3–FT4 dissociation becomes increasingly apparent following dose escalation of L-T4, an alternate treatment modality, possibly T3/T4 combination therapy,*	Thank you for your comment. This is beyond the level of detail that is compiled for research recommendations in NICE guidelines.

				should be considered, but further randomized controlled trials are required to assess the benefit versus risk in this particular group." Thyroid UK suggests that any further studies take their conclusion into account.	
Thyroid UK	Evidence Review F	12	23	**Subclinical thyroid dysfunction:** It is disappointing that there was no clinical evidence for this review.	Thank you for your comment. The committee agree that it is disappointing there is no evidence to guide recommendations in this area.
Thyroid UK	Evidence Review F	13	4	**Hypothyroidism**: Since there was no clinically important difference between having a low-normal TSH or a high-normal TSH Thyroid UK believes the other thyroid function tests (FT4 and FT3) need to be done to clarify whether a patient needs more or less levothyroxine.	Thank you for your comment. Despite not being identified in the evidence, the committee recognises that there may be a benefit of targeting different TSH levels for different individuals as people may have different optimal TSH set points. Therefore recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being. The usefulness of FT4 in addition to TSH measures for monitoring people with hypothyroidism who continue to have symptoms has been captured by the recommendations (1.4.6). Measuring FT3 was not considered to further assist in monitoring.
Thyroid UK	Evidence Review F	13	10	**Hypothyroidism**: Every patient is an individual and will have their own set point in regard to both TSH, FT4 and FT3.	Thank you for your comment. The committee acknowledges that individuals may differ in the TSH levels that are optimal for them and recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being.
Thyroid UK	Evidence Review F	13	15	**Hypothyroidism**: We are aware that many doctors only prescribe levothyroxine to a point where the patient just about reaches the TSH range. In our experience, many hypothyroid patients still feel very unwell unless their TSH level is near the bottom of the range.	Thank you for your comment. The committee acknowledges the point you raise and recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being. The committee agreed that measuring FT4 would be useful where patients continue to have symptoms, but

				Without testing FT4 and FT3 it is not known whether these are either within the range or optimal within the range. When testing privately, many patients find that their FT4 is normal but their FT3 is right at the bottom of the range or below and therefore Thyroid UK suggests that both these tests are undertaken for monitoring hypothyroid patients who still have symptoms. It is disappointing that the committee could not come to a consensus about this.	FT3 testing was not considered to further inform monitoring of people with primary hypothyroidism (recommendation 1.4.6).
Thyroid UK	Evidence Review F	13	20	**Hypothyroidism**: In our experience, many clinicians only test for TSH whether the patient has remaining symptoms or not.	Thank you for your comment. A recommendation for measuring FT4 as well as TSH if people continue to have symptoms has been made (1.4.6).
Thyroid UK	Evidence Review F	13	23	**Hypothyroidism**: Thyroid UK does not understand why clinicians can do an FT4 test to check for adherence (presumably to see if the FT4 level is low) but feel it is not necessary to do an FT4 test to check that it is not low due to non-absorption.	Thank you for your comment. This is not a recommendation to use FT4 for that purpose but a descriptor of what the committee is aware is done in some circumstances.
Thyroid UK	Evidence Review F	14	5	**Cost effectiveness and resource use:** Doing combined thyroid function tests (TSH; FT4 AND FT3) would show more quickly what the problem was rather than the patient continually visiting the doctor with symptoms therefore costing the NHS more money.	The guideline outlines the cascade approach in testing which highlights the need for test in a synchronised strategy. The committee is confident that TSH testing in the first instance is sufficient to diagnose thyroid dysfunction when taken into account with the wider clinical picture and with the possibility of further tests as cascaded options. That is if TSH is above the reference range to measure FT4 in the same sample and if TSH is below the reference range to measure FT3 in the same sample. This approach to testing would be both clinically and cost effective for the diagnosis of thyroid disease. Please note that the test would be carried out on the same sample in the lab and therefore patients would not be continually visiting the doctor.

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Thyroid UK	Evidence Review F	15	7	**Hypothyroidism**: Since it has already been mentioned that every patient is an individual and that some patients feel much better at the lower end of the reference range, Thyroid UK is concerned that recommending that the TSH only be maintained within the reference range would continue to allow patients to be unwell if their set point is at the bottom of the range. If patients are well at the bottom of the TSH range, then monitoring could remain once a year unless the patient returns to the doctor with symptoms of overactivity.	Thank you for your comment. Recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being. This line describes the identified evidence which supports a default position of aiming for within the reference range as a starting point. The recommendations have been amended to make the committee's stance on titration within the reference range (i.e. may be appropriate in response to symptoms) clearer.
Thyroid UK	Evidence Review F	15	17	**Hypothyroidism**: Testing TSH only until the patient is within the TSH range is acceptable but if the patient still has symptoms, allowing them to increase dosage to bring their TSH level further down the range would possibly be better for the patient. If the patient still has symptoms, then their FT4 and FT3 should be tested.	Thank you for your comment. The point you raise has been considered by the committee who recognises that individuals may have different optimal TSH levels and targeting TSH at the lower end of the reference range could be beneficial for some people. Thus recommendation 1.4.1 has been amended to suggest adjusting the dose of treatment if symptoms persist when TSH levels are within the reference range to achieve optimal well-being.FT3 testing has not been considered to further assist in monitoring people with hypothyroidism.
Thyroid UK	Evidence Review F	15	43	**Subclinical thyroid dysfunction (subclinical hypothyroidism and hyperthyroidism):** Thyroid UK is concerned that only annual testing is being recommended for patients diagnosed with subclinical hypothyroidism. There has been no differentiation with regard to whether the patient has symptoms or not. At the moment, doctors tend to test 3 or 6 monthly if the patient is borderline. Leaving a patient with symptoms for a year is not fair to the patient.	Thank you for your comment. More frequent monitoring of less than one year was not considered to provide any additional benefit to people with untreated subclinical hypothyroidism. The committee is confident based on their clinical expertise that the current recommendations reflect best clinical practice. The presence or absence of symptoms affects the decision to treat or not which in turn will lead to more or less intensive monitoring.

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Thyroid UK	Evidence Review F	6	36	**Thyrotoxicosis**: In our experience, many patients who have had a thyroidectomy, especially a total thyroidectomy, require the addition of T3 before they feel well.	Thank you for your comment. The wording has been amended to refer to 'thyroid hormone replacement'. The treatment of hypothyroidism is covered in evidence review E.
Thyroid UK	Evidence Review F	8	3	**Included studies**: It is disappointing that only one study was included in this review and that the quality was classed as low or very low due to high risk of bias and imprecision. It is also disappointing that there were no relevant clinical studies assessing the impact of treating subclinical thyrotoxicosis. Thyroid UK has been approached by patients who have subclinical thyrotoxicosis but who have been sent away without any treatment. This affects their quality of life, their home, work and social life because they are in a constant state of anxiety. Thyroid UK is pleased to see that the committee made a recommendation for research.	Thank you for your comment. For intervention reviews, NICE guidelines prioritise evidence from randomised controlled trials, as these studies address confounding and are most appropriate to show causal benefits of an intervention. Where no RCT evidence was available, the committee considered looking at non-randomised evidence/lower quality evidence a priori on a question-by- question basis. The details of this can be found in the protocols in appendix A of the evidence reports. Currently there was only one RCT study that met the pre-specified inclusion criteria, and this was relevant to hypothyroidism. The committee considered that lower quality evidence was more likely to be unreliable and performing a systematic review of lower quality studies would not further assist in making recommendations. Please note that committee members were able to use their collective experience to make consensus recommendations. The committee has made recommendations for the management of people with subclinical hyperthyroidism but making those specific to people with subclinical thyrotoxicosis is outside the remit of this guideline.
Thyroid UK	Evidence Review G	15	17	**Levothyroxine vs placebo in adults**: Most of the research used for this review was below the "high" quality level. Thyroid UK agrees with the committee that much of the current research has short follow ups. Further research in this area would be prudent.	Thank you for your comment. The quality and limitations of the evidence identified for this comparison was reviewed by the committee, who was able to draw upon their clinical expertise and make recommendations that reflect best practice. We agree that further research is needed, however the committee is only able to make a limited set of recommendations for future research and

					hence considers making those based on the careful consideration of factors including their importance for patients, their potential impact on the NHS and technical feasibility. Evidence relevant to treatment with selenium and iodine was particularly lacking in the area of sub-clinical hypothyroidism and has hence been prioritised.
Thyroid UK	Evidence Review G	17	21	**Levothyroxine vs placebo in adults**: In our experience, most doctors take into account symptoms before testing. However, as soon as a TSH test is done (FT4 or antibody testing is often not done) and the level is above the top of the range but below 10, the symptoms are then immediately discounted as being thyroid disease and the patient, in some cases, is involved in many other visits to specialists and tests to exclude other conditions, even when thyroid disease is already within the family. This is such a waste of NHS time and money and causes the patient distress because they continue to have the symptoms while being sent to various specialists to find the cause of them. If there is thyroid disease within the family, especially parents or siblings, Thyroid UK feels that patients should be given a trial of levothyroxine. We also have many people come to us because they have all the symptoms of hypothyroidism, family members who have hypothyroidism but a TSH near the top of the range. In this case, the patients are either sent away to put up with their symptoms for a period of time before the doctor will test again or they are sent off on a round of specialists to find the cause of their symptoms which inevitably shows up nothing. If an FT4 test is done, it is often near the bottom of the range. Antibody testing is often not done. An FT3 test is never done to see what level the active hormone is. Patients are therefore	Thank you for your comment. A trial of levothyroxine for people with a TSH above the reference range but lower than 10 mIU/L who have symptoms has been considered appropriate by the committee (recommendation 1.5.4). The committee revisited the importance of antibody testing for subclinical hypothyroidism and a new recommendation has been added (1.5.1). The circumstances under which FT3 and FT4 should be measured when thyroid dysfunction is suspected have been specified in the recommendations (1.2.8 to 1.2.10), and the committee is confident these reflect best practice.

				testing privately. Thyroid UK believes that giving a trial of levothyroxine to these patients would be very helpful and much more cost effective. More research needs to be done.	
Thyroid UK	Evidence Review G	17	30	**Benefits and harms – Levothyroxine vs placebo in adults:** In our experience, antibody testing is often not done. Patients are therefore testing for these privately.	Thank you for your comment. The committee has updated the recommendations on the management of subclinical hypothyroidism to include antibody testing (recommendation 1.5.1).
Thyroid UK	Evidence Review G	18	18	**Cost effectiveness and resource use – Levothyroxine vs placebo in adults**: In our experience, many patients, whether older adults or adults, with symptoms of hypothyroidism are not given treatment until their TSH level reaches 10. This is based on the previous guidance – UK Guidance on Thyroid Function Testing 2006. However, Healthcare Improvement Scotland stated in their Technologies Scoping Report of February 2014 "*UK guidelines for the use of thyroid function tests published in 20062 were based on a non-systematic review of generally poor quality evidence from the United States (US) National Academy of Clinical Biochemistry (now archived)8."* Doctors may need to be reminded that they can give a trial of levothyroxine to patients who are above the reference range but less than 10.	Thank you for your comment. A trial of levothyroxine for people with a TSH above the reference range but lower than 10 mIU/L who have symptoms has been considered appropriate and has been recommended by the committee (recommendation 1.5.4).
Thyroid UK	Evidence Review G	18	24	**Other factors the committee took into account**: Thyroid UK is pleased to see a recommendation of research into selenium and iodine.	Thank you for your comment.
Thyroid UK	Evidence Review G	65	16	**Research question – Why is this important**?: Thyroid UK suggests that as the patients in this study were asymptomatic, a low dose of levothyroxine (particularly 25mcg) would not bring them into the TSH range very far and this probably would not have any effect. However, on patients with symptoms, a relief of at least some of the symptoms would occur.	Thank you for your comment. The point you raise has been carefully considered by the committee and the circumstances under which symptomatic patients should be treated have been specified in the recommendations (1.5.2 to 1.5.6)

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Thyroid UK	General	General	General	We have received lots of comments from patients so I have taken some extracts and placed them below. This shows you how upset and concerned patients are in regard to this guidance and also how very individual patients are. One size most definitely does not fit all patients: • *"I have autoimmune thyroiditis and am a victim of that "Impossible" situation. There were still some hypothyroid symptoms when TSH was 0.01 (T3 and T4 within range). As a result, I had to accept a decrease of levothyroxine which brought all the results within "Normal" parameters, and not surprisingly made symptoms gradually but definitely worse over a six-month period.* *The presence of symptoms, in spite of in-range blood tests should prompt treatment.* *A small decrease (by 12.5mcg/day) in my levothyroxine really had produced an increase in hypothyroid symptoms instead of the usual fluctuation.* *There is also diurnal variation. TSH probably varies the most – another reason why, though it helps in initial diagnosis, it is not a reliable guide to treatment.* *The guideline, while in theory allowing for exceptions, strongly discourages prescribing anything besides Levothyroxine. This results in many remaining ill or being forced to self-medicate."*	Thank you for this information. We have responded to more specific comments throughout the document. In relation to the examples you provide, it may be helpful to know that following stakeholder comments the recommendations have been changed to ensure that treatment is not targeted to TSH levels alone but to patient symptoms. In relation to liothyronine the evidence was not adequate to make a recommendation for the routine use of liothyronine, but a research recommendation has been made to ensure the importance of this topic is recognised and more information is available to inform treatment options. No evidence was found for use of selenium or iodine. The costs in the NICE guideline are based on current UK list prices available across the NHS. Liothyronine is subject to CMA investigation and this has been raised with the NICE surveillance team which monitors guidelines to ensure they are up to date. The guideline recommendation is to calculate starting dose by weight of the patient which should improve the experience of people who have previously been started on very low doses.

				• *"I get T3 (Thybon Henning) in the UK from a specialist pharmacy with a prescription from a private GP. The T3 costs me about £40 per month. I really don't understand why the NHS pays such a huge amount for the same drugs. It is wrong and makes a mockery of the NHS.* *I haven't felt so fit and healthy for over 14 years. I was diagnosed only 18 months ago and had T4 on the NHS but was not converting to T3. This medication has totally changed my life for the better and has caused other long-term issues to disappear. I've also lost 20Kg and am no longer in the "obese" range on a height / weight chart. I have been to the GP since I went on the T3 because I have no other medical issues - I used to need an appointment at least on e a monthly for various ailments. I would be devastated if I couldn't have this medication. But it's unfair that I have to pay for it and even more unfair that other folk can't afford to see a private GP and pay for medication."* • *"So, I find the committee's conclusion about combination therapy to be very disappointing. I say this because of my experience of using combination therapy for over 22 years and also because I worked as a part-time GP for around 30 years. In my GP work if a patient had problems with medication, I would change it to find another medication that suited him or her better. I am convinced that combination therapy does suit a smallish percentage of hypo people better than T4 alone and that it most definitely ought to be an option for these people now and into the future."*	

				• *"I am a newly diagnosed Hashimoto's patient with high antibodies, a TSH at the upper end of normal (but having gone up and up in the last five years) and quite a number of hypothyroid symptoms. I was surprised to find that my GP did not think this needed further investigation, saying there was nothing to treat. With help of Thyroid UK, I have now found a doctor who is willing to treat patients by symptoms, rather than just TSH levels. I am having to pay for this myself, as I cannot get a referral from my GP. Had I not found this doctor, I would have considered to consult German doctors, who seem to be more likely to consider hypothyroidism with a TSH from above 2."* • *Where is the list of hypothyroid symptoms to aid GPs etc in understanding disease of hypothyroidism? I tried Levothyroxine for two years at various doses, with TSH at times being within range without getting my health back. Liothyronine was a game changer for me, enabling me the return of my health significantly. I know there are tens of thousands of patients like me who had the same results and I do not know why this has been disregarded because supposedly the evidence does not exist in enough numbers to prove this. As a well educated mental health nurse I had to strongly advocate for myself and do so much research to get access to liothyronine which is routinely prescribed in many countries around the world, including Europe at a fraction of the price of the UK (due to massively poor decision making regarding manufacturing of the drug).*	

				This guideline is severely lacking as for some reason it focusses on a one size fits all approach. If Levothyroxine was truly the best treatment for all, there would not be thousands of UK patients like myself continuing to suffer with symptoms of this disease, being misdiagnosed with numerous other illnesses, *So many people are risking their health acquiring alternative medications to Levothyroxine (which they have tried for months and years without improvement/resolution of symptoms) from obscure sources around the world because guidelines such as these deny patients choice regarding their health treatments. I am glad I have the intelligence, education and ability to advocate for myself to ensure I am not one of those people being forced into a position of risking my health further due to the lack of choice guidelines like this provide.* • *Levothyroxine was not working for my hypothyroidism. I was puffing up like a bloated frog. I was in constant pain and I had a docile affect. I was in my early 50's but felt like I was in my 80's. I had to fight with my GP to even start treatment at all because I was within normal range. They started me on 25mcg. What a laugh. I was already 20kg overweight. Over the years as they increased the dose up to 125mcg I called it death by 1000 cuts. I am bitterly disappointed that the NHS has failed me. They took an oath and they betrayed that oath! First do no harm!* *I now don't trust my GP and self medicate with NDT. I also supplement with iodine and selenium. My kidney*	

				function has gone from under 50% to almost 70%. I have lost that bloated frog look. I no longer want to step out in front of a bus. My wits are sharp again. Getting onto a natural regime has been truly miraculous." *I live in the Bristol area and have been unable to get treatment for subclinical hypothyroidism because my TSH is at 7.5. I have been very unwell for a few years with the symptoms and I'm desperate to see someone, who recognises that I may need treatment.*	
Thyroid UK	Guideline	10	2	**Treating primary hypothyroidism – adults:** Thyroid UK has never known doctors to weigh their patients and calculate how much levothyroxine they need. Some patients would find this amount too much for them and it would give them symptoms of an overactive thyroid. If a person has been hypothyroid for some time (and this happens often) they are very sensitive to levothyroxine. We know of a patient who was prescribed 200mcg to take per day five days after her thyroidectomy (which was actually less than the patient's weight times 1.6). She was concerned and cut it back to 100mcg and this still made her very ill for two days. Doctors should be aware that this might happen to patients and inform them of this.	Thank you for your comment. The committee believe a lot of patients have been left on a low dose of levothyroxine and feel unwell which is why they made the recommendation. It is a weaker 'consider' recommendation to reflect that a clinician needs to decide whether this is an appropriate starting dose. The recommendation has been edited to state "Consider starting levothyroxine at a dosage of 1.6 micrograms per kilogram of body weight per day (rounded to the nearest 25 micrograms) for adults under 65 with primary hypothyroidism and no history of cardiovascular disease
Thyroid UK	Guideline	10	10	**Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine.** In our experience most patients on levothyroxine only become well when their TSH is right at the bottom of the range or suppressed. We are constantly hearing from patients who have only been replaced to the middle of the TSH range and	Thank you for your comment. We have amended the first recommendation (1.4.1) to state "Aim to maintain TSH levels within the reference range when treating primary hypothyroidism with levothyroxine. If symptoms persist, consider adjusting the dose of levothyroxine further to achieve optimal wellbeing."

				when their dosage is increased and their level is near the bottom of the range, their symptoms improve.	
Thyroid UK	Guideline	10	17	**Tests for follow-up and monitoring of primary hypothyroidism:** We suggest that patients should be informed that if they have a return of their symptoms, they should visit the doctor immediately as something may have changed in their lifestyle to warrant testing before a year has passed.	Thank you for your comment. The committee suggest providing information to patients relating to symptoms and assumes that patients with troublesome symptoms will seek medical advice. Recommendation 1.4.6. of the draft version of the guideline indicates that TSH and FT4 testing is appropriate when symptoms continue. This recommendation (now number 1.4.4) has been moved up to immediately follow the recommendation on TSH testing every 3 months (recommendation 1.4.3). 1.4.3 For adults who are taking levothyroxine for primary hypothyroidism, consider measuring TSH every 3 months until the level has stabilised (2 similar measurements within the reference range 3 months apart), and then once a year. 1.4.4 Consider measuring FT4 as well as TSH for adults who continue to have symptoms of hypothyroidism after starting levothyroxine.
Thyroid UK	Guideline	11	20	**Managing and monitoring subclinical hypothyroidism – Adults**: This is acceptable if a patient does not have symptoms. However, if a patient has a lot of symptoms that are impairing their quality of life, then waiting for 6 months before doing other thyroid tests i.e. FT4 and TPO would be very distressing for them. Consider doing further testing immediately if they have symptoms and a family history of hypothyroidism.	Thank you for your comment. The recommendation advises levothyroxine if TSH is above 10 on 2 occasions 3 months apart rather than 6 months. The committee agreed that 3 months is an appropriate time point and that testing sooner could lead to false positive results and the wrong management choice.
Thyroid UK	Guideline	13	7	**Monitoring untreated subclinical hypothyroidism and monitoring after stopping treating – Adults**: Thyroid UK suggests 3-6 monthly monitoring for patients with subclinical hypothyroidism who have symptoms that cannot be attributed to any other condition.	Thank you for your comment. The committee agreed that subclinical hypothyroidism progresses slowly, and that annual testing should be sufficient for this group.

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

Thyroid UK	Guideline	15	10	**Adults with Graves disease**: We are aware that some patients with Graves' disease do not want radioactive iodine. After a full discussion of the benefits and harms of both, patients should have a choice of antithyroid drugs if, for some reason, they do not want to have radioactive iodine.	Thank you for your comment. This is included as part of the recommendations.
Thyroid UK	Guideline	17	21	**Antithyroid drugs for adults, children and young people with hyperthyroidism**: We are aware of patients being on antithyroid drugs, particularly carbimazole, for many years without harm. They do not want radioactive iodine. After a full discussion of the benefits and harms of both, patients should have a choice of staying on antithyroid drugs for longer if, for some reason, they do not want to have radioactive iodine and they feel well.	Thank you for your comment. The recommendations relating to first-line definitive treatment offer patients the choice of radioactive iodine or antithyroid drugs if drugs are likely to achieve remission.
Thyroid UK	Guideline	19	6	**Monitoring after radioactive iodine treatment**: Thyroid UK has never known doctors to weigh their patients and calculate how much levothyroxine they need. Some patients would find this amount too much for them and it would give them symptoms of an overactive thyroid. If a person has been hypothyroid for some time (and this happens often) they are very sensitive to levothyroxine.	Thank you for your comment. The committee agreed that it is good practice to start levothyroxine based on a weight calculated dosage and also recommend monitoring thyroid function after starting levothyroxine and repeating thyroid function tests if there are ongoing symptoms.
Thyroid UK	Guideline	19	9	**Monitoring after radio active iodine treatment**: If the patient has symptoms of hypothyroidism, we suggest testing for FT4 also.	Thank you for our comment. This recommendation has been amended to recommend measuring TSH and measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range.
Thyroid UK	Guideline	19	12	**Monitoring after radio active iodine treatment**: If the patient has symptoms of hypothyroidism, we suggest testing for FT4 also.	Thank you for our comment. Recommendation 1.7.3 has been amended to recommend measuring TSH and measuring FT4 in the same sample if TSH is above the reference range and measuring FT4 and FT3 in the same sample if TSH is below the reference range.
Thyroid UK	Guideline	21	7	**Untreated subclinical hyperthyroidism**: If patients have symptoms, we suggest testing for TSH and FT4 more regularly than once a year. Symptoms of hyperthyroidism are very	Thank you for your comment. This recommendation has been amended to testing every 6 months.

				distressing for patients and it is unfair to leave them without treatment for so long.	
Thyroid UK	Guideline	22	18	**Untreated subclinical hyperthyroidism**: We suggest, after discussion with the patient, to also offer them treatment if they feel uncomfortable and have a hoarse voice due to a non-malignant thyroid enlargement. I have personal experience of this. It can cause a patient to become depressed if they are left without treatment.	Thank you for your comment. The recommendation does allow for clinicians to offer treatment should they have concerns. The committee agreed that not all scenarios could be covered in this recommendation and marked airway narrowing was seen as a good example.
Thyroid UK	Guideline	24	14	**Key recommendations for research**: In the study, "Variation in the biochemical response to L-thyroxine therapy and relationship with peripheral thyroid hormone conversion efficiency", the authors, John E M Midgley, Rolf Larisch , Johannes W Dietrich and Rudolf Hoermann conclude, *"The findings of the present study have several clinical implications. First, they recognize thyroid hormone conversion efficiency, as defined by the calculated global deiodinase activity or more simply the T3–T4 ratio, is an important determinant of L-T4 dose requirements and the biochemical response to treatment. Second, in view of a T4-related FT3–TSH disjoint, FT3 measurement should be adopted as an additional treatment target. Third, in cases where an FT3–FT4 dissociation becomes increasingly apparent following dose escalation of L-T4, an alternate treatment modality, possibly T3/T4 combination therapy, should be considered, but further randomized controlled trials are required to assess the benefit versus risk in this particular group."* Thyroid UK suggests that any further studies take their conclusion into account.	Thank you for your comment. The research recommendation seeks to establish if there is a benefit of combination therapy in people who are non-responders to levothyroxine monotherapy and provides sufficient detail at this stage to give preliminary study design guidance. The notes you provide on possible mechanisms are beyond the level of detail typically provided in NICE research recommendations.
Thyroid UK	Guideline	28	21	**Tests for when thyroid dysfunction is suspected:** Since there was no evidence identified for tests when thyroid dysfunction is suspected, we were disappointed to see that there was no research recommendation on this. We believe more research in this area would be advantageous.	Thank you for your comment. While further research could inform updates to recommendations, the committee agreed based on their experience, awareness of other evidence and the practicalities and feasibility of research in this area that consensus based

					recommendations with no further research recommendations were an appropriate response.
Thyroid UK	Guideline	29	17	**Why the committee made the recommendations**: Since there was no evidence identified for tests for people with confirmed primary hypothyroidism, we were disappointed to see that there was no research recommendation on tests for people with confirmed primary hypothyroidism. Thyroid UK suggests that a recommendation is made to find out if doing all thyroid tests including the ratio of T4 to T3 would be useful in patients with symptoms that do not resolve on levothyroxine.	Thank you for your comment. While further research could inform updates to recommendations, the committee agreed based on their experience, awareness of other evidence and the practicalities and feasibility of research in this area that consensus based recommendations with no further research recommendations were an appropriate response. The particular issue with regards to those whose symptoms do not respond well to levothyroxine alone should be addressed by recommendations for research in the area of combination therapy.
Thyroid UK	Guideline	30	4	**Treating primary hypothyroidism – Why the committee made the recommendations**: It does not state what the committee based their recommendation on as it does in other sections. We are aware that some endocrinologists are anti liothyronine and we trust that the clinicians on the committee have had experience of attempting to treat at least some patients with liothyronine.	Thank you for your comment. This section has been edited to provide clearer information about the decision behind this recommendation. Based on the available evidence liothyronine is not routinely recommended.
Thyroid UK	Guideline	30	19	**Treating primary hypothyroidism – Why the committee made the recommendations**: We are extremely pleased to see a recommendation for research into the use of liothyronine in primary hypothyroidism. However, as previously mentioned, we disagree with the wording regarding liothyronine. We suggest changing the wording, “Do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine” to similar wording in the RMOC and British Thyroid Association guidance documents, otherwise clinicians and CCGs will misinterpret this wording and many patients will be left to purchase their own liothyronine.	Thank you for your comment. The wording reflects the committee’s opinion that liothyronine should not be routinely offered. A footnote has been added to the rationale and impact section for recommendation 1.3.4 on liothyronine cross referring to the latest Regional Medicines Optimisation Committee (RMOC) guidance issued to Clinical Commissioning Groups (CCGs) on the prescribing of liothyronine (https://www.sps.nhs.uk/wp-content/uploads/2019/07/RMOC-Liothyronine-guidance-V2.6-final-1.pdf).

				We suggest that this research should include all thyroid function tests including the ratio of T4 to T3.	
Thyroid UK	Guideline	30	24	**Treating primary hypothyroidism – Why the committee made the recommendations**: It is disappointing that the committee did not allow some leeway for patients who do not do well on synthetic levothyroxine and liothyronine to be prescribed natural thyroid extract. Natural thyroid extract has been used for many years and, in fact, has had less problems in respect of side effects than levothyroxine - https://webarchive.nationalarchives.gov.uk/20141206112420/http://www.mhra.gov.uk/home/groups/pl-p/documents/drugsafetymessage/con222566.pdf The manufacture of natural thyroid extracts has changed considerably over recent years and is monitored very carefully as to the amount of hormone in each tablet with very similar levels to levothyroxine i.e. levothyroxine - 90.0 to 105.0% of hormone in each tablet and for natural thyroid extract it is 90 – 110% of each hormone. Many patients feel very much better on natural thyroid extract and it is much cheaper than liothyronine at the moment so would be more cost effective.	Thank you for your comment. NDT is an unlicensed treatment in the UK and there was no evidence to suggest it was beneficial over a licensed alternative.
Thyroid UK	Guideline	32	24	**Managing and monitoring subclinical hypothyroidism – Why the committee make the recommendations**: In our experience, many patients who have symptoms of hypothyroidism whether older adults or adults, are not given treatment until their TSH level reaches 10. This is based on the previous guidance – UK Guidance on Thyroid Function Testing 2006. However, Healthcare Improvement Scotland stated in their Technologies Scoping Report of February 2014 "*UK guidelines for the use of thyroid function tests published in 20062 were based on a non-systematic review of generally poor quality evidence from the United States (US) National Academy of Clinical Biochemistry (now archived)8."* Doctors	Thank you for your comment. The recommendations on considerations for those with a TSH greater than the reference range but less than 10 are aimed at addressing this issue.

				may need to be reminded that they give a trial of levothyroxine to patients who are above the reference range but less than 10.	
Thyroid UK	Guideline	33	2	**Managing and monitoring subclinical hypothyroidism - Why the committee made the recommendations**: Thyroid UK is pleased to see this research recommendation.	Thank you for this comment and positive feedback.
Thyroid UK	Guideline	42	14	**Managing and monitoring subclinical hyperthyroidism: Why the committee made the recommendations**: Thyroid UK is pleased to see this research recommendation.	Thank you for your comment.
Thyroid UK	Guideline	5	8	**Information for people with thyroid disease, their families and carers – General information**: There is no mention of liothyronine. This is a medication that helps some patients. If patients are not informed of this possible option, there is no transparency and patients are being treated very paternally. Under "shared decision making" doctors should be informing patients about liothyronine including the possible benefits and harms. Also, there is no mention of possible side effects of the excipients i.e. mannitol. We have recently been inundated with people whose levothyroxine generic had a change of the excipient lactose to mannitol and has caused them extremely bad side effects. Patients should be informed that if their pharmacy gives them a different brand, they should be aware that if they have new symptoms or if some of their previous symptoms return, this could be due to the different excipients in that particular brand.	Thank you for your comment. We have changed the first bullet point to 'possible drug interactions of hormone replacement therapy, including interactions with over-the-counter medicines. Both this bullet point and the bullet point in the preceding recommendation (1.1.3, previously 1.1.2) on providing information on medicines are intended to cover all aspects of information related to a person's medicines including interactions. There are many interactions with levothyroxine mentioned in the BNF and it is anticipated that prescribing clinicians will take these into account.
Thyroid UK	Guideline	7	16	**Investigating suspected thyroid dysfunction or thyroid enlargement – Indications for tests for thyroid dysfunction:** Thyroid UK suggests offering tests for patients with symptoms of thyroid disease and who have close family members who already have thyroid disease.	Thank you for your comment. We did not find evidence for family history as a clear indication of thyroid disease. The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease

					but may also be symptoms of other conditions and a definitive list could not be generated. The guideline does include specific symptoms/conditions where we found evidence for an association.
Thyroid UK	Guideline	8	10	**Tests when thyroid dysfunction is suspected**: In our experience, patients prefer to know the cause of their thyroid disease and indeed have a right to know, especially if it is autoimmune, so doing antibody testing at this stage would give the patient more information about their disease and be more cost effective in terms of the doctor's time and the patient's time.	Thank you for your comment. These recommendations relate to the initial tests to use when thyroid dysfunction is suspected. Antibody testing is also recommended once thyroid disease is confirmed.
Thyroid UK	Guideline	9	5	**Managing primary hypothyroidism – Tests for people with confirmed primary hypothyroidism:** We see many members of Thyroid UK who ONLY have high thyroglobulin antibodies and they often struggle to get diagnosed. It's less common, but its not rare to only have high thyroglobulin antibodies.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management choices. This was appropriate as TPO testing is in line with current practice. The committee agreed that it would not be appropriate to recommend further testing that is not current practice (i.e. thyroglobulin antibodies) when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Thyroid UK	Guideline	9	6	In our experience, patients prefer to be retested for TPO as this shows the progression of the autoimmune disease whether on levothyroxine or not. Patients find it helpful to the improvement of their health to see levels decrease. Patients with high levels of TPO prior to levothyroxine treatment have informed us that reducing gluten in their diet and/or reducing stress in their life has reduced their TPO levels. Further research into this area is very much needed.	Thank you for your comment. No evidence was identified to support a benefit of testing for TPO antibodies or thyroglobulin antibodies in management of primary hypothyroidism. Based on their consensus and experience the committee agreed it was appropriate to test TPO antibodies to provide people with hypothyroidism more information on their cause of their disease even if it was unlikely to affect management

					choices. This was appropriate as TPO testing is in line with current practice. The committee also agreed that it would not be appropriate to recommend repeating tests when this is unlikely to affect management and there is no evidence to support a benefit of this approach.
Thyroid UK	Guideline	9	14	**Treating primary hypothyroidism**: Many patients feel much better on a combination of levothyroxine and liothyronine and, indeed, liothyronine alone and as long as the benefits and harms that we know about are explained to them, they should have the choice of a drug that may improve their health or, indeed, has already improved their health immensely. It is not ethical to take away a drug that is known to give a huge benefit to a patient. NHS England, in their consultation "Items which should not be routinely prescribed in primary care" initially stated that liothyronine should not routinely be prescribed. However, after receiving feedback from patient organisations, clinicians and patients they changed the wording to "The joint clinical working group changed the recommendations so that initiation of prescribing of liothyronine in appropriate patients should be initiated by a consultant endocrinologist in the NHS, and that deprescribing in 'all' patients is not appropriate as there are recognised exceptions." When it was known that many CCGs were misinterpreting this guidance (due to it being unclear), Thyroid UK met with NHS England. They explained that they did not want patients to have their T3 stopped. We then had a meeting with Lord Philip Hunt who organised a debate in the House of Lords. This then led to Lord O'Shaughnessy requesting a dossier of evidence to show exactly what was happening. This was achieved by a working group of thyroid organisations who co-	Thank you for your comment. The available evidence at this stage from randomised controlled trials is that there is no overall benefit to the population of people on T4 currently, from being randomised to combination T3/T4 vs staying on T4 alone. No evidence was identified for T3 alone. The committee agrees it is possible that in the group that fails to respond to T4, combination therapy may have some benefits. However, this has not been borne out in any research thus far. Therefore the guideline recommends that liothyronine should not be routinely prescribed. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine). T3 Liothyronine is subject to CMA investigation and a cross reference to the CMA investigation has now been added in the committee discussion in the evidence review (https://www.gov.uk/cma-cases/pharmaceutical-sector-anti-competitive-conduct). However, until the new prices are transparent, consistently available across the NHS and guaranteed for a sufficient period of time, they cannot be considered in the guideline. Therefore the guideline recommends that liothyronine should not be routinely offered. Discretion is available to healthcare professionals for individual patients (including those already taking liothyronine).

				wrote a dossier of evidence. The dossier can be found here: http://www.thyroiduk.org/tuk/campaigns/T3-Campaign/Press%20Release%201%20Liothyronine%20Dossier%202018%20FINAL.pdf The British Thyroid Association commented within the dossier, " *"Guidance from NHS England has specified that liothyronine (L-T3) will continue to be available on prescription in exceptional cases, in accordance with a position statement from the British Thyroid Association.* *It is disappointing that such guidance is not being followed and this document, containing case studies from nationwide, provides evidence of this. The current uncertainty, with liothyronine-treated individuals either being denied ongoing prescriptions or needing to source the treatment themselves at their own cost, seems very much against patients' interests.* *Following such representation, it is hoped that there will be further clarification of how guidance on liothyronine treatment will operate. Whilst the role of specialist endocrinologists in assessing exceptionality and monitoring liothyronine therapy is clear, we suggest that, similar to levothyroxine (L-T4), responsibility for prescribing liothyronine should continue to be in primary care.* *The British Thyroid Association remains committed to working with the Department of Health, health professionals and patient groups to safeguard a role for liothyronine treatment in UK clinical practice."*	

				The Regional Medicines Optimisation Committee (South) (RMOC) then prepared its own guidance for CCGs. However, this was similarly unclear, and the working group of thyroid organisations have been working with RMOC to make changes. The final document has now been published and can be found here: https://www.sps.nhs.uk/articles/updated-rmoc-guidance-prescribing-of-liothyronine/ Within this update it states, *"NHS England guidance states that prescribers in primary care should not initiate liothyronine (L-T3) for any new patient and that individuals currently prescribed liothyronine should be reviewed by a consultant NHS endocrinologist with consideration to switching to levothyroxine (L-T4) where clinically appropriate. Prescriptions for individuals receiving liothyronine should continue until that review has taken place.* *The majority of patients suffering from hypothyroidism can be treated effectively with levothyroxine alone, but liothyronine is perceived to be an important medicine for a small proportion of patients in order to maintain health and wellbeing. The prescribing of liothyronine is only supported if initiated by or considered appropriate following a review by an NHS consultant endocrinologist. General Practitioners (GPs) should not independently withdraw or adjust liothyronine treatment for patients who are stable and well on therapy as any such changes should be overseen by an endocrinologist."* It also states, *"As noted by the British Thyroid Association (BTA) Executive Committee (1), 'clinicians have an ethical responsibility to adhere to the highest professional standards of good medical practice rooted in sound evidence. This includes not prescribing potentially harmful therapies without*	

				proven advantages over existing treatments. Also 'If a decision is made to embark on a trial of L-T4/L-T3 combination therapy in patients who have unambiguously not benefited from L-T4 then this should be reached following an open and balanced discussion of the uncertain benefits, likely risks of over-replacement and lack of long-term safety data. Such patients should be supervised by accredited endocrinologists with documentation of agreement after fully informed and understood discussion of the risks and potential adverse consequences. Many clinicians may not agree that a trial of L-T4/L-T3 combination therapy is warranted in these circumstances and their clinical judgment must be recognised as being valid given the current understanding of the science and evidence of the treatments'." We are concerned that the experiences of a small group of endocrinologists are overriding the guidance of NHS England, RMOC and the British Thyroid Association, as well as the experiences of all thyroid patient organisations and thousands of patients. NHS England, RMOC and the British Thyroid Association are listening to patients and patient groups and they are happy to state that the subgroup of patients can have liothyronine prescribed. We suggest changing the wording, "Do not routinely offer liothyronine for primary hypothyroidism, either alone or in combination with levothyroxine" to similar wording in the other guidance documents otherwise clinicians and CCGs will misinterpret this wording and many patients will be left to purchase their own liothyronine. The British Thyroid Association have guidance on T3 for clinicians and for patients - https://www.british-thyroid-	

				association.org/current-bta-guidelines- - and these should be taken into account as they are the experts. You may not be aware that the Scottish Minister for Public Health, Sport and Wellbeing, Joe FitzPatrick MSP, wrote a letter to the Health and Sport Committee of 23 May 2019 in regard to petition PE01463: Effective thyroid and adrenal testing, diagnosis and treatment: At the debate, I made a commitment to write to all Health Boards in Scotland to clarify the Scottish Government position on T3 prescribing. I therefore sent a letter out on 13th February 2019, after seeking advice from the endocrine specialist community, which is reproduced in Annex C. The letter asked boards to confirm that they were committed to: 1. a holistic and safe review of patients prescribed T3 which is undertaken by a healthcare professional based on the needs of the individual patient. 2. clinicians initiating and continuing T3 where it is safe and clinically appropriate to do so, as agreed with a consultant who specialises in endocrinology. All boards replied, confirming that they were committed to this. At the debate, I stated that “If people cannot access the treatment that we all think and their endocrinologist says that they should get, I ask members to please write to me”. Since then, I have received several letters from patients who have queried the way in which T3 initiation requests and appeals policy works in their board. We are currently working with relevant boards to better understand their processes.	

				Please ensure that the anecdotal evidence of patients' views is also taken into account.	
Thyroid UK	Guideline	9	17	**Treating primary hypothyroidism**: Many patients feel much better on natural thyroid extract and as long as the benefits and harms that we know about are explained to them, they should have the choice of a drug that may improve their health especially if they have been taking it for years. It is not ethical to take away a drug that is known to give a huge benefit to a patient.	Thank you for your comment. The committee recommended against the use of natural thyroid extracts because there was no evidence of benefit over levothyroxine, they are not licenced for use in the UK and the committee was concerned about unknown adverse effects because of the high proportion of T3 to T4 in them. The guideline recommendations relate to people newly diagnosed with hypothyroidism rather than those already receiving treatment. The committee has not made recommendations on withdrawing treatment as it did not review the evidence in this area.
UK Drugs in Lactation Advisory Service	Guideline	5	7	It is acknowledged that pregnant people with thyroid disease need written information on how the medicines may affect pregnancy and fertility. It would be good if the breastfeeding population were also identified in this list	Thank you for your comment. Pregnancy was outside the scope of this guideline because the RCOG is expected to publish a guideline on this topic shortly.
UK Iodine Group	Guideline	Miscellanous		As a clinician and a representative of the UK Iodine group, we read with interest the NICE Guidleines on thyroid disease. Given iodine is an essential component of thyroid hormone and is particularly important in pregnancy, we feel it would be useful if the forthcoming Green-top Royal College of Obstetrics and Gynacologists guidance for thyroid in pregnancy could be signposted from these NICE guidelines. In the signposting we would recommend iodine is explicitly mentioned as people seeking guidance from NICE on iodine in pregnancy are likely to come across the thyroid guidelines.	Thank you for your comment. We are aware of the forthcoming RCOG guidance, and as you suggest, will include a link to it from the guideline when that guidance publishes.
Welsh Endocrine and Diabetes Society	Evidence Review I: Management of thyrotoxicosis: drugs vs	6	1—32	In paragraph 1.2 (Page 6, lines 19—23) it is correctly stated "*Although many patients with Graves' thyrotoxicosis are managed with ATD (carbimazole or propylthiouracil) initially, a majority will relapse and become thyrotoxic again when the drug*	Thank you for your comment. The committee agree that there is insufficient evidence currently available on the efficacy of long term

	surgery vs radioactive iodine			*is stopped. Patients will then be faced with the prospect of long term ATD therapy or choosing radioactive iodine or surgery – both of which will usually result in hypothyroidism and a requirement for life-long thyroid hormone replacement."* Thus, the key issue when comparing anti-thyroid drugs (ATDs) with the other two treatment options is the difference between life-long levothyroxine replacement and long term anti-thyroid drugs in terms of- • Tolerability and safety • Efficacy in achieving biochemical euthyroidism • Impact on other metabolic parameters • Quality of life and wellbeing • Relapse rate **Antithyroid drugs** The review correctly highlights the paucity of good evidence in this area. Understanding the efficacy of long term ATDs is made more difficult by the fact that in most studies of "long term" ATDs the drugs are discontinued after a variable period. There have been few studies of continuous (intended lifelong) ATDs. Of the 6 studies quoted in the review only that by Azizi et al (1) examines the efficacy of continuous ATDs. In four studies (2-5) the ATDs are discontinued. In the study by Chen et al it is not clear in how many patients the ATDs were discontinued (6). Thus, the study by Azizi et al (1) is perhaps the only randomised study comparing continuous ATDs with radioiodine and it reported 26 out of 28 patients on methimazole were euthyroid after at least 9 years follow up. The available evidence from other studies suggests that in Graves' disease euthyroidism is restored whilst the patient	antithyroid drugs as a treatment option compared with other definitive treatments. The committee have made research recommendations relating to antithyroid drug regimens in thyrotoxicosis, particularly in those with T3 thyrotoxicosis and to determine whether block and replace or titration regimens are more clinically and cost effective. The committee did not consider the specific issue of long term antithyroid drug regimens as a key area for further research. The references you list are either included in the relevant evidence reviews within the guideline or did not meet criteria for inclusion, for example because they are systematic reviews or guidelines on areas which NICE conducted their own independent systematic evidence review on or as they published after the final searches were run for the guideline.

				remains on an ATD in the vast majority of patients and the relapse rate is low (1, 7-9). Since the review was made available for consultation, one study has been published examining the efficacy of long-term efficacy of ATDs in toxic multinodular goitre (MNG). This reported that 96.2% of patients on continuous ATDs remained euthyroid after 6 years follow up (10). Therefore, the evidence suggests that ATDs are effective at maintaining euthyroidism in Graves' disease and toxic MNG whilst the patient continues to take them. The limited evidence available also suggests they are effective long term in these conditions. **Levothyroxine replacement therapy** Levothyroxine is effective at achieving biochemical euthyroidism in the majority of patients and the American Thyroid association recommend that it "should remain the standard of care for treating hypothyroidism" (11). However, there has been increasing realisation that a normal serum TSH in a patient on levothyroxine replacement does not necessarily equate with having entirely normal thyroid physiology. Peterson et al reported that subjects on levothyroxine had lower serum T3 levels relative to T4 than serum TSH-matched controls (12). Those on levothyroxine also had higher a higher body mass index and abnormal lipid profiles. Samuels et al reported that subjects on levothyroxine had reduced resting energy compared with controls despite having a normal serum TSH (13). Subjects on levothyroxine also has reduced well-being and quality of life. Saravanan et al reported in a large community-based study that these patients had reduced thyroid-specific	

				and general quality of life scores, despite adequate replacement and a normal serum TSH (14). **Levothyroxine vs long-term ATDs** Radioiodine ablation followed by levothyroxine and continuous ATDs are both effective at achieving and maintaining biochemical euthyroidism in Graves' disease and toxic multinodular goitre. However, patients on levothyroxine have reduced well-being and abnormal thyroid hormone and lipid profiles despite adequate replacement. It is not known whether ATDs achieve a better quality of life or more physiological thyroid hormone profiles than levothyroxine as, to our knowledge, no relevant studies have been done. Some of the shortcomings of levothyroxine replacement may be as a result of relative triiodothyronine (T3) deficiency and consequently several studies of combined levothyroxine and T3 replacement have been done and are discussed elsewhere in the draft guidance. There are good theoretical reasons to assume that relative T3 deficiency does not occur in stable euthyroid patients on ATDs. Indeed, a patient with Graves' disease successfully treated with ATDs may have a thyroid gland that functions entirely normally physiologically. There is no evidence to suggest otherwise. We believe more research into long-term ATDs needs to be done. **Reference List** 1. Azizi F, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami F. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. European Journal of Endocrinology. 2005;152(5):695-701.	

				2. Abraham-Nordling M, Torring O, Hamberger B, Lundell G, Tallstedt L, Calissendorff J, et al. Graves' disease: a long-term quality-of-life follow up of patients randomized to treatment with antithyroid drugs, radioiodine, or surgery. Thyroid. 2005;15(11):1279-86. 3. Bartalena L, Marcocci C, Bogazzi F, Manetti L, Tanda ML, Dell'Unto E, et al. Relation between therapy for hyperthyroidism and the course of Graves' ophthalmopathy. N Engl J Med. 1998;338(2):73-8. 4. Benker G, Reinwein D, Kahaly G, Tegler L, Alexander WD, Fassbinder J, et al. Is there a methimazole dose effect on remission rate in Graves' disease? Results from a long-term prospective study. The European Multicentre Trial Group of the Treatment of Hyperthyroidism with Antithyroid Drugs. Clin Endocrinol (Oxf). 1998;49(4):451-7. 5. Kansara S, Kotwal N, Kumar K, Singh Y, Upreti V, Nachankar A. Effect of Antithyroid Therapies on Bone and Body Composition: A Prospective, Randomized, Clinical Study Comparing Antithyroid Drugs with Radioiodine Therapy. Indian J Endocrinol Metab. 2017;21(4):531-4. 6. Chen DY, Jing J, Schneider PF, Chen TH. Comparison of the long-term efficacy of low dose 131I versus antithyroid drugs in the treatment of hyperthyroidism. Nucl Med Commun. 2009;30(2):160-8. 7. Abraham P, Avenell A, McGeoch SC, Clark LF, Bevan JS. Antithyroid drug regimen for treating Graves' hyperthyroidism. Cochrane Database Syst Rev. 2010(1):CD003420. 8. Benker G, Vitti P, Kahaly G, Raue F, Tegler L, Hirche H, et al. Response to methimazole in Graves' disease. The European Multicenter Study Group. Clin Endocrinol (Oxf). 1995;43(3):257-63.	

				9. Torring O, Tallstedt L, Wallin G, Lundell G, Ljunggren JG, Taube A, et al. Graves' hyperthyroidism: treatment with antithyroid drugs, surgery, or radioiodine--a prospective, randomized study. Thyroid Study Group. J Clin Endocrinol Metab. 1996;81(8):2986-93. 10. Fereidoun A, Miralireza T, Elham M, Atieh A. Treatment of Toxic Multinodular Goiter: Comparison of Radioiodine and Long-Term Methimazole Treatment. Thyroid. 2019;29(5):625-30. 11. Jonklaas J, Bianco AC, Bauer AJ, Burman KD, Cappola AR, Celi FS, et al. Guidelines for the treatment of hypothyroidism: prepared by the american thyroid association task force on thyroid hormone replacement. Thyroid. 2014;24(12):1670-751. 12. Peterson SJ, McAninch EA, Bianco AC. Is a Normal TSH Synonymous With "Euthyroidism" in Levothyroxine Monotherapy? J Clin Endocrinol Metab. 2016;101(12):4964-73. 13. Samuels MH, Kolobova I, Smeraglio A, Peters D, Purnell JQ, Schuff KG. Effects of Levothyroxine Replacement or Suppressive Therapy on Energy Expenditure and Body Composition. Thyroid. 2016;26(3):347-55. 14. Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R, Dayan CM. Psychological well-being in patients on 'adequate' doses of l-thyroxine: results of a large, controlled community-based questionnaire study. Clin Endocrinol (Oxf). 2002;57(5):577-85.	
Welsh Endocrine and Diabetes Society	General	General	General	We congratulate the committee on these carefully considered recommendations. The guidelines are timely and should hopefully contribute to improving the care of patients with various thyroid disorders.	Thank you for your comment and for contributing to the consultation process.
Welsh Endocrine and Diabetes Society	Guideline	12	1 - 9	Section 1.5.3 *"Consider a 6-month trial of levothyroxine for adults under 65*	Thank you for your comment. The guideline does not cover managing thyroid disease in pregnancy.

				with subclinical hypothyroidism who have: a TSH above the reference range but lower than 10 mIU/litre on 2 separate occasions 3 months apart, ***and*** *symptoms of hypothyroidism. If symptoms do not improve after starting levothyroxine, re-measure TSH and if the level remains raised, adjust the dose. If symptoms persist when serum TSH is within the reference range, consider stopping levothyroxine and follow recommendation 1.5.6 on monitoring."* Suggest adding an additional bullet point • In women considering pregnancy. There is evidence that lowering the TSH to the reference range reduced the risk of foetal loss (Taylor et al, 2014). **Reference** Taylor PN, Minassian C, Rehman A, Iqbal A, Draman MS, Hamilton W, Dunlop D, Robinson A, Vaidya B, Lazarus JH, Thomas S, Dayan CM, Okosieme OE. TSH levels and risk of miscarriage in women on long-term levothyroxine: a community-based study. J Clin Endocrinol Metab. 2014; 99:3895-902.	
Welsh Endocrine and Diabetes Society	Guideline	14 - 20		In the management of overt hyperthyroidism, the importance of hyperthyroidism control is not emphasised and specific recommendations on therapeutic targets have not been made. It is well-established that uncorrected hyperthyroidism carries an increased risk of cardiovascular morbidity and mortality and it is important that thyroid function is normalised as early as possible in patients with hyperthyroidism. There are no randomised controlled trials addressing the impact of treatment intensity on outcomes in patients with overt hyperthyroidism as such trials would clearly be unethical. However, three high-quality observational cohort studies in	Thank you for your comment. NICE guidelines are not meant to be exhaustive guidance on every aspect of a topic but focus on critical areas raised during scoping by stakeholders. The specific therapeutic target in the management of overt hyperthyroidism was not an area prioritised in scoping and therefore the committee did not review the evidence in this area and are unable to make recommendations.

				treated patients with hyperthyroidism have shown that uncorrected or incompletely resolved hyperthyroidism carries an increased mortality risk (1-3). In a large Danish hyperthyroidism cohort, mortality increased per cumulative six-month period of hyperthyroidism (low TSH) in treated and untreated patients (1). Another study in a Birmingham thyroid clinic showed a positive association between serial FT4 concentrations and risk of death (2). In a third study from thyroid clinics in South Wales, UK, persistently low TSH concentration one year after Graves' disease diagnosis was associated with a higher mortality than a normal TSH regardless of therapy modality (3). In addition, this study showed a positive association between one-year post-diagnosis FT4 concentration and long-term mortality and cardiovascular event risk (3). These data underpin the importance of maintaining a normal thyroid status throughout the duration of treatment but particularly in the early post-diagnosis period. This may seem logical but is not always adhered to in practice. Thus, we suggest that rapid correction of hyperthyroidism and maintenance of a euthyroid state (normal FT4 and TSH) is recommended as a specific therapeutic goal in treating hyperthyroidism. References [1] Lillevang-Johansen M, Abrahamsen B, Jorgensen HL, et al. Excess mortality in treated and untreated hyperthyroidism is related to cumulative periods of low serum TSH. J Clin Endocrinol Metab 2017. [2] Boelaert K, Maisonneuve P, Torlinska B, et al. Comparison of mortality in hyperthyroidism during periods of treatment with thionamides and after radioiodine. J Clin Endocrinol Metab 2013; 98: 1869-82.	

				[3] Okosieme OE, Taylor PN, Evans C, *et al*. Primary therapy of Graves' disease and cardiovascular morbidity and mortality: a linked-record cohort study. Lancet Diabetes Endocrinol. 2019 Apr;7(4):278-287	
Welsh Endocrine and Diabetes Society	Guideline	15 - 16		Section 1.6.8—1.6.15 *Additional note on pre-treatment with antithyroid drugs before radioiodine in patients with severe and symptomatic thyrotoxicosis.* These new NICE guidelines are likely to result in an increased use of radioiodine which is appropriate. However, this will include primary radioiodine for some patients with severe hyperthyroidism. In this situation it is important to pre-treat the patients with antithyroid drugs as (a) the effect of radioiodine may take 2-3 months to be seen exposing patients to hyperthyroidism for a longer period and (b) radioiodine may exacerbate hyperthyroidism in some patients for the first 4-6 weeks. This is particularly dangerous in subjects at risk of cardiac disease. It is therefore recommended that the NICE committee consider adding a note suggesting consideration of pre-treatment with antithyroid drugs in patients with severe, symptomatic hyperthyroidism and/or underlying cardiac disease to achieve euthyroidism prior to radioiodine. However, it is important to additionally note that antithyroid drugs need to be withdrawn at least 1 week prior to radioiodine dosing so as not to impair uptake and efficacy of the radioiodine. Treatment of patients after radioiodine with antithyroid drugs e.g. block and replace is more controversial and need not be considered.	Thank you for your comment. An additional recommendation has been added to stabilise hyperthyroidism with antithyroid drugs before radioactive iodine or surgery.
Welsh Endocrine and Diabetes Society	Guideline	16	1 - 5	Section 1.6.11 *“Offer total thyroidectomy as first-line treatment for adults with Graves’ disease if: there are concerns about compression, or*	Thank you for your comment. Thyroid drugs being unsuitable is covered by the last bullet point. Where the patient can choose an option it is listed in the recommendation. For adults with Graves’ disease the

				thyroid malignancy is suspected, or radioactive iodine and antithyroid drugs are unsuitable." Suggest also adding to other indications • there is patient preference for this option There is a need for urgent control of thyroid function and antithyroid drugs are unsuitable (e.g. in the presence of cardiac disease, severe side effects of antithyroid drugs, poor compliance with medication)	committee believe that radioactive iodine and antithyroid drugs would be offered first unless there are specific indications for surgery.
Welsh Endocrine and Diabetes Society	Guideline	16	19 - 21	Section 1.6.15 *"Offer radioactive iodine (if suitable) or surgery (hemithyroidectomy) as first-line treatment for adults with hyperthyroidism secondary to a single nodule, or long-term antithyroid drugs if these options are unsuitable."* Should radioiodine not be the first line here (for solitary nodule) even more so than with multinodular goiter as it offers a very high chance of long-term remission with very low risk of hypothyroidism or any of the complications of surgery.	Thank you for your comment. No evidence was identified for toxic nodular goitre and the committee used their expert knowledge to make recommendations. While the committee believe radioactive iodine should be the first line treatment for multinodular goitre they did not think this would always be the case for a single nodule and agreed that hemithyroidectomy may also be appropriate.
Welsh Endocrine and Diabetes Society	Guideline	18	13 - 14	Section 1.6.24 *"Stop and do not restart any antithyroid drugs if a person develops agranulocytosis.* Agranulocytosis should be clearly defined as a neutrophil count of <1.0. Low white cell counts are frequently seen with thyrotoxicosis and patients on antithyroid drugs but are of no consequence if above this value and ATDs can be continued. It could be mentioned that values between 1 and 1.5 could be repeated. **Additional note on warning regarding antithyroid drugs.** The recommendation that written advice be given prior to	Thank you for your comment. This recommendation is just to highlight to primary and secondary care physicians that treatment should be stopped. NICE guidelines expect clinicians to read the summary of product characteristics and the extra detail you provide would be covered by this.

				starting antithyroid drugs should be made clearer. This is important because the commonest time for severe side effects to develop is in the first few weeks of treatment when the doses are highest. Hence if treatment is initiated in primary care, it is not infrequent that this problem will develop before the patients is seen for the first time in secondary care. Draft wording may be supplied for the avoidance of doubt. Possible draft wording: **Warning: PLEASE READ THIS NOW.** **Carbimazole/PTU treatment and sore mouth/throat** You have been started on carbimazole or propylthiouracil (PTU) treatment for an overactive thyroid. This is a very safe treatment that has been used for over 50 years. However, very rarely, a patient reacts to the drug with a sudden loss of white blood cells ("neutrophils") from the blood. This puts him/her at very high risk from infections and the drug **MUST BE STOPPED IMMEDIATELY.** The first sign of this happening is A SEVERE SORE MOUTH OR THROAT FOR NO OBVIOUS REASON. If you suspect this may have happened: 1. Do NOT take any more doses of the tablet. 2. Contact an emergency doctor or a casualty department THE SAME DAY (even if it is a weekend) and show him this card or the tablets. TO THE DOCTOR: This patient is on CARBIMAZOLE or PTU. If he/she has a sore throat or mouth it may indicate aganulocytosis, which is a very rare side effect.	

				Please: Stop carbimazole immediately 1. Check neutrophil count urgently, NOT just the total white cell count (which may be normal). If the neutrophil count is < 1.0 do NOT recommence treatment and admit patient for neutropenia. If level is 1.0 - 2.0, repeat level the next day off treatment. If level is >2.0, it is safe to continue treatment. Both carbimazole and thyrotoxicosis also cause a mild reduction in white cell count which is of no significance. A skin rash on carbimazole is also common and does not indicate neutropenia.	
Welsh Endocrine and Diabetes Society	Guideline	19	1 - 3	Section 1.7.1 *Consider measuring TSH, FT4 and FT3 levels in adults, children and young people every 6 weeks for the first 6 months after radioactive iodine treatment until TSH is within the reference range.* It should be noted that in this period, a low FT4 level even in the presence of a low TSH represents hypothyroidism and should be treated. This is often missed causing significant morbidity from delayed treatment.	Thank you for your comment. The reason the committee recommend monitoring FT4 and FT3 rather than TSH alone is so that appropriate treatment can be started if FT4 and FT3 are outside the reference range.
Welsh Endocrine and Diabetes Society	Guideline	24	21	Recommendations for Research 2. Long-term health outcomes for people with subclinical hyperthyroidism A similar recommendation should be made for subclinical hypothyroidism – there is only one large prospective RCT in this area and this was limited to the elderly and was underpowered for the key outcome of cardiovascular outcomes. Meta-analysis of observational studies suggest that the greatest benefit would be in the under 65s. Hence this is a key area of research for well-designed studies.	Thank you for your comment. The committee has made a research recommendation along these lines.

				This is currently number 7 in additional recommendations, but it affects over half a million people in the UK i.e. 5-10-fold more than subclinical hyperthyroidism and so should be a key priority.	
Welsh Endocrine and Diabetes Society	Guideline	25	6	Recommendations for Research 4. Long-term effectiveness and safety of radioactive iodine therapy *This should include the development of regimes to minimise the side effects (e.g. optimal combination with short term antithyroid drugs) including radiation thyroiditis, post-I-131 hypothyroidism, weight gain and thyroid eye disease.*	Thank you for your comment. NICE guidelines make specific research recommendations when specific questions raised and reviewed during the guideline development process, retrieve insufficient evidence to make strong recommendations and the committee considers there is a need for further research. The suggestion you make here does not meet these criteria.
Welsh Endocrine and Diabetes Society	Guideline	25	11	Recommendations for Research 5. Radioactive iodine therapy for hyperthyroidism *What is the clinical and cost effectiveness of dosimetry-guided radioactive iodine strategies for hyperthyroidism?* There have been a very large number of studies on this topic. A systematic review would seem more appropriate than primary research.	Thank you for your comment. A systematic review was done for this guideline. The committee considered that the evidence available was insufficient to make strong recommendations, hence the requirement for further research.
Welsh Endocrine and Diabetes Society	Guideline	4	16 - 17	Section 1.1.1 *"Symptoms may lag behind treatment changes because the body has a large reservoir of thyroxine that lasts 7 to 14 days."* The delay in symptom change may also related to the delayed biological response and clinically it can sometimes take 4-6 weeks or more for benefit to be clearly felt from a treatment change. This longer time frame is important for patients to appreciate, to explain why it is usually inappropriate to repeat blood tests for thyroid function and make dose changes in medication more frequently than every 2-3 months.	Thank you for your comment. We have amended this bullet point to read "Symptoms may lag behind treatment changes for several weeks to months." We have also amended the subsequent bullet point to read "Day-to-day changes in symptoms are unlikely to be due to underlying thyroid disease because the body has a large reservoir of thyroxine".

Thyroid disease

Consultation on draft guideline - Stakeholder comments table
5 June 2019 – 17 July 2019

Welsh Endocrine and Diabetes Society	Guideline	5	20	Section 1.1.4 "*The risk and impact of thyroid eye disease".* Suggest adding: "and the importance of smoking cessation in reducing this risk". All studies including RCTs (e.g. Träisk et al, 2009) have shown that smoking increases the risk of thyroid eye disease. We would also suggest that the phrase includes specific reference to Graves' disease as only those with thyrotoxicosis due to Graves' disease are at risk of eye disease e.g. suggested wording "the risk and impact of thyroid eye disease in people with Graves disease, and the importance of smoking cessation in reducing this risk". Reference Träisk F, Tallstedt L, Abraham-Nordling M, Andersson T, Berg G, Calissendorff J, Hallengren B, Hedner P, Lantz M, Nyström E, Ponjavic V, Taube A, Törring O, Wallin G, Asman P, Lundell G; Thyroid Study Group of TT 96. Thyroid-associated ophthalmopathy after treatment for Graves' hyperthyroidism with antithyroid drugs or iodine-131. J Clin Endocrinol Metab. 2009; 94:3700-7	Thank you for your comment. We have not included advice on smoking cessation as we did not review the evidence for this. The committee consider advising people to stop smoking is generic advice given to all people. We have amended the bullet point to read "• the risk of and impact of different treatment options on new and existing thyroid eye disease (for example, radioactive iodine may precipitate or worsen thyroid eye disease)"
Welsh Endocrine and Diabetes Society	Guideline	7	16 - 19	Section 1.2.2 *"Offer tests for thyroid dysfunction to adults, children and young people with type 1 diabetes or other autoimmune diseases,* ***or*** *new-onset atrial fibrillation. "* Suggest adding also "unexplained weight loss". Especially in the elderly in whom symptoms may be isolated (Boelaert et al, 2010). **Reference** Boelaert K, Torlinska B, Holder RL, Franklyn JA. Older subjects with hyperthyroidism present with a paucity of	Thank you for your comment and for highlighting this reference. The study you reference and many similar studies available do show an association between symptoms such as weight loss and thyroid disease but being cross-sectional in design, this does not inform us about causality and whether these are in fact due to underlying thyroid disease. We did not find evidence for unexplained weight loss as a clear indication of thyroid disease and there could be a number of other reasons causing this. Therefore, we have not included it in our recommendations.

				symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab. 2010; 95:2715-26.	The committee acknowledged that there are a number of common symptoms which may be associated with thyroid disease but may also be symptoms of other conditions and a definitive list could not be generated. The guideline does include specific symptoms/conditions where we found evidence for an association.
Welsh Endocrine and Diabetes Society	Guideline	8	15 - 18	Section 1.2.8 *Consider measuring both TSH and FT4 for: adults when secondary thyroid dysfunction (pituitary disease) is suspected; for children and young people, if the TSH is below the reference range, measure FT3 in the same sample.* Suggest noting that 22% of normal young children have FT3 levels above the reference range (Taylor et al, 2015) emphasizing the importance of **not** measuring FT3 in children if the TSH is normal unless there is a high suspicion of disease. **Reference** Taylor PN, Sayers A, Okosieme O, Das G, Draman MS, Tabasum A, Abusahmin H, Rahman M, Stevenson K, Groom A, Northstone K, Woltersdorf W, Taylor A, Ring S, Lazarus JH, Gregory JW, Rees A, Timpson N, Dayan CM. Maturation in Serum Thyroid Function Parameters Over Childhood and Puberty: Results of a Longitudinal Study. J Clin Endocrinol Metab. 2017; 102:2508-2515.	Thank you for your comment and reference. Although given the lack of randomised controlled trials, non-randomised studies were eligible for inclusion, the cohort study you highlight does not meet the inclusion criteria pre-specified in the review protocol as it did not compare any thyroid function test strategies. Nevertheless, we do agree that FT3 should only be tested if TSH is below the reference range and this is captured in the recommendations. However, the recommendations only advise clinicians what to do rather than provide all the detail.
Welsh Endocrine and Diabetes Society	Guideline	9	17-19	Section 1.3.5 *"Do not offer natural thyroid extract for primary hypothyroidism because there is not enough evidence that it offers benefits over levothyroxine, and its long-term adverse effects are uncertain."* This statement is correct, but it should be noted that because of the high cost of T3 in the UK, natural thyroid extract is the	Thank you for your comment. We have noted the high list price of liothyronine in the rationale and impact section.

				only permitted form of T3 to be prescribed in several commissioning areas of the UK.	