Thyroid disease

Consultation on draft scope
Stakeholder comments table

16 October 2017 –13 November 2017

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
British & Irish Orthoptic society	5	130-1	The draft scope has specifically excluded Thyroid Eye Disease. We feel that this condition should be included as this is a significant complication of thyroid disorder, Graves' disease. It is a difficult condition to accurately diagnose and as such requires clear guidelines which are essential for primary care users who rely on them. Early detection can lead to referral and effective treatment otherwise these patients may be easily misdiagnosed of a condition which can impact on visual function, quality of life and their psychological well being.	Thank you for your comment. Thyroiditis will be considered as part of the questions on hypothyroidism and thyrotoxicosis. Post-partum thyroiditis will not be covered as we anticipate it will be part of a new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists.
British Thyroid Foundation		General	The draft scope does not currently refer specifically to thyroiditis but we believe it should be included in sections covering hypothyroidism and hyperthyroidism. Guidance should also cover post partum thyroiditis which is probably the most common thyroid disease now seen in the UK. Post partum thyroiditis is often overlooked and symptoms are dismissed or attributed to the patient having a young baby.	Thank you for your comment. Thyroiditis will be considered as part of the questions on hypothyroidism and thyrotoxicosis. Post-partum thyroiditis will not be covered as we anticipate it will be part of a new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists.
British Thyroid Foundation		General	We believe that there are significant opportunities throughout this document to reiterate that improved diagnosis and management of thyroid disorders can lead to cost savings to the NHS. Better informed patients and GPs will have an improved understanding of the impact of the thyroid health, leading to fewer primary care appointments, and a reduced burden on secondary care thyroid specialists.	Thank you for your comment and for participating in the consultation process.
British Thyroid Foundation		General	We welcome this document as an important vehicle not only to educate patients but also to inform and update professionals in a succinct way. Many professionals will not have had recent opportunities to learn about the management of thyroid disease.	Thank you for your comment and for participating in the consultation process.
British Thyroid Foundation	3	77	This is a large group of patients who require follow up for a considerable length of time and who may be at risk of complications from their treatment in addition to further adverse effects from their disease which would impact their quality of life.	Thank you for your comment.
British Thyroid	3	82	We understand that some ethnic groups may be more likely to be	Thank you for your comment. This section of

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Foundation			diagnosed with thyroid disorders than others. For equality purposes this issue should be considered and included in this guideline. Since thyroid disease affects far more women than men, the diagnosis of men is often missed or significantly delayed. To address this potential inequality the guidance should make it clear that men are affected too and support for this group of patients should be improved.	the scope identifies subgroups in whom the evidence will need separate analysis in all situations. There may well be groups, as you have suggested, where specific consideration is needed in certain reviews. The committee will consider subgroups relevant to each review at the protocol setting stage.
British Thyroid Foundation	4	95-96	The draft scope currently excludes pregnant women but we feel that the guideline should include important information about management of pregnant women (and women who wish to become pregnant). There should be clear guidance about importance of good control of thyroid function pre-conception and information about possible increase of dose as soon as pregnancy is confirmed. It is important to include pregnancy because GPs are instructed to follow NICE guidelines much more than other guidelines from other organisations. Thyroid dysfunction is common in pregnancy. Suboptimal management may adversely affect both and maternal and fetal/child outcomes.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists work. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
British Thyroid Foundation	4	130	The draft scope currently excludes thyroid eye disease (TED) but reference to TED should be included as an important aspect of the management of Graves' disease. Early diagnosis and correct management of TED is vital and we believe that the guideline should include the relevant information that will help avoid missed and delayed diagnoses and speed up referrals to relevant specialists.	Thank you for your comment. The scope specifically excludes the management of TED as it was not prioritised for inclusion and would not be possible to cover in appropriate depth; however, TED is likely to be a topic that features in the section on "information for people with the thyroid disease" to reflect the importance of recognition.
British Thyroid Foundation	5	122-123	Important to include clear guidelines to alert patients and professionals to symptoms of agranulocytosis and neutropenia, and other side effects of treatment.	Thank you for your comment. The adverse effects of treatment will be considered in any reviews of the overall effectiveness of treatment.
British Thyroid Foundation	5	130, 131 and 134	We recognise that the management of TED, thyroid cancer and pregnancy may not be included but if not in this document how will GPs gain understanding of the seriousness of these diseases and	Thyroid cancer and pregnancy are to be covered by other guidance: NICE has been referred a separate guideline on thyroid

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			the potential significant psychological impact of them?	cancer from the Department of Health; and The Royal College of Obstetricians and Gynaecologists a producing a green top guideline on thyroid disease in pregnancy. Unfortunately, we could not cover every aspect of thyroid disease therefore have had to leave thyroid eye disease out of this scope.
British Thyroid Foundation	5	131	The draft scope currently excludes thyroid cancer (except preliminary investigation). We believe the guideline should also include other important information that will help professionals and patients manage this diagnosis. eg use of liothyronine for patients undergoing radioactive iodine ablation, TSH suppression (for patients who have been treated) etc.	Thank you for your comment. Management of thyroid cancer is not included as it would not be possible to cover the topic in sufficient detail as part of a single guideline here with the other aspects of thyroid disease. NICE has been referred a separate guideline on thyroid cancer from the Department of Health. Aspects of management of people who have previously had thyroid cancer but may now require information or management for hypothyroidism as per other people with thyroid disease will be considered on a review by review basis and recommendations will be made where evidence and committee consensus allows.
British Thyroid Foundation	5	133	Why is acute thyroid dysfunction not covered? Would it not be important to include indications/symptoms to help patients/professionals?	Thank you for your comment. This was not raised as a high priority issue during scope development and stakeholder meetings. Acute thyroid dysfunction is relatively rare compared with chronic thyroid disease and therefore has not been included in this scope, it is always managed in a specialist setting and there is very little controversy regarding its management.
British Thyroid Foundation	5	134	The draft scope currently excludes pregnant women but we feel that the guideline should include important information about	Thank you for your comment. Given the breadth of the current guideline scope and

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			management of pregnant women (and women who wish to become pregnant). See above point 1. Important to include pregnancy because GPs are instructed to follow NICE guidelines much more than other guidelines from other organisations. Thyroid dysfunction is common in pregnancy. Suboptimal management may adversely affect both and maternal and fetal/child outcomes.	the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists work. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
British Thyroid Foundation	6	159	Include guidance to improve diagnostic testing and awareness of symptoms of mismanagement. This could lead to cost reduction and better outcomes for patients with all thyroid disorders. In particular: • Interaction with other medications (eg calcium, iron and cholesterol-lowering drugs) • Pregnancy (need for iodine supplementation pre-conception and during pregnancy) • Thyroid eye disease (selenium)	Thank you for your comment. Section 1 of the scope would covers the clinical and cost effectiveness of thyroid function tests, antibodies tests and imaging tests. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming RCOG work. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
British Thyroid Foundation	6	171	If it is agreed that pregnancy can be covered this section could include • women who are having trouble conceiving, have had repeated miscarriages, or have a risk of pre-eclampsia • women who report a history of family thyroid disease who have an increased risk of post partum thyroiditis • Management of women who are found to have hyper or hypothyroidism in pregnancy • Management of a woman who presents with a thyroid lump in pregnancy • Recommendations concerning nutrition before conception and during pregnancy with particular reference to iodine intake.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists work. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			Include important guidance that might pick up a patient presenting with thyroid cancer	
British Thyroid Foundation	6	172	Clear guidance needed for TFTs. This will help professionals and patients understand which are required and when, and will also avoid costs or unnecessary repeat testing. It would be helpful if the guidance explained about the TFT reference ranges. They are currently very broad and it appears that patients are sometimes 'kept' at the wrong end of them. ie most patients report they feel well when they have a TSH in lower half of reference range and a T4 towards the top of the reference range or even slightly above it. The guideline should also clarify which (if different) reference ranges should be used in pregnancy, children and the elderly.	Thank you for your comment. The guideline will seek to address the most appropriate ways of investigating thyroid dysfunction. Children and older people are included in the population covered by the guideline. However, given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
British Thyroid Foundation	6	173	Clear guidance needed for antibody testing. This will help professionals and patients understand which are required and when, and will also avoid costs or unnecessary repeat testing. Eg TRAb antibody test will detect Graves' and indicate need for early referral for patients with possible TED.	Thank you for your comment. The guideline will seek to address the most appropriate ways of investigating thyroid dysfunction.
British Thyroid Foundation	7	186-188	L-T4, L-T3 and combination therapy There is a significant minority of patients who do not feel well on T4 alone. Clear and consistent guidance is needed to ensure patients are treated equally and fairly. Patients who do not feel well on T4 alone may be curious about the use and availability of thyroid extracts. It is therefore important that this guidance helps GPs understand more about these products and explains clearly why they are not licensed for use in the UK.	Thank you for your comment. The guideline will seek to address the most appropriate management of primary hypothyroidism and the role of T3 and thyroid extract will be considered in this area. We have not included thyroid cancer in this guideline because NICE has been referred a separate guideline on thyroid cancer from

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			Guidance needs to cover thyroid cancer patients who may need to maintain a suppressed TSH. T3 may also be required for these patients as part of the preparation for RAI treatment.	the Department of Health.
British Thyroid Foundation	7	189	Important that professionals take note of the symptoms patients report and not just the TFT results. The guidelines should reiterate the importance of adjusting the dose (where possible) with a view to better symptom control. The guidelines should make it clear when and how often patients should be seen following a change of dose.	Thank you for your comment. The guideline will seek to address appropriate monitoring of people with thyroid disease.
British Thyroid Foundation	7	191-193	Managing thyrotoxicosis – we believe there needs to be clear guidance for primary care doctors as to treatment for patients waiting for diagnosis of thyrotoxicosis. Should ATDs be started? How long should the patient wait for a referral? If it will be more than X weeks can GP get guidance to initiate treatment? Patients must not be left suffering with uncontrolled thyrotoxicosis symptoms for too long. Where treatment is started patients must be fully aware of risks of treatment and potential serious side effects.	Thank you for your comment. The guideline will seek to address the most appropriate management of thyrotoxicosis and this may include the period you refer to, however any recommendations would need to be based on clinical and cost effectiveness evidence in that situation.
British Thyroid Foundation	8	207-208	Clear guidance would help ensure that patients are treated consistently. Many patients are trialled with L-T4 when sub-clinical and then are frustrated when the treatment does not control their symptoms. Guidance should be clear that women and men with subclinical hypothyroidism who are trying to conceive may benefit from L-T4 treatment with careful monitoring of therapy. Important to emphasise that any infertile woman who is being referred for any implantation technique should be tested routinely for thyroid function and thyroid antibodies.	Thank you for your comment. The guideline will seek to address appropriate treatment of subclinical hypothyroidism.

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British Thyroid Foundation	8	212-214	If given reliable information more patients will better be able to manage their diagnosis and understand the basis for the treatment decisions. This should include suggestions about how and when to take the medication. Ideally good quality information (to patient organisations whose information is endorsed by NHS recognised thyroid experts) will be available (or signposted) at diagnosis and at follow up appointments. If support at this stage is thorough, fewer patients would seek information from the internet which can be confusing, frightening and misleading. Current NHS information focuses on physical symptoms and could be improved with more detail about the ways thyroid disease can affect people psychologically. Many patients, and their carers, struggle to understand and manage these symptoms. There may also be guidance about other ways in which patients can help themselves. Some people feel that diet can affect well being, and a healthy lifestyle usually benefits people managing a chronic health condition.	Thank you for your comment. The guideline will seek to address appropriate information to provide people with.
British Thyroid Foundation	8	223	Clear information about the adverse effect of treatments in some circumstances eg patients with active TED should be made aware of the risks of treatment with radioactive iodine and the potential solutions (eg use of steroids).	Thank you for your comment. The guideline will seek to address appropriate information to provide people with thyroid disease.
Butterfly Thyroid Cancer Trust	General	General	The draft scope currently excludes people who have been diagnosed by thyroid cancer .We feel this group should be included to ensure fairness across thyroid disorders.	Thank you for your comment. Management of thyroid cancer is not included as it would not be possible to cover the topic in sufficient detail as part of a single guideline here with the other aspects of thyroid disease. NICE has been referred a separate guideline on thyroid cancer from the Department of Health. Aspects of management of people who have previously had thyroid cancer but may now require

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				information or management for hypothyroidism as per other people with thyroid disease will be considered on a review by review basis and recommendations will be made where evidence and committee consensus allows.
Coeliac UK	5	138	Management of thyroid disease with dietary and lifestyle interventions is listed as an area that will not be covered by the guideline. From anecdotal information, a number of patients are being advised to commence a gluten free diet as part of their management for thyroid disease. This advice appears to be given without first excluding coeliac disease. Following a strict gluten free diet is challenging and gluten free staple foods are significantly more expensive than gluten containing equivalents [1, 2]. In addition, patients following a gluten free diet should receive dietetic support and follow up, to ensure that their diet is nutritionally adequate. An evidence based recommendation on dietary interventions for the management of thyroid disease and in particular the role of a gluten free diet (where coeliac disease has been excluded) as part of thyroid disease management would be welcomed. [1] Singh, J. & Whelan, K. (2011). Limited availability and higher cost of gluten free foods. Journal of Human Nutrition and Dietetics, 24, 479-486. [2] Burden, M., et al., (2015) Cost and availability of gluten free food in the UK: in store and online. Postgraduate Medical Journal, 2015: p. postgradmedj-2015-133395	Thank you for your comment. The scope excludes consideration of the management of thyroid diseases with dietary and lifestyle interventions; however, the scope does not seek to exclude any consideration of the role of diet and lifestyle in thyroid disease as a whole and it is anticipated that this may feature in the question on information for people with thyroid disease, although this will depend on the evidence identified and committee discussions.
Coeliac UK	6	144	We are reassured to see reference to the NICE guideline on coeliac disease, NG20 which includes a relevant recommendation to offer serological testing to people with autoimmune thyroid disease, at diagnosis.	Thank you for your comment.
Improve Thyroid Treatment	1	23	*"Most people with non-malignant enlarged thyroid gland and normal thyroid function need no treatment "*	Thank you for this information.

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Campaign Group			Enlargement is swelling, inflammation, therefore a sign that there is something wrong. An enlargement may be caused by injury or illness, such as a virus. It may be self-limiting. Any enlargement should undergo physical examination to check for further abnormality, such as nodules. If nodules, or other abnormality is evident, scans should be requested to establish the nature of the abnormality. Family history should be established and should be given due consideration and should influence decisions to investigate further. If symptoms are present, full thyroid function blood work will need careful consideration and scrutiny. It is likely that antibody testing will be required. If there is no other symptoms, or family history, evident then the patient needs to be monitored to ensure that the enlargement is self-limiting, dissipates and is not reoccurring. Causes and Signs of Edema [2016] https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072593/	
Improve Thyroid Treatment Campaign Group	1	27	"Hypothyroidism is prevalent in 2% of the UK population and in more than 5% of people aged over 60" ITT believes this could be significantly underestimating the number of patients with a thyroid disorder because of the TSH reference ranges used. Studies in Canada found that there was a one in 10 chance of having a thyroid problem. In America, the American Thyroid Association estimate 12% of the population and one in 8 of their women will be affected. Working on the figures from the Office of National Statistics, showing a population of 66.6 million. 2% of the population with hypothyroidism equates to 1.3 million. 5% of the 60+ age group is 38,000.	Thank you for this information.

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			The increased percentage in the over 60's bracket would indicate that hypothyroidism is more prevalent in this age group. However, these figures are based on the current diagnostic criteria, which ITT believe is flawed in the use of an inadequate blood test, using 'normal' ranges that are disputable. Hence many patients suffering with hypothyroid symptoms are left for years and decades, undiagnosed and untreated. Perhaps it should be considered that this increase in the prevalence of hypothyroidism in the older population is in fact a worsening of an existing unrecognised and undiagnosed hypothyroid health issue. It is generally recognised that "Hypothyroidism often has an insidious onset, but has a significant morbidity." [Tidy: 2015] This 'insidious onset' is very much underestimated. The 6 -8% of patients deemed to be 'subclinical' also skews the figures, as subclinical or overt hypothyroidism are both hypothyroidism. It is a life long condition that, left untreated, will cause deterioration of health. 90% of hypothyroidism in the UK is caused by the autoimmune thyroid disease (Hashimoto's thyroiditis), where antibodies will progressively destroy the thyroid gland. Madariaga et al [2014] conducted a 'Meta-Analysis' of the prevalence of thyroid dysfunction in Europe. Their findings suggest that the figure is likely to be 11% but they acknowledge that half of these people are unaware they have thyroid disease.	
Improve Thyroid Treatment Campaign Group	2	47-52	*"The prevalence of subclinical thyrotoxicosis is 0.5-10% and that of subclinical hypothyroidism is 4-20%, these wide ranges reflect differences in the studied population Data on long-term consequences of subclinical thyroid dysfunction have been largely derived from populations aged more than 65 years."* ITT believes that the figures quoted do not indicate the clinical effects, or the severity, of the 'subclinical' disease. Nor do they reflect the varying progression and severity of thyroid disease over time. Especially considering that it is difficult to differentiate between subclinical and overt thyroid dysfunction, and the controversies that surround the understanding of the normality of the Thyroid	Thank you for your comment. This brief introduction is not meant to be comprehensive. The most clinical and cost effective management of subclinical thyroid dysfunction is an area that this guideline will seek to address. The guideline will go into more detail on the investigation of thyroid disease.

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			Stimulating Hormone [TSH] range. The consequences referred to of increased risks of 'cardiovascular morbidity and mortality, increased osteoporosis and potential links to dementia', may well be reduced if the distinction between subclinical and overt thyroid disease is eradicated. Leonard Wartofsky 2011 https://academic.oup.com/jcem/article/96/1/59/2833230 "The ideal approach for adequate management of subclinical hyperthyroidism (low levels of thyroid-stimulating hormone [TSH] and normal thyroid hormone level) is a matter of intense debate among endocrinologists." Silvia Santos Palacios 2012 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3693616/ ITT advocate that the consequences outlined reflect the importance of treatment within the current 'subclinical' diagnosis and they are indicative of the need for lowered TSH 'normal' ranges to better reflect the healthy population, and identify early onset of thyroid disease. Alun Stevens MSc FIAA, 2001 http://web.archive.org/web/20040606132447/http://www.thyroid.org.au/Information/NormalTSH.html The language of the term 'subclinical' generates a belief that the 'sub' insinuates the lack of need for treatment with 'sub' meaning under or near to, and 'clinical' meaning treatment. ITT feel this language is influencing how doctors perceive and treat patients with 'Subclinical' thyroid disease. The result is that many primary care professionals appear to be reluctant or feel unable to treat subclinical thyrotoxicosis, therefore, with the knowledge that even subclinical dysfunction can lead to increased risk of cardiovascular complications, amongst others, patients should be referred to an endocrinologist for further investigation, sooner, rather than later. Within patient groups, the struggle for diagnosis is often reported to take years, or even decades. With some patients not being medically diagnosed, within the current protocols, at all. Subclinical results usually, at best, lead to the suggestion to retest in 3 – 6 months time. Unless 'overt' thyroid disease is detected, under the current	

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			parameters, patients are often left untreated and suffering with debilitating symptoms. Current parameters and regimes are putting patients under long-term health risk. ITT recommends that thyroid disease be seen on a scale of symptoms supported by clinical tests. "There is variation in how thyroid disease is investigated and managed in primary and secondary care settings". ITT recommends that the scope of the review should address the variation in investigation and management in primary and secondary care. ITT suggests that a rebalance towards primary care would be in the interests of both patients and the care sectors. ITT also recommends that NICE should review the way that care is delivered through the CCGs to remove the postcode lottery that exists. Various issues, which are debated, are embedded in the understanding of thyroid disease. These lead to variations in diagnosis and treatment. ITT patient evidence indicates that many primary care practitioners have limited knowledge of thyroid disease, leading to an over reliance on the Thyroid Stimulating Hormone [TSH] blood level, to define thyroid function. This understanding and reliance on the TSH has been disputed by many and is explained in a letter (linked below) by Dr John Midgely. This variance creates the effect of a 'post-code lottery' that in turn leaves patients feeling unfairly or inadequately treated. ITT also believes that it is a problem because it impacts on patient choices. Choices are limited, inconsistent and largely inadequate. Lack of training and knowledge within primary care is becoming increasingly evident to more enlightened patients. There is too much reliance on blood tests with too little consideration for clinical observations and a dialogue with patients about symptoms. ITT also has a file of patient stories that indicate financial constraints	

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			have been applied, providing evidence that doctors are being restricted from ordering certain blood tests and CCG's are limiting patient treatment to certain medication e.g. for hypothyroid patients increasingly, this is levothyroxine (T4) monotherapy. Some doctors are giving patients private prescriptions for more expensive thyroid replacement hormones e.g. liothyronine and some NHS hospital trusts are informing patients to go private to obtain liothyronine. This goes against the ethos of the NHS. There is also patient evidence that recommendations from secondary care on the thyroid hormone replacement therapy are being over ruled by primary care because of CCG direction and even secondary care are limiting thyroid hormone treatment options because of CCG direction. Unfortunately, there are incidents where some doctors admit to not knowing about thyroid hormones other than TSH and T4. Lack of training in this area means they are often unable to interpret certain blood results. http://www.parliament.scot/S4_PublicPetitionsCommittee/General%20Documents/PE1463_K_John_E_Midgley_19.02.13.pdf	
Improve Thyroid Treatment Campaign Group	2	43-46	"Subclinical thyroid dysfunction is a biochemical diagnosis of abnormal levels of serum thyroid stimulating hormone with normal circulating thyroid hormone levels (thyroxine [T4] and tri-iodothyronine [T3] often detected incidentally" Incidentally detected, or symptomatically, ITT believes that the distinction between subclinical and overt thyroid dysfunction is an unnecessary and confusing variance. Thyroid disease is thyroid disease. This unmerited distinction is leaving patients ineffectually diagnosed, and without treatment, with risk of ongoing irreparable damage to their thyroid gland.	Thank you for your comment. The guideline seeks to demonstrate the most appropriate management of subclinical thyroid dysfunction and overt thyroid dysfunction. Should the evidence suggest that no distinction is merited, then the recommendations will reflect this.
Improve Thyroid Treatment Campaign Group	2	29-30	*"Long-term consequences of hypothyroidism include cardiovascular disease and an increase in cardiovascular risk factors, including hypercholesterolaemia".* ITT recommends that the scope should reflect a full list of the health consequences for hypothyroid patients. The thyroid is an integral	Thank you for your comment. This is a brief introduction and not meant to be comprehensive. The clinical and cost effectiveness analyses will seek to include all relevant consequences of thyroid

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			and essential gland to the proper working of nearly every bodily function. Some of the consequences are set out here. This is not an exhaustive list, but it demonstrates the range of health issues for hypothyroid patients; i) Psychological and cognitive e.g. brain fog, peripheral brain neuropathy, anxiety, depression, dementia, Alzheimer's, Parkinson's ii) gastro complications e.g. constipation, bloating, bowel obstruction, gallstones iii) slow metabolism and associated weight gain hair loss, negative impact on adrenal cortex, eyebrow thinning, diabetes (hypoglycaemia), breathing difficulties, menstrual changes, dry skin, hives, urticarial, angioedema, gum and dental issues, lower energy levels and general weakness iv) Musculoskeletal e.g. fibromyalgia, carpel tunnel, arthritis v. Cardiovascular e.g. blood pressure abnormalities, cholesterol abnormalities. vi) Infertility including miscarriage, PCOS, Endometritis vii) liver and kidney function including chronic kidney disease. Other symptoms include migraine, tinnitus, and vertigo. ITT believe the scope should include the full range of symptoms to ensure the health impacts of thyroid disorder are understood and that patient outcomes of this review are fully assessed. I. Franklyn JA1 Nov 1999 Thyroid disease and its treatment: short- and long-term consequences. Edgbaston Birmingham https://www.ncbi.nlm.nih.gov/pubmed/10633337 II. Dr. P. Perros, R.J. McCrimmon, G. Shaw, B.M. Frier Frequency of Thyroid Dysfunction in Diabetic Patients: Value of Annual Screening http://onlinelibrary.wiley.com/doi/10.1111/j.1464-5491.1995.tb00553.x/full III. Nov 1999 Thyroid disease and its treatment: short- and long-term consequences. Franklyn JA1. Edgbaston Birmingham **https://www.ncbi.nlm.nih.gov/pubmed/10633337** IV. Tanaka Y, et al. Correlation between Thyroid Stimulating Hormone and Renal Function in Euthyroid Residents of Japan: Results from the Kyushu and Okinawa Population Study (KOPS). 2017. https://www.ncbi.nlm.nih.gov/pubmed/29046502 V. Hypothyroidism concealed by Parkinson's disease. García-Moreno JM, Chacón J.2002.	dysfunction.

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			https://www.ncbi.nlm.nih.gov/pubmed/12402227 VI. Sanai T, et al. Thyroid function in patients on continuous ambulatory peritoneal dialysis in comparison with chronic kidney disease. 2017. https://www.ncbi.nlm.nih.gov/pubmed/29035196 VII. Huang X, et al. 2016. Thyroid hormones associate with risk of incident chronic kidney disease and rapid decline in renal function: a prospective investigation. https://www.ncbi.nlm.nih.gov/pubmed/27914474 VIII. van-Tienhoven-Wind LJ & Dullaart LP. Low-normal thyroid function and the pathogenesis of common cardio-metabolic disorders. https://www.ncbi.nlm.nih.gov/pubmed/25690560 IX. van-Tienhoven-Wind LJ & Dullaart LP. 2015. Low-normal thyroid function and novel cardiometabolic biomarkers. https://www.ncbi.nlm.nih.gov/pubmed/25690422 X. Carta, MG., Hardoy, MC., Carpiniello, B., Murru, A., Marci, AR., Carbone, F., Deiana, l., Cadeddu, M., Mariotti, S. (2005). A case control study on psychiatric disorders in Hashimoto disease and Euthyroid Goitre: not only depressive but also anxiety disorders are associated with thyroid autoimmunity. Clin Pract Epidemiol Ment Health; 10:1-23. https://www.ncbi.nlm.nih.gov/pubmed/16285879 XI. Hage, M.P., Azar, S.T. (2011). The Link between Thyroid Function and Depression. Journal of Thyroid Research; Vol. 2012 (Article ID 590648). XII. Arash Ordookhani1 and Kenneth D. Burman2, Mar 2017 Hemostasis in Hypothyroidism and Autoimmune Thyroid Disorders https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5626118/ XIII. Lowe, J.C., Honeyman, G., and Yellin, J.: Lower resting metabolic rate and basal body temperature of fibromyalgia patients compared to matched healthy controls. Thyroid Science, 1:T1-T18, 2006. B. Lowe, J.C., Yellin, J., and Honeyman-Lowe, G.: Female fibromyalgia patients: lower resting metabolic rates than matched healthy controls. Medical Science Monitor, 12(8):CR1-CR8, 2006. XIV. T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid. Dr. John C. Lowe. Originally published in the *J. Myofascial Ther.*, 1(4):26-31, 1995	

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			http://www.thyroidscience.com/cases/lowe.9.6.10/lowe.t3.fms.9.6.10.htm XV. A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. Garrison RL, Breeding PC. http://www.ncbi.nlm.nih.gov/pubmed/12888300	
Improve Thyroid Treatment Campaign Group	2	28	*"women being 5-10 times more commonly affected than men"* ITT have found the figure usually used is one in 10 thyroid patients are men.	Thank you for this information.
Improve Thyroid Treatment Campaign Group	2	31	*"Thyrotoxicosis is a disorder of excess circulating thyroid hormones caused by an increased production and secretion (hyperthyroidism) or by release of stored thyroid hormones (thyroiditis)"* Thyrotoxicosis is the clinical effects of too much thyroid hormone, caused by over activity of the thyroid (hyperthyroidism). Thyrotoxicosis can be the result of hyperthyroidism caused by Graves' disease, which is an autoimmune disorder. Though largely caused by Graves' autoimmune hyperthyroidism, thyrotoxicosis can be evident in other less common causes: pituitary problems, inflammation [thyroiditis], toxic multi nodular goitre, toxic adenoma, excess intake of thyroid hormone and certain medications. I. Society of Endocrinology: You and Your Hormones http://www.yourhormones.info/endocrine-conditions/thyrotoxicosis/	Thank you for this information.
Improve Thyroid Treatment Campaign Group	2	33	*"In the UK, autoimmune hyperthyroidism (Graves' disease) is the most common form in 60-80% of cases "* The main cause of thyroid disease, both Hypothyroidism and Hyperthyroidism, is autoimmune. It is the raised thyroid stimulating immunoglobulin antibodies [TSI Ab] that are the main cause of Graves' disease. The clinical triad of Graves' includes hyperthyroidism, diffused goitre and the associated ocular condition. Bahn [2015] Bahn [2015] suggests that there is growing evidence that it is the Thyroid Stimulating Hormone Receptor antibodies [TSHR Ab] that should be targeted as these antibodies play a significant role in the	Thank you for your comment. The committee may make research recommendations if they identify areas in which insufficient evidence has currently been conducted to justify recommendations.

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			development of Graves' and thyroid eye disease [TED]. ITT recommends that NICE commissions extensive research into the causes, management and treatment of autoimmune thyroid dysfunction. Until research is concluded and counteractive measures found, patients should be advised of dietary and nutritional considerations that can help to control antibodies. Bahn R.S. [2015] Graves' Disease. A comprehensive guide for clinicians. Bahn R.S. [2015]	
Improve Thyroid Treatment Campaign Group	2	35	*Thyrotoxicosis is a common endocrine disorder with a prevalence of 2% in UK women and 0.2% in men.* ITT disputes the distinction between sub-clinical and overt thyroid disease. As both are equally as important in terms of assessment, diagnosis and treatment. Recognising that 'subclinical' thyrotoxicosis is defined by low thyroid stimulating hormone [TSH] with normal T4 and/or T3 hormone levels, as opposed to 'overt' hyperthyroidism, with low TSH and raised T4 and/or T3, we believe the condition to be one and the same. Whilst it may be useful as a distinction of severity, perhaps the term 'mild' as opposed to 'subclinical' would suffice. Subclinical seems to suggest a lack of need for treatment. Thyrotoxicosis, sub or overt, needs assessment, and monitoring, whatever stage it is at. Combining sub and overt 'thyrotoxicosis', figures then equate to, between, 2.7% and 12.2%. This wide range draws the question as to what is causing this wide differential, between 'subclinical' diagnostics? ITT ask that the distinction be removed and it be acknowledged that as many as 8 million people overall may suffer from thyrotoxicosis in the UK, particularly as subclinical thyrotoxicosis is just as likely to have complications as overt thyrotoxicosis which include: Graves' disease, atrial fibrillation, heart failure, osteoporosis, increased mortality, anxiety and depression, thyrotoxic periodic paralysis and thyroid storm. Serious complications can present in pregnancy, which include the	Thank you for your comment. The guideline seeks to demonstrate the most appropriate management of subclinical thyroid dysfunction and overt thyroid dysfunction. Should the evidence suggest that no distinction is merited, then the recommendations will reflect this.

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			risk of miscarriage, fetal death, pre-eclampsia, low birth weight and others. NICE Hyperthyroidism Clinical Knowledge Summary [2016] http://cks.nice.org.uk/hyperthyroidims#!backgroundsub:1	
Improve Thyroid Treatment Campaign Group	2	36	*"Graves' disease is caused by a genetic predisposition to the development of stimulation thyroid hormones auto-antibodies."* DeGroot,2015, defines Graves' disease as "a syndrome characterized by hyperthyroidism, a particular ophthalmopathy, and pretibial myxoedema. Rarely thyroid acropachy is associated. Usually thyroid enlargement, goitre, not be hyperthyroid to have Graves' disease." ITT ask that the in the scope particular note is made to the fact that a I. Graves' Disease and the Manifestations of Thyrotoxicosis. Leslie J.	Thank you for this information. This is a brief introduction and not meant to be comprehensive.
Improve Thyroid Treatment Campaign Group	2	55	*"There are currently no standardised diagnostic or referral criteria in the UK to guide decisions-making in primary care for people with structural thyroid abnormalities or enlargement."* Swelling of any kind is a sign that there is cell injury. It may be mild and self-limiting. However, it can also be indicative of serious disease, allergy or a potential chronic condition. I. Causes and Signs of Edema [2016] https://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0072593/ Any sign of structural thyroid abnormality where obvious cause, such as infection, is not present, should be referred to secondary care for further investigation and diagnosis. ITT is concerned that patients have been told that their goitre is cosmetic and treatment therefore denied. Goitres have the potential to be diagnosed as cancerous at a later date.	Thank you for this information. These are issues that will be considered by the committee during the guideline development process.

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			ITT feels that full clinical assessment should be undertaken, to establish genetic histories and establish the clinical physical structure of any thyroid abnormality. Full thyroid blood testing should be carried out alongside thyroid antibody testing, Thyroid Peroxidase Antibodies [TPO AB], Thyroid Stimulating Immunoglobulin Antibodies [TSI Ab] and Antithyroglobulin Antibodies [TG Ab]. The scope should include guidance that multi nodule enlargement should be investigated using ultrasound and FNA, alongside ultrasound scanning, where necessary.	
Improve Thyroid Treatment Campaign Group	2	57	*"In secondary care, there is significant variation in the types of diagnostic tests and imaging used, as well as in surgical and non-surgical management and follow up protocols."* ITT recommends a review of the variations to clearly establish which testing and diagnostics are most accurate and effective. ITT considers the current over reliance on the Thyroid Stimulating Hormone [TSH] blood test level, as accurate diagnosis of all thyroid dysfunction, is inadequate and increasingly unacceptable to patients. Without the full thyroid function testing, to include T3 levels and antibodies to give the full picture, diagnosis is inadequate and delayed. ITT believe that clinical observations and patient experience should take precedence over testing, which should act as a support to diagnosis. The nature of autoimmune thyroiditis is for antibodies to flare and reduce, making the thyroid stimulating hormone test unreliable. ITT believes that due consideration in the guidelines should be given to the timing of testing, to ensure the most accurate chance of diagnostics, whilst symptoms are present. If blood results are negative, retesting should be arranged. If symptoms persist, treatment should be considered to reduce flare-ups and further thyroid damage. Management and follow up protocols, after RAI and surgery treatments, are in dire need of revision. Patient stories indicate that liothyronine [L-T3] treatments should be introduced into	Thank you for this information. The guideline will seek to address appropriate investigation of thyroid dysfunction.

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			standard practice in hormone replacement therapy. The current regime of levothyroxine [L-T4] monotherapy does not meet the natural physiology of the thyroid gland production of 20% triiodothyronine [T3]: 80% thyroxine [T4], and does not restore patients to full health. The poor restoration of health via L-T4 mono therapy regime is exacerbated when the defect DIO2 gene is present. Poor understanding of the symptoms of thyroid disease is reflected in the quality of information offered to patients regarding consequences of treatments (line 212 – 214). Patients are told that T4 replacement therapy will be issued. However, many patients are oblivious to the genetic DIO2 fault or issues with reverse T3 that leaves up to 20% of patients unable to convert T4. Follow up protocol is one particular area that patients seem dissatisfied with. From patient feedback, ITT feels there is a need for better intra-multidisciplinary communication, to ensure patient follow up is controlled and systematic. Follow up screening should take place within six weeks of initial treatments or earlier if there is concern, and further screening should be in place to ensure the patient is helped to a euthyroid stage. Following definitive treatments antibodies can remain and in some patient cases be high, as the RAI treatment forces the dying thyroid to 'dump' hormones into the bloodstream. This can cause very low TSH, which may confuse clinicians, as patients appear to be hyperthyroid when they are actually hypothyroid. This can lead to misleading and misunderstanding of TSH results. It is important for FT-4 and FT- 3 levels to be monitored following treatments.	
Improve Thyroid Treatment Campaign Group	3	62 -64	*"guidance on optimal treatment and follow-up strategies is needed for managing thyrotoxicosis, which is usually done in a shared care setting between primary and secondary setting."* ITT agrees that there needs to be a variety of options to facilitate optimal treatment. Many patients prefer to start with the anti-thyroid drugs as this treatment presents the best chance of remission and	Thank you for this information. The guideline will seek to address the most clinically and cost effective management of thyrotoxicosis.

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			the better chance of avoiding permanent hypothyroidism. Unfortunately, RAI and thyroidectomy usually result in hypothyroidism. Antithyroid drugs, of which, Carbimazole, is the UK preferred option, have been known to be controversial in regard to long-term use. This concern is now thought to be unfounded. However, there are numerous research studies pertaining to the birth defects and death, caused by the use of Carbimazole during pregnancy, hence Propylthiuoracil is the preferred choice in the first trimester. Patients using anti-thyroid drugs should undergo liver function testing and should be monitored taking into consideration the possible adverse side effects of: changes in taste; rash; nausea or gastric problems; elevated liver enzymes; cholestasis and agranulocytosis. Some patients may not be able to tolerate ATDs and some of the Indicators, which are thought to impact on the failure of antithyroid drug use are: high baseline TSH, high T4 levels, heavy smoking and greater iodine uptake, and this should be give due diligent consideration. In these cases, other treatment options may need to be explored. In some cases, following RAI or surgery, partial thyroid remains and this may be able to produce adequate thyroid hormone. Following definitive treatment, with total thyroidectomy or where the thyroid gland is completely destroyed by RAI, patients may be issued liothyronine, [L-T3] following treatment but tend to be switched to levothyroxine [L-T4] before being referred back to primary care. Patients are being released to primary care following RAI treatments and/or thyroidectomy, with T4 monotherapy treatment, with no planned follow up to ensure that this treatment is appropriate. ITT would recommend ssecondary care work with patients to find the follow up treatment [medication] that suits the patient. Only when medication is established, and stable, should patients be returned to primary care for ongoing monitoring.	

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			"*It is important to investigate for other causes of primary hyperthyroidism when thyrotoxicosis persists after total thyroidectomy. TSH receptor antibody may persist after total thyroidectomy and may potentially contribute to the development of de novo Graves' ophthalmopathy."* Tay et al. [2017]. Should further problems arise patients should be referred back to secondary care for further investigations, alterations to treatment and advice. I. Persistent hyperthyroidism and de novo Graves' ophthalmopathy after total thyroidectomy. Abstract. Tay WL, Loh WJ, Lee LAL, Chng CL https://www.ncbi.nlm.nih.gov/pubmed/29062485 II. Aziz et al [2005] found that *"Long-term continuous treatment of hyperthyroidism with MMI is safe. The complications and the expense of the treatment do not exceed those of radioactive iodine therapy."* Some patients report that they have used carbimazole, successfully, more long term. III. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. Azizi F1, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami Fhttps://www.ncbi.nlm.nih.gov/pubmed/15879354 IV. Radioactive Iodine Considered Optimal for Graves Disease. Christine Rhodes MS. [Updated 2017] https://www.endocrineweb.com/professional/graves-disease/radioactive-iodine-considered-optimal-graves-disease	
Improve Thyroid Treatment Campaign Group	3	60	*"Standardisation in thyroid hormone replacement strategies for people with hypothyroidism is currently lacking."* ITT patient experience testifies to the limitations of the thyroid hormone replacement strategies offered. The NHS is now trying to	Thank you for your comment. The guideline will seek to address the most clinically and cost effective management of hypothyroidism.

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			limit these further, to one medication. This medication is known to not suit all. Knowledge of the DIO2 gene, and other conversion inhibiting factors must be taken into consideration. The gene defect impedes conversion of T4 to T3. Also high reverse T3 levels are often ignored in both primary and secondary care. Liothyronine treatment is being actively withdrawn from many patients as their treatment is being reverted back to a one size fits all L-T4 monotherapy. ITT encourages the NICE scope to include a variety of patient treatment options.	
Improve Thyroid Treatment Campaign Group	3	64	*Opinions regarding the need to treat subclinical thyroid dysfunction, especially in older people, are widely varied globally*. Opinions do vary considerably, however subclinical or overt, thyroid dysfunction is thyroid dysfunction. Recognition that subclinical thyroid dysfunction is still thyroid dysfunction should be acknowledged. Symptoms need to be assessed and full thyroid function should be investigated. Treatments considered and designed to suit early stages of thyroid dysfunction to prevent further deterioration. Discussion shows that both subclinical hyperthyroidism and hypothyroidism, over, or under treated lead to an increasing number of symptoms and increased risks of cardiac disease. See lines 124, 125, 126	Thank you for your comment. The appropriate management of subclinical thyroid dysfunction will be considered by this guideline.
Improve Thyroid Treatment Campaign Group	4	95-96	*"Pregnant women (guidance is currently being developed by the Royal College of Obstetricians & Gynaecologists)."* Including consideration of the 19 September scoping workshop recommendation *"- Agreed that special consideration should be given to pregnant women as pregnancy is a common trigger for hypoparathyroidism and hyperparathyroidism"* and whether or not this is undertaken within this scoping exercise or	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green top guideline on thyroid disease in pregnancy produced by the Royal College of Obstetricians and Gynaecologists. The most

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			by RCOG A literature search indicates some evidence of a serious and potentially fatal issue for both mother and baby during and post pregnancy arising from the development of hyperparathyroidism in the mother following RAI treatment. Nothing could be found that indicates screening for this for the woman either post RAI or in pregnancy. This should be carefully considered and rectified. And should include the development of appropriate patient information for both pre and post RAI & for pregnancy. I. Post RAI development of hyperparathyroidism in women https://www.ncbi.nlm.nih.gov/m/pubmed/17693276/ "In this collective experience, the average latency time to the development of HPT after RAI treatment was 13.5 +/- 9.1 years and was found to be inversely correlated with age at RAI exposure." II. https://www.ncbi.nlm.nih.gov/m/pubmed/2588108/?i=7&from=/6689566/related "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. III. Consequences of maternal hyperparathyroidism http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2008.03495.x/abstract "Conclusions HPT during pregnancy is under recognized and is associated with a 3·5-fold increase in miscarriage rates. Pregnancy loss often occurs in the second trimester and is	appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			associated with multiple miscarriages when not addressed. Pregnancy loss is more common as calcium levels exceed 11·4 mg/dl (2·85 mmol/l), but can be seen at all elevated calcium levels. Emphasis is placed on earlier recognition and surgical cure before becoming pregnant, however, once pregnant, surgery should be offered early in the second trimester for those with calcium levels above 11·4 mg/dl." IV. http://www.parathyroid.com/pregnancy.htm "Hyperparathyroidism (parathyroid disease with high calcium) occurring during pregnancy is a very serious problem. Hyperparathyroidism during pregnancy puts both the mother and child's life at risk, and the chance for life-long calcium problems for the child exists. Hyperparathyroidism during pregnancy is treated with mom's surgery during the late first or early second trimester	
Improve Thyroid Treatment Campaign Group	4	91	*"No specific subgroups of people have been identified as needing specific consideration".* ITT considers that the following subgroups require specific consideration. I. Coeliac. This is because as the draft scope recognises 90% of thyroid dysfunction is autoimmune. Coeliac is an autoimmune disorder associated with thyroid dysfunction. 14% of coeliac patients have thyroid disease: 10.3% were hypothyroid and 3.7% hyperthyroid, both significantly more than expected. People with autoimmune thyroid disease are at a higher risk than the general population of having coeliac disease. Between 1.5% and 3.8% of people with autoimmune thyroid disease also have coeliac disease compared to 1% in the general population. a. C E Counsell, A Taha, W S J Ruddell 1994 Coeliac	Thank you for your comment. This section of the scope identifies subgroups in whom the evidence will need separate analysis in all situations. There may well be groups, as you have suggested, where specific consideration is needed in certain reviews. The committee will consider subgroups relevant to each review at the protocol setting stage.

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			disease and autoimmune thyroid disease http://gut.bmj.com/content/gutjnl/35/6/844.full.pdf b. Coeliac UK. https://www.coeliac.org.uk/coeliac-disease/associated-conditions-and-complications/autoimmune-thyroid-disease/ II. Diabetics. As line 146 of the draft scope recognises there is a link between thyroid dysfunction and diabetes. We believe it is important to recognise this, and diabetics as a subgroup. a. Shun CB, et al. Thyroid autoimmunity in Type 1 diabetes: systematic review and meta-analysis. 2014. https://www.ncbi.nlm.nih.gov/pubmed/24103027 b. Yang M, et al. CD19+CD24hiCD38hi regulatory B cells are associated with insulin resistance in type I Hashimoto's thyroiditis in Chinese females. 2017. https://www.ncbi.nlm.nih.gov/pubmed/29042997 c. Buscemi S, et al. Association of obesity and diabetes with thyroid nodules. 2017. https://www.ncbi.nlm.nih.gov/pubmed/28836113 III. Women. We believe that, given the predominance in females, women are a specific sub group. Women comprise up to 9/10ths of hypothyroid patients. Many of these women are not diagnosed until the age of 40 onwards. The draft scope recognises that Graves' disease, particularly, is found in women of the ages 30 – 60. IV. Pernicious Anaemia is highly associated with autoimmune thyroid disease with a higher prevalence of pernicious anemia compared with the general population. Clinical signs of B12 deficiency may be subtle and missed, particularly in	

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			patients with known autoimmune disease. B12 deficiency is found in approximately 40% of hypothyroid patients. a. Osborne D & Sobczynska-Malefora A. 2015. Autoimmune mechanisms in pernicious anaemia & thyroid disease. https://www.ncbi.nlm.nih.gov/pubmed/25936607 b. Velarde-Mayol C, et al. 2015. Pernicious anemia and autoimmune thyroid diseases in elderly people. https://www.ncbi.nlm.nih.gov/pubmed/25579235 V. Patients with Chronic Kidney or Liver disease. a. Thyroid Disorders and Chronic Kidney Disease. January 2014. BioPortfolio https://www.bioportfolio.com/resources/pmarticle/1003771/Thyroid-Disorders-and-Chronic-Kidney-Disease.html b. Tanaka Y, et al. Correlation between Thyroid Stimulating Hormone and Renal Function in Euthyroid Residents of Japan: Results from the Kyushu and Okinawa Population Study (KOPS). 2017. https://www.ncbi.nlm.nih.gov/pubmed/29046502 c. Zhang Y, et al. 2014. Thyroid hormone levels and incident chronic kidney disease in euthyroid individuals: the Kangbuk Samsung Health Study. https://www.ncbi.nlm.nih.gov/pubmed/25011453 d. Sakurai S, et al. 1988. Thyroid functions before and after maintenance hemodialysis in patients with chronic renal failure. https://www.ncbi.nlm.nih.gov/pubmed/3250862 e. Shimada T, et al. Thyroid functions in patients with various chronic liver diseases. https://www.ncbi.nlm.nih.gov/pubmed/3143545	

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			VI. Patients with another autoimmune condition. Autoimmune thyroid disease (AITD) is often observed together with other autoimmune diseases. The coexistence of two or more autoimmune diseases in the same patient is referred to as polyautoimmunity, and AITD is the autoimmune disease most frequently involved. a. Biddal S, et al. 2017. Recent advances in understanding autoimmune thyroid disease: the tallest tree in the forest of polyautoimmunity. https://www.ncbi.nlm.nih.gov/pubmed/29043075 b. Wiebolt J, et al. 2010. Clustering of additional autoimmunity behaves differently in Hashimoto's patients compared with Graves' patients. https://www.ncbi.nlm.nih.gov/pubmed/21378091 c. Boelaert K, et al. 2010. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. https://www.ncbi.nlm.nih.gov/pubmed/20103030 Sinclair D. 2008. Clinical and laboratory aspects of thyroid autoantibodies. https://www.ncbi.nlm.nih.gov/pubmed/16704751 d. Thyroid dysfunction in rheumatoid arthritis. F. Mohammadi, S. Zayeni, A. Jafarnejhad, M Hedayati Omami & N. Amini. 2012. http://www.endocrine-abstracts.org/ea/0029/ea0029P1638.htm VII. Patients presenting with fibromyalgia Fibromyalgia and Hypothyroidism present with almost the exact same symptoms. Dr J C Lowe linked tissue level hypothyroidism as one of the main causes of fibromyalgia through a concept known as 'deductively formulated theory'. Through his research he found that the majority of patients who have fibromyalgia either have undiagnosed hypothyroidism or they are being inadequately treated	

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			with Levothyroxine or Synthroid (T4 medications). Dr Lowe's research showed that in order for patients to have complete remission of their pain and fibromyalgia most of them needed the active form of thyroid hormone known as T3. a. A. Lowe, J.C., Honeyman, G., and Yellin, J.: Lower resting metabolic rate and basal body temperature of fibromyalgia patients compared to matched healthy controls. Thyroid Science, 1:T1-T18, 2006. B. Lowe, J.C., Yellin, J., and Honeyman-Lowe, G.: Female fibromyalgia patients: lower resting metabolic rates than matched healthy controls. Medical Science Monitor, 12(8):CR1-CR8, 2006. b. T3-Induced Recovery from Fibromyalgia by a Hypothyroid Patient Resistant to T4 and Desiccated Thyroid. Dr. John C. Lowe. Originally published in the *J. Myofascial Ther*., 1(4):26-31, 1995 http://www.thyroidscience.com/cases/lowe.9.6.10/lowe.t3.fms.9.6.10.htm c. A metabolic basis for fibromyalgia and its related disorders: the possible role of resistance to thyroid hormone. Garrison RL, Breeding PC. http://www.ncbi.nlm.nih.gov/pubmed/12888300 VIII. Pregnancy. ITT welcomes the guidance being reviewed by the Royal College of Obstetricians and Gynaecologists, but believes that pregnancy should additionally be mentioned specifically in NICE guidance for consultation. We believe that the omission from the scope of a significant life event for women is limiting. In pregnancy, the prevalence of overt and subclinical hypothyroidism is estimated at 0.5 and 4-8% respectively although higher rates are reported when the	

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			gestational upper TSH limits recommended by International guidelines are applied. Untreated or inadequately treated hypothyroidism is associated with anaemia, myopathy, congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants and postpartum haemorrhage. We believe the scope should include fertility and pregnancy. IX. Vitamin D deficiency, Iron and Selenium deficiencies in patients. https://www.holtorfmed.com/vitamin-d-autoimmune-thyroid-disease/ Clinical research has concluded that low vitamin D is involved in the disease process that causes Hashimoto's thyroiditis, and that vitamin D and autoimmune thyroid disease are linked. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3921055/ Hypovitaminosis D with hypocalcaemia is significantly associated with the degree and severity of the hypothyroidism.	
Improve Thyroid Treatment Campaign Group	4	94	*"Neonates"* Despite the scoping exercise declining to cover neonates, or include this in the RCOG brief, a literature search indicates evidence of a serious and potentially fatal issue for both mother and baby during and post pregnancy arising from the development of hyperparathyroidism in the mother following RAI treatment. Nothing could be found that indicates screening for this for the woman either post RAI or in pregnancy. ITT consider this should be carefully considered and rectified. I. Post RAI development of hyperparathyroidism in women https://www.ncbi.nlm.nih.gov/m/pubmed/17693276/	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green top guideline on thyroid disease in pregnancy produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			"In this collective experience, the average latency time to the development of HPT after RAI treatment was 13.5 +/- 9.1 years and was found to be inversely correlated with age at RAI exposure." II. https://www.ncbi.nlm.nih.gov/m/pubmed/2588108/?i=7&from=/6689566/related "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. III. Consequences of maternal hyperparathyroidism http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2008.03495.x/abstract "Conclusions: HPT during pregnancy is under recognized and is associated with a 3·5-fold increase in miscarriage rates. Pregnancy loss often occurs in the second trimester and is associated with multiple miscarriages when not addressed. Pregnancy loss is more common as calcium levels exceed 11·4 mg/dl (2·85 mmol/l), but can be seen at all elevated calcium levels. Emphasis is placed on earlier recognition and surgical cure before becoming pregnant, however, once pregnant, surgery should be offered early in the second trimester for those with calcium levels above 11·4 mg/dl." IV. http://www.parathyroid.com/pregnancy.htm "Hyperparathyroidism (parathyroid disease with high calcium) occurring during pregnancy is a very serious problem. Hyperparathyroidism during pregnancy puts both	

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			the mother and child's life at risk, and the chance for life-long calcium problems for the child exists. Hyperparathyroidism during pregnancy is treated with mom's surgery during the late first or early second trimester."	
Improve Thyroid Treatment Campaign Group	4	105	*Note that guideline recommendations for medicines will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended.* Recommendations for medicines for treating thyroid disease generally fall within the licensing indications. Two possible exceptions to this are: 1. The knowledge of the existence of the DIO2 Gene defect, which implies that many patients cannot partially, or fully, convert thyroxine, will promote more routine and widespread need of liothyronine. 2. In relation to point 1, and the knowledge that some patients cannot tolerate synthetic medications or some element in the make up of synthetics, there is a clinical need to make Natural Desiccated thyroid [NDT] available. The current licensing of L-T3 covers its use. "Therapeutic indications: Liothyronine is indicated in adults and children for the treatment of coma of myxoedema, the management of severe chronic thyroid deficiency and hypothyroid states occurring in the treatment of thyrotoxicosis." This may need to be addressed, reviewed and reassessed by Medicines & Healthcare products Regulatory Agency [MHRA] NDT was used successfully, for decades, prior to the development and prescribing of synthetic L-T4. It was never licensed in the UK as its use predated 1938. However it continued to be prescribed, in the UK until 2012. NDT never lost it's 'Grandfathered' status. Patients are choosing to self-source and treat with NDT as it is considered to be the nearest in physiological make up to the human thyroid. There	Thank you for this information.

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			is some thinking that the current use of the molecular equivalent ratio of 11-20:1 T4:T3 is outdated and incorrect, focusing on the 'weight' equivalence rather than the therapeutic equivalence. And that a therapeutic ratio of 4:1 is a much more accurate ratio to use. Patient experience of the success of treatment using NDT should be considered. The pharmacodynamic equivalence of levothyroxine and liothyronine: a randomized, double blind, crossover study in thyroidectomized patients. Celi FS, Zemskova M, Linderman JD, Babar NI, Skarulis MC, Csako G, Wesley R, Costello R, Penzak SR, Pucino F. https://www.ncbi.nlm.nih.gov/pubmed/20447070 SUMMARY OF PRODUCT CHARACTERISTICS http://www.mhra.gov.uk/home/groups/spcpil/documents/spcpil/con1503033237510.pdf Accessed 07/11/17 Facts about Natural Thyroid Extract, Compiled by Sheila Turner. http://www.tpauk.com/main/article/facts-about-natural-thyroid-extract/ Accessed 10/11/17	
Improve Thyroid Treatment Campaign Group	4	111	*" – indications of thyroid function tests"* ITT believes a patient-centred approach is required and signs and symptoms are as important as the clinical tests. Patient signs and symptoms are very important to the diagnosis of thyroid disease. Recognition of the expertise that the patient brings, as well as test evidence base, form a stronger diagnostic methodology and would engage patients in shared decision making. We believe routine evaluation of patients' signs and symptoms would be valuable. These can include, but not exclusively, cholesterol changes, blood pressure changes, polycystic ovary syndrome, weight gain, generalized weakness, tiredness or fatigue, infertility, depression and mood changes, and would improve the diagnosis of this chronic illness. *"It is important to recognise that the upper TSH reference*	Thank you for this information. The exact tests and investigations for consideration in each review will be discussed with the committee members.

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			limit is not the therapeutic threshold for initiating levothyroxine replacement therapy. *Instead, the clinical response to a confirmed mildly elevated TSH should be determined on an individual basis"* Carole Spencer, MD, PhD, is a Professor of Research at the Keck School of Medicine at the University of Southern California. Many patients have access to health and fitness apps (my fitness pal, Garmin, butterfly) on smart devices, which provide a wealth of information on exercise, diet, sleep and heart rate that can be used by primary care. Patients would be more likely to seek and obtain the right treatment in primary care. The scope should include recommendations that signs and symptoms will be treated as significantly as clinical tests and patients who present unexplained symptoms associated with thyroid disorders should be routinely checked for thyroid disease.	
Improve Thyroid Treatment Campaign Group	4	111	*" – indications of thyroid function tests"* The scope considers investigations into thyroid disorders. When investigating the health of the thyroid during diagnosis ITT believes the scope should include the requirement of a physical examination by the physician.	Thank you for this information. The exact tests and investigations for consideration in each review will be discussed with the committee members.
Improve Thyroid Treatment Campaign Group	4	111	*" – indications of thyroid function tests"* ITT believes the thyroid hormone test ranges currently used require update since they are significantly out of date when compared those in America and Europe. ITT advocates that the scope should include the use of a narrower TSH range than is currently in use in the UK to identify thyroid disorder earlier (with a maximum of 2.0). This will result in better patient health outcomes and improved patient quality of life. There has been significant progress in diagnostic technique and efficiency. New evidence supports the use of updated and narrower thyroid hormone test ranges, both for diagnosis and monitoring. Thyroid Stimulating Hormone (TSH) reference ranges in the UK, are significantly wider than those used in America and Europe. The test ranges used for diagnosis are also inconsistent	Thank you for your comment. The committee will consider the role of TSH ranges during the development of the guideline. Through addressing the appropriate management of subclinical thyroid dysfunction, the guideline will aim to ensure that all people in who treatment is clinically and cost effective, receive treatment.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			with the TSH used for management of thyroid hormone levels once a patient is under treatment. Typically in the UK, the TSH reference range used for diagnosis is between 0.3 – 5.0 mIU/l but treatment is not considered in many cases until TSH is above 10 mIU/l. For example, if Thyroid Stimulating Hormone is measured as 10 mIU/l or there is clinical evidence of significant health consequences, including chronic heart disease. However once treatment commences the current NICE guidelines are to attain a TSH of below 2.5 mIU/l. In 2002 the American Association of Clinical Endocrinologists narrowed the reference range to 0.3 – 3.0 mIU/l. In 2003 the National Academy of Clinical Biochemistry recommended an upper TSH limit of 2.5 mIU/l. "But recognition that the mean of normal TSH values is only between 1.18 mIU/l and 1.4 mIU/l and that more than 95% of the population will have a TSH of less than 2.5 mIU/l clearly implies that anyone with a higher value should be carefully assessed for early thyroid failure" (Wartofsky and Dickey). We advocate that the scope includes the use of a narrower TSH range than is currently in use in the UK to identify thyroid disorder earlier. This will result in better patient health outcomes and improved patient quality of life. I. "Is a normal TSH Synonymous with "Euthryoidism" in levothyroxine monotherapy," http://doi.org/10.1210/jc.2016-2660 by Peterson SJ et al J Clin Endocrinol Metab Dec 2016 II. Subclinical hypothyroidism and the risk of coronary heart disease and mortality, Rodondi N et al JAMA 304(12):1365-74 http://doi.org/10.1001/jama.2010.1361 III. Dietrich JW, et al Calculated Parameters of Thyroid Homeostasis: Emerging Tools for Differential Diagnosis and Clinical Research, https://www.frontiersin.org/articles/10.3389/fendo.2016.00057/full IV. Dietrich JW, Landgrafe G, Fotiadou EH. TSH and thyrotrophic agonists: key actors in thyroid homeostasis. J Thyroid Res (2012) 2012:1–	

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			29.10.1155/2012/351864 https://www.hindawi.com/journals/jtr/2012/351864/ V. Larisch R, Giacobino A, Eckl WA, Wahl HG, Midgley JEM, Hoermann R. Reference range for thyrotropin. Post hoc assessment. Nuklearmedizin (2015) 54:112–7.10.3413/Nukmed-0671-14-06 [PubMed] [Cross Ref VI. Wartofsky L1, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. https://www.ncbi.nlm.nih.gov/pubmed/16148345 VII. Brabant G, Beck-Peccoz P, Jarzab B, Laurberg P, Orgiazzi J, Szabolcs I, et al. Is there a need to redefine the upper normal limit of TSH? Eur J Endocrinol (2006) 154:633–7.10.1530/eje.1.02136 https://www.ncbi.nlm.nih.gov/pubmed/16645008	
Improve Thyroid Treatment Campaign Group	4	111	*" indications of thyroid function tests"* ITT believes the scope should consider a broader set of clinical tests than are currently performed. Tests currently used to diagnose and monitor hypothyroidism require update to reflect 1) the limitations of the sole use of Thyroid Stimulating Hormone tests (TSH) 2) new research on the complex interactions of the thyroid and other hormones. Diagnostic and monitoring tests should be expanded from TSH to include the full range of thyroid hormones. There are many reasons why TSH may be misleading: a) abnormalities in hypothalamic or pituitary function, including TSH producing tumours; b) transition periods such as the early stages of treatment; c) episodes of thyroiditis; and d) certain drugs which influence TSH secretion. There is significant research evidence that TSH should be scaled back to a supporting role that is more in keeping with its role within peripheral thyroid hormones. We recommend that the scope should include a full panel of thyroid tests on diagnosis; Free thyroxine (T4), Total thyroxine (T4), Free T3, Total T3, Reverse T3 and thyroid antibodies. To properly treat the thyroid, there must be clear understanding of	Thank you for your comment. The guideline seeks to address appropriate investigation of thyroid dysfunction.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			the intricacies of the endocrine system. Currently, many patients achieve better thyroid health through trial and error, but that takes significantly longer with a poorer patient and primary care outcome. Thyroid disorders are often associated with poor vitamin (especially B12 and D3) and mineral levels (e.g. magnesium, selenium, iodine). We believe that the scope should also consider vitamins and minerals, for example Vit D, Vit B, ferritin, magnesium, selenium. Vitamin D is required for the metabolic process that allows thyroid hormones to enter and act in the cells. If a patient is lacking vitamin D, thyroid hormones cannot chemically metabolise resulting in continuing dysfunction. Patients with autoimmune thyroid disorders frequently experience vitamin D deficiency. Early recognition of a vitamin D deficiency will allow primary care to detect and resolve thyroid issues earlier. The thyroid hormones rely on biochemical actions. Approximately 20% of the T4 produced by the thyroid is converted into the active thyroid hormone T3 in the gastrointestinal tract. Thyroid treatment should also include testing of digestion. The thyroid and adrenal glands are closely connected. Issues with one can result in dysfunction in the other. Adrenal issues are associated with i) poor hypothalamus and pituitary function and signalling to the thyroid gland, ii) increase in thyroid binding protein activity, iii) reduced conversion of T4 to active T3 (forms reverse T3 which is inactive) iv) reduced cell sensitivity to thyroid hormones v) promotes poor immune regulation associated with autoimmune disorders. ITT recommends the use of saliva tests for adrenal testing. I. Hoermann R, Eckl WA, Hoermann C, Larisch R. Complex relationship between free thyroxine and TSH in the regulation of thyroid function. Eur J Endocrinol (2010) 162:1123–9.10.1530/EJE-10-0106. https://www.ncbi.nlm.nih.gov/pubmed/20299491 II. Ehrenkranz J1, Bach PR2, Snow GL3, Schneider A4, Lee JL5, Ilstrup S2, Bennett ST2, Benvenga S. Circadian and Circannual Rhythms in Thyroid Hormones: Determining the	

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			TSH and Free T4 Reference Intervals Based Upon Time of Day, Age, and Sex. https://www.ncbi.nlm.nih.gov/pubmed/26061389 III. Hadlow NC, Rothacker KM, Wardrop R, Brown SJ, Lim EM, Walsh JP. Metab (2013) 98:2936–43.10.1210/jc.2012-4223 [PubMed] [Cross Ref]. The relationship between TSH and free T4 in a large population is complex and nonlinear and differs by age and sex. J Clin Endocrinol Metab (2013) 98:2936–43.10.1210/jc.2012-4223 https://www.ncbi.nlm.nih.gov/pubmed/23671314 IV. Hoermann R, Midgley JEM. TSH measurement and its implications for personalised clinical decision-making. J Thyroid Res (2012) 2012:1–9.10.1089/thy.2008.0155. https://www.ncbi.nlm.nih.gov/pubmed/23304636 V. Homeostatic control of the thyroid-pituitary axis: Perspective for diagnosis and treatment. Prof Hoermann, J Midgley et al Front Endocrinol (Lausanne) 2015 Nov 20;6:177 http://doi.org/10.3389/fendo.2015.00177 VI. Does Normal TSH Mean Euthyroidism in L-T4 Treatment? Peterson SJ, McAninch EA, Bianco AC. Is a normal TSH synonymous with "euthyroidism" in levothyroxine monotherapy? J Clin Endocrinol Metab. October 4, 2016 [Epub ahead of print]. http://online.liebertpub.com/doi/full/10.1089/ct.2016%3B28.325-328 VII. Rev Endocr Metab Disord. 2017; 18(3): 347–354. Published online 2017 Jan 14. doi: 10.1007/s11154-017-9406-3 PMCID: PMC5543192 Sunshine vitamin and thyroid Immacolata Cristina Nettore,1 Luigi Albano,2 Paola Ungaro,3 Annamaria Colao,1 and Paolo Emidio Macchia 1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5543192/ VIII. Thyroid. 2014 Nov;24(11):1618-24. doi: 10.1089/thy.2014.0090. Epub 2014 Sep 19. IX. Low serum 25 hydroxyvitamin D is associated with poor clinicopathologic characteristics in female patients with	

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			papillary thyroid cancer. Kim JR1, Kim BH, Kim SM, Oh MY, Kim WJ, Jeon YK, Kim SS, Lee BJ, Kim YK https://www.ncbi.nlm.nih.gov/pubmed/25133449/ X. Sibilla R, et al. Chronic unexplained anaemia in isolated autoimmune thyroid disease or associated with autoimmune related disorders. 2008. https://www.ncbi.nlm.nih.gov/pubmed/18062801 XI. Abdullatif HD, Ashraf AP. Reversible subclinical hypothyroidism in the presence of adrenal insufficiency. 2006. https://www.ncbi.nlm.nih.gov/pubmed/17002934 XII. Alevizaki, M., Mantzou, E., Cimponeriu, A. T., Alevizaki, C. C., & Koutras, D. A. (2005). TSH may not be a good marker for adequate thyroid hormone replacement therapy. *Wiener Klinische Wochenschrift*, *117*(18), 636-640.	
Improve Thyroid Treatment Campaign Group	4	111	*" indications of thyroid function tests"* ITT believes that tests undertaken should have age, gender and pregnancy-specific reference ranges for the thyroid hormone tests. This patient centric approach will result in more accurate diagnosis and improved outcomes. I.Boelaert K, Torlinska B, Holder RL, Franklyn JA 2010 Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab 95:2715–2726. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab (2007) 92: https://www.ncbi.nlm.nih.gov/pubmed/17911171	Thank you for your comment. The committee will consider the role of TSH ranges during the development of the guideline. Through addressing the appropriate management of subclinical thyroid dysfunction, the guideline will aim to ensure that all people in who treatment is clinically and cost effective, receive treatment.
Improve Thyroid Treatment Campaign Group	4	112	*" indications of thyroid function tests"* See 4 111 above. ITT believes that tests undertaken should have age, gender and pregnancy-specific reference ranges for the thyroid hormone tests. This patient centric approach will result in more	Thank you for your comment. The committee will consider the role of TSH ranges during the development of the guideline. Through addressing the appropriate management of subclinical

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			accurate diagnosis and improved outcomes. I. Boelaert K, Torlinska B, Holder RL, Franklyn JA 2010 Older subjects with hyperthyroidism present with a paucity of symptoms and signs: a large cross-sectional study. J Clin Endocrinol Metab 95:2715–2726. II. Surks MI, Hollowell JG. Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab (2007) 92: https://www.ncbi.nlm.nih.gov/pubmed/17911171	thyroid dysfunction, the guideline will aim to ensure that all people in who treatment is clinically and cost effective, receive treatment.
Improve Thyroid Treatment Campaign Group	4	112	*"Investigation of thyroid dysfunction or thyroid enlargement - indications for other tests or imaging"* The draft scope recognises that about 90% of hypothyroidism is caused by autoimmune (Hashimoto) thyroiditis. The draft scope does not set out the tests that are in scope to identify autoimmune thyroiditis. An increasing number of individuals throughout the world are affected by autoimmune disease. Autoimmune attacks cause instability in the thyroid hormone levels and result in patients being symptomatic, visiting their GP and possibly undergoing other clinical/blood numerous tests and changing hormone replacement doses. That instability is not in the patient or primary care best interest and early diagnosis will give both the patient and primary care a better outcome. Understanding the antibody levels allows the patient to make an informed and shared decision on lifestyle changes that could minimise autoimmune attacks. I. Series Introduction: Autoimmune diseases: are markers ready for prediction? Åke Lernmark. https://www.jci.org/articles/view/14234	Thank you for your comment. The guideline seeks to address appropriate investigation of thyroid dysfunction. The exact tests that will be considered for each situation will be determined in discussions with the committee.
Improve Thyroid	4	112	*"Investigation of thyroid dysfunction or thyroid enlargement - indications for other tests or imaging"*	Thank you for your comment. Given the breadth of the current guideline scope and

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Treatment Campaign Group			ITT recommends that the draft scope include autoantibodies. The draft scope currently excludes any reference to the overwhelming evidence that thyroid autoantibodies increase the risk of infertility, pregnancy complications and miscarriage rates. We feel this information should be included and recommend that screening as standard for these antibodies is of paramount importance. Knowledge regarding the interaction between the thyroid and pregnancy is advancing at a rapid pace. Only recently has a TSH of 2.5mIU/L been accepted as the upper limit of normal for TSH in the first trimester. Overt hypothyroidism, overt hyperthyroidism, subclinical hypothyroidism and subclinical hyperthyroidism all have a potential impact on maternal and fetal health. The American Thyroid Association charged a task force with developing clinical guidelines for Management of Thyroid Disease and Postpartum. We have taken information from these 2017 guidelines and included some other expert opinions from Europe and from the UK specifically in our review. https://www.thyroid.org/association-guidelines-management/ TPOAb antibodies themselves carry a risk of miscarriage and premature delivery without the extra risk factor of hypothyroidism. Hashimoto's thyroiditis or chronic autoimmune thyroiditis is the most common cause of hypothyroidism. Hashimoto's is categorized clinically by gradual thyroid failure, with or without goitre formation due to autoimmune mediated destruction of the thyroid gland involving apoptosis of thyroid epithelial cells. Nearly all patients have high serum concentrations of antibodies against one or more thyroid antigens; diffuse lymphocytic infiltration of the thyroid, which includes predominantly thyroid specific B and T cells; and follicular destruction, which is a characteristic hallmark of thyroiditis. https://www.uptodate.com/contents/pathogenesis-of-hashimotos-thyroiditis-chronic-autoimmune-thyroiditis Thyroid antibodies and pregnancy loss, Spontaneous pregnancy	the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green top guideline on thyroid disease in pregnancy produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			loss or miscarriage has been reported to occur between 17% and 31% of all gestations. I. A prospective study of early pregnancy loss. Ellish NJ, Saboda K, O'Connor J, Nasca PC, Stanek EJ, Boyle C. https://www.ncbi.nlm.nih.gov/pubmed/8671233 II. Incidence of early loss of pregnancy Wilcox AJ, Weinberg CR, O'Connor JF, Baird DD,Schlatterer JP, Canfield RE, Armstrong EG, Nisula BC https://www.ncbi.nlm.nih.gov/pubmed/3393170 Evidence shows a direct correlation between thyroid antibody (Ab)-positive women and a serum TSH>4mU/L We therefore recommend the draft scope considers that women who are TPOAb or TGAb positive should have measurement of serum Thyroid Stimulating Hormone (TSH) concentration performed at time of pregnancy and every four weeks through midpregnancy. A high TSH level is another cause of miscarriage as discussed under thyroid function testing in pregnancy. Even mild or subclinical hypothyroidism increases pregnancy complications. According to the American Thyroid Association Pregnancy Guidelines there is double the rate of miscarriage in women with Hashimoto's who are subclinically hypothyroid, with TSH levels between 2.5 and 5.0 mIU/L, versus women who have Hashimotos disease with TSH levels below 2.5 mIU/L III. Gilinoer et al 1994. The Risk of Subclinical Hypothyroidism in Pregnant Women with Asymptomatic Autoimmune Thyroid Disorders. https://www.researchgate.net/publication/15172473-_Risk_of_subclinical_hypothyroidism_in_pregnant_women_with_autoimmune_thyroid_disorders IV. Negro et al 2006. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications.	

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			http://www.thyroidclub.be/documents/2006iii5.pdf An enormous number of studies document the risk of pregnancy complications, miscarriage and infertility in thyroid antibody positive women. Not only would there be increased positive outcomes if there were testing as standard for the TPOAb and TGAb antibodies for all women of childbearing age, but there would also be a saving on the cost of preterm births. The cost of which is estimated at £93 million a year in the United Kingdom. V. Mangham LJ, Petrous S, Doyle LW, Draper ES, Marlow N. The Cost of Preterm Birth throughout Childhood in England and Wales. Paediatrics 2009 123:e312-27 https://www.researchgate.net/publication/23950722_The_Cost_of_Preterm_Birth_Throughout_Childhood_in_England_and_Wales We have confirmed the association between miscarriage and increased TPOAb levels. Furthermore, it appears TPOAb levels in maternal blood are not influenced by serum hCG levels therefore, we propose the day nulliparous women present for management for miscarriage is a clinically relevant and pragmatic time to screen for TPOAb. VI. Mathis Grossmann et al. Measuring thyroid peroxidase antibodies on the day nulliparous women present for management of miscarriage: a descriptive cohort study. 2013 https://link.springer.com/article/10.1186/1477-7827-11-40 Thyroid autoantibodies are detected in 50% of pregnant women with subclinical hypothyroidism and in more than 80% with overt hypothyroidism. The presence of thyroid autoantibodies is relatively common in all women of reproductive age who have biochemically normal thyroid function.	

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			VII. Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ 2004. The reference range and within-person variability of thyroid stimulating hormone during the first and second trimesters of pregnancy. J Med Screen 11: 170-174 https://www.ncbi.nlm.nih.gov/pubmed/15563772 In an unselected population of women, the prevalence of pregnancy loss ranges from 6% to 20% (1,2) being even higher in women with a history of recurrent pregnancy loss at around 17-33% (3,4,5) and in women with subfertility at around 10-31% (6,7,8) Given the importance of the association between thyroid antibodies and pregnancy, Shakila Thangaratinam et al. Association between thyroid antibodies and miscarriage and pre term birth meta- analysis of evidence articles with 31 studies (19 cohort and 12 case control) involving 12,126 women assessed the association between thyroid antibodies and miscarriage. Five studies with 12,566 women evaluated the association with preterm birth. Of the 31 studies evaluating miscarriage, 28 showed positive association between thyroid antibodies and miscarriage. Meta-analysis of the cohort studies showed more than a tripling in the odds of miscarriage with the presence of thyroid antibodies (odds ratio 3.90, 95% confidence interval 2.48 to 6.12; P<0.001). For case control studies the odds ratio for miscarriage was (1.80, 1.25 to 2.60; P=0.002). These had a significant doubling in the odds of preterm birth with the presence of thyroid autoantibodies (2.07, 1.17 to 3.68; P=001). Two randomised studies evaluated the effect of treatment with Levothyroxine on miscarriage. Both showed a significant 52% relative risk reduction in miscarriages with Levothyroxine (relative risk 0.48, 0.25 to 0.92; P=0.03). One study reported on the effect of Levothyroxine on the rate of preterm birth and noted a 69% relative risk reduction (0.31, 0.11 to 0>90). The conclusion was the presence of maternal thyroid antibodies is strongly associated with miscarriage and preterm delivery. There is	

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			evidence that treatment with Levothyroxine can attenuate the risks. Shakila Thangaratinam et al. Association between thyroid antibodies and miscarriage and pre-term birth meta- analysis of evidence. BMJ2011; 342 doi https://doi.org/10.1136/bmj.d2616 30 The opposition to universal screening has stemmed from the lack of clarity regarding aspects of screening such as the choice and timing of screening tests. However, the onus is on the advocates of screening to propose concise evidence-based algorithms to support an effective strategy. Additional data comparing the performance and cost–effectiveness of different screening tests such as FT4, TSH and TPOAb, will be useful. Audits of existing screening practices in routine pregnancy care will provide a more realistic picture of clinician preferences and practices and will guide in the planning and implementation of future screening programs. Such surveys need not be restricted to endocrine or specialist obstetric units but should involve practices run by generalists, community midwives and obstetricians who provide the greater part of routine pregnancy care. Furthermore, it is important to clarify whether in the absence of universal screening we can reliably predict which woman will develop thyroid dysfunction in pregnancy. To this end the sensitivity of the more comprehensive case-finding stratifications should be evaluated in real world settings. Lastly, it is arguable whether in the light of the proven benefits of correcting overt hypothyroidism it is justifiable to continue to await future intervention data in subclinical hypothyroidism before adopting a universal screening policy. Levothyroxine intervention trials in pregnancy are enormously challenging to undertake, often span many years and face major obstacles in recruiting trial participants from early gestation due to the fact that many pregnancies are unplanned or unnoticed in the early phase. Thus, there is no guarantee that future trials will be free of the limitations of past studies. Meanwhile there is increasing public awareness of the potential associations between thyroid dysfunction and adverse pregnancy outcomes and a growing	

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			proportion of clinicians now opt for universal screening in pregnancy. In a single academic centre in Boston, for example, 85% of women underwent thyroid testing under routine care settings and of these 80% of women with thyroid dysfunction would have been missed if a case-finding approach had been adopted. Thus, with the current trend it is not inconceivable that future ethical committees may struggle to justify withholding therapy in the control arm of subsequent trials. VIII. Peter N Taylor, Onyebuchi E Okosieme, Lakdasa Premawardhana, and John H Lazarus 2015. Should all women be screened for thyroid dysfunction in pregnancy? Thyroid Research Group, Institute of Molecular & Experimental Medicine, Cardiff University School of Medicine. The need for systematic thyroid function and TGAb evaluation in early pregnancy may seem fairly obvious, but this is far from being a unanimous opinion.-It has been 8 years since we called for thyroid function screening in pregnancy and 5 years since the American Association of Clinical Endocrinologists (AACE) recommended thyroid function screening in all women during the first trimester of pregnancy. The most recent joint guideline published by the Endocrine Society recommends an aggressive case-finding approach during early pregnancy in high-risk populations rather than routine screening. According to these most recent guidelines, additional evidence is required prior to the recommendation of routine thyroid function screening before and during pregnancy. The issues to be answered include the thyroid test(s) to be used, timing of the determination, thresholds to characterize as an abnormality, appropriate intervention mechanisms, and methods of monitoring. Although these issues appear to have clear answers and because the association of thyroid abnormalities and adverse outcomes during pregnancy and the postpartum is impossible to ignore, we continue to advocate for routine screening in all women in early, and	

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			preferably before, pregnancy. Thyroid diseases, especially those of autoimmune origin, are common in women of childbearing age. These disorders are significantly influenced not only by a variety of changes in thyroid function that take place during normal gestation but also by the privileged immune state that occurs in pregnancy. Therefore, interpretation of thyroid function tests during gestation requires specific pregnancy ranges that are not widely available. In our opinion, adequate screening programs should be established in order to prevent the consequences of delay in, or misdiagnosis of, thyroid dysfunction during pregnancy, which can pose potentially significant adverse effects to both mother and child. The correct approach to the diagnosis and therapy of thyroid dysfunction in pregnancy requires monthly fetal and maternal monitoring and its continuation into the postpartum period when the onset of the postpartum thyroid syndromes should be expected. IX. Juan C. Galofre, M.D., Ph.D and Terry F. Davies M.D.2008 Autoimmune Thyroid Disease in Pregnancy: A Review A new study by Peter N Taylor is to be published soon, in which he examined all the Lazarus trial data collected. All the obstetric outcomes were logged electronically and show a big difference in miscarriage in those treated and encourages universal screening. We ask the draft scope to examine this paper as soon as it is published. For non- converters of Levothyroxine (T4) to Liothyronine (T3) and for those unable to take T4 we would like the draft scope to acknowledge that more studies are needed to assess the taking of T3 medications and Natural Desiccated Thyroid (NDT) in pregnancy. Both Levothyroxine and Liothyronine are designated by the FDA as Category A in pregnancy, meaning that "adequate and well-	

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			controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters.)" Generations of women had successful pregnancies on NDT before it fell out of favour and synthetic T4 was brought to the market. It is undoubtable that Levothyroxine in pregnancy saves babies and is a proven treatment. Our concern is for those patients with deiodinase polymorphisms, or other reasons for non- conversion, that they will suffer unduly during pregnancy as has been reported to us in patient stories. Undermedicated patients who don't convert are more at risk of miscarriage. Surely it is better for the mothers' treatment to be optimal and to let them have a choice of combination treatment or NDT. Richard Shames, Harvard Professor and author of several books on thyroid disease has helped many patients to optimize treatment and become pregnant. "I think that the warnings regarding using T3 can cause unnecessary fear and concern in women who are stabilized and doing well on natural desiccated thyroid or T4/T3 combination therapy. Before Levothyroxine was on the market, generations of women had successful pregnancies and healthy babies using desiccated thyroid." We have several patient stories of successful outcomes medicated on combination T4/T3 and NDT. Some women who had trouble with infertility fell pregnant as soon as they were medicated with T3. More studies are needed. Retrospective studies could be done with doctors who use T4/T3 treatment and NDT in pregnancy. A protocol is needed for monitoring and testing during pregnancy, with follow-ups once the babies have been born and into childhood. Rates of miscarriage, preterm labour and infertility as well as other pregnancy related complications could also be evaluated.	

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			X. https://academic.oup.com/edrv/article-lookup/doi/10.1210/edrv.18.3.0300 XI. https://www.ncbi.nlm.nih.gov/m/pubmed/7158229 XII. https://www.researchgate.net/publication/10865905_Laboratory_medicine_practice_guidelines_Laboratory_support_for_the_diagnosis_and_monitoring_of_thyroid_disease XIII. http://www.academia.edu/1130433/Trimester-specific_changes_in_maternal_thyroid_hormone_thyrotropin_and_thyroglobulin_concentrations_during_gestation_trends_and_associations_across_trimesters_in_iodine_sufficiency XIV. https://www.ncbi.nlm.nih.gov/m/pubmed/17465859/ XV. https://www.researchgate.net/publication/24174694_Thyroid_Function_in_Early_Pregnancy_in_Japanese_Healthy_Women_Relation_to_Urinary_Iodine_Excretion_Emesis_and_Fetal_and_Child_Development XVI. https://link.springer.com/article/10.1007/BF03350244 XVII. https://www.ncbi.nlm.nih.gov/m/pubmed/15481634/ Postpartum thyroiditis (PPT) is the occurrence of de novo autoimmune thyroid disease, excluding Graves' disease, in the first year postpartum. The incidence of PPT is 5.4% in the general population, and it is increased in individuals with other autoimmune diseases such as type 1 diabetes mellitus. The classic presentation of PPT of hyperthyroidism followed by hypothyroidism is seen in 22% of cases. The majority of women with PPT experience an isolated hypothyroid phase (48%), with the remainder experiencing isolated thyrotoxicosis (30%). Up to 50% of women who are thyroid antibody positive (thyroid peroxidase antibody and/or thyroglobulin antibody) in the first trimester will develop PPT. Symptoms are more common in the hypothyroid phase of PPT and include fatigue, dry skin, and impaired memory. Despite multiple studies exploring the relationship between PPT and postpartum depression, or	

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			postpartum depression in thyroid antibody positive euthyroid women, the data are conflicting, and no firm conclusions can be reached. Long-term follow-up of women who had an episode of PPT reveals a 20 – 40% incidence of permanent primary hypothyroidism. In a single study, selenium administration significantly decreased the incidence of PPT, but replication of the findings is needed before the recommendation can be made that all pregnant thyroid peroxidase antibody-positive women receive selenium. The indication for treating the hyperthyroid phase of PPT is control of symptoms, whereas treatment of the hypothyroid phase of PPT is indicated for symptomatic relief as well as in women who are either breastfeeding or attempting to conceive. (J Clin Endocrinol Metab 97: 334 –342, 2012) Approach to the Patient with Postpartum Thyroiditis Alex Stagnaro-Green George Washington University School of Medicine and Health Sciences, Washington, D.C. The exact cause of postpartum thyroiditis is not known but it is believed to be an autoimmune disease very similar to Hashimoto's thyroiditis. In fact, these two disorders cannot be distinguished from one another on pathology specimens. As in Hashimoto's thyroiditis, postpartum thyroiditis is associated with the development of anti-thyroid (anti-thyroid peroxidase, antithyroglobulin) antibodies. Women with positive antithyroid antibodies are at a much higher risk of developing postpartum thyroiditis than women who do not have positive antibodies. It is believed that women who develop postpartum thyroiditis have an underlying asymptomatic autoimmune thyroiditis that flares in the postpartum period when there are fluctuations in immune function. Treatment depends on the phase of thyroiditis and degree of symptoms that patients exhibit. Women presenting with thyrotoxicosis may be treated with beta-blockers to decrease palpitations and reduce shakes and tremors. As symptoms improve, the medication is tapered off since the thyrotoxic phase is transient. Antithyroid medications are not used for the thyrotoxic phase since the thyroid is not overactive. The hypothyroid phase is often treated with thyroid hormone replacement. If the	

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			hypothyroidism is mild, and the patient has few, if any, symptoms, no therapy may be necessary. If thyroid hormone therapy is begun, treatment should be continued for approximately 6-12 months and then tapered to see if thyroid hormone is required permanently. It is always important to try to discontinue thyroid hormone after postpartum thyroiditis, since 80% of patients will regain normal thyroid function and not require chronic therapy American Thyroid Association, thyroid.org We recommend to the draft scope that thyroid antibodies TPOAb and TGAb be checked to differentiate between postpartum thyroiditis and Hashimoto's disease. Treatment for Hashimotos is to try and stabilise inflammatory responses. 50% of people with gluten sensitivity experience molecular mimicry with casein (a protein found in dairy). This is known as cross-reactivity, where you react not only to your original trigger, but also to another trigger that resembles the first one. Every time gluten and dairy are ingested their proteins are able to escape into the bloodstream, where they trigger an attack from the immune system. Because of the molecular mimicry phenomenon, the thyroid tissues are attacked also. Interestingly, the immune system's attack can affect the thyroid in two completely different ways. In the case of autoimmune hypothyroidism (Hashimoto's disease) the immune system's attacks decrease thyroid functionality, so that metabolic processes slow down. In (Grave's disease), the antibodies act like Thyroid Stimulating Hormone, causing the thyroid to overproduce its hormones and sending the metabolism into overdrive. It is imperative therefore to be gluten and casein free. A good probiotic is also recommended to assist in gut repair. Vitamin B12, Vitamin D, Folate and ferritin all need to be optimum and it is advisable to check magnesium, selenium and zinc as all are	

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			known to be deficient in autoimmunity. Adrenals and sex hormones are all too often imbalanced and require levels checking. It is undeniable that the diet of the industrialized and urbanized parts of the world today is vastly different from what it was even two or three decades ago, with a whole new range of novel food experiences that come from new food component sources, new breeds of food plants and food animals, genetic modifications, chemical ingredients, flavours, and preservatives. Over recent decades, a significant increase in the incidence of autoimmune diseases such as diabetes and MS in industrialized countries has led to the postulation that diet is a potential environmental risk factor for such disorders. The link between gluten ingestion and gluten sensitive enteropathies is already well established and accepted. High levels of dietary sodium are associated with raised blood pressure and adverse cardiovascular health and have been shown to affect the immune system. Low levels of vitamin D have been linked with MS, systemic lupus erythematosus (SLE), RA, and other autoimmune disorders. Lactose intolerance is no laughing matter for those afflicted with it or other milk-related disorders. The pleasures of a modern diet unfortunately come with caveats and unexpected catches that urgently need investigation. A number of experimental studies and clinical reports have shown that autoimmune reactivity and/or autoimmune diseases are induced in humans and chronic exposure to various chemicals in animal models. These studies were summarized by Bigazzi in 1997. Furthermore, very recently, the role of environmental chemicals, in particular, the induction of autoimmunities by toxicants, was summarized by Pollard et al. in his paper, "Toxicology of autoimmune diseases." The mechanism of toxicant-induced autoimmunity is described by either toxicant induction of aberrant cell death making the hidden cellular material available to antigen presenting cells or by immune reactions to xenobiotics through	

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			covalent binding of chemicals or haptens to human tissue proteins and formation of neoantigens I. A Potential Link between Environmental Triggers and Autoimmunity Aristo Vojdani 2014 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3945069/	
Improve Thyroid Treatment Campaign Group	5	113-115	*"Management of non-malignant thyroid enlargement with normal thyroid function. Referral for surgery."* Enlargement is swelling, which is a sign that there is a problem. Goitres should not be ignored, nor should corrective surgery be deemed to be cosmetic. ITT recommend that all goitres be monitored. If hypothyroid symptoms are present and thyroid function testing is deemed 'normal' ITT recommends that the scope guidelines include a recommendation that antibody testing must be requested to check for toxic multi-nodular goitre. ITT recommends that surgery should only be considered where there is immediate health concern i.e. goitres that are restricting breathing or where other options are not viable. ITT guides that surgeons need to be sure that the enlargement is not a toxic multi-nodular goitre where tests can be misleading and the patient may initially present as hypothyroid. ITT recommends that the scope should set out that clear identification of the enlargement needs to be made, to ensure non-malignancy. Full thyroid panel blood testing in conjunction with antibody testing, along with relevant scans should be sought, and Fine Needle Aspiration if necessary. The extent of the swelling should be determined through initial choices. Swelling leading to obvious blockage should warrant immediate attention. If surgery is deemed applicable this reasoning should be explained to the patient clearly, in detail, with expected procedures and timescales.	Thank you for your comment. The appropriate investigation and management of thyroid enlargement are topics that the guideline will seek to address.

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			ITT recommends that the scope sets out that patients' expectations should be managed through full disclosure of available options, expected outcomes and clear understanding of the benefits and disadvantages of the follow-up procedures. Patients should have access to all options available including any non-standard treatment. Patients must have assurances that they will remain with secondary care until their treatment is optimised.	
Improve Thyroid Treatment Campaign Group	5	121-122	*"Management of thyrotoxicosis"* As a patient group, the extensive feedback ITT received is that patients initially struggle to get a diagnosis. ITT feels this is not only putting patient long-term health at risk but, equally important, it leaves patients struggling with unnecessary symptoms. ITT believes that the scope should include detailed guidance on thyrotoxicosis. There are several reasons why diagnosis of thyrotoxicosis, and thyroid disease in general, are difficult to determine. 1. Failings in GP training: The thyroid system is complex, yet GPs are taught to rely on the TSH blood level test to ascertain thyroid function. If deemed to be 'out of range', the Free T4 levels may be requested. GPs are not taught how to test for, read and interpret Free T3 levels or reverse T3. This limited training is leaving GPs inadequately prepared, with little understanding, to diagnose anything other than obviously overt hypothyroidism or hyperthyroidism. 2. The importance of testing for thyroid antibodies, on more than one occasion, if necessary, is underestimated. Autoimmune thyroiditis may result in instability in the thyroid. Antibodies can inform the nature of the thyrotoxicosis and the severity of disease. Antibody results should inform treatment and advice to patients. 3. Patient signs and symptoms are undervalued.	Thank you for your comment. The appropriate investigation of thyroid dysfunction is a topic the guideline will seek to address.

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			4. Relevant clinical observations and evaluation are not adhered to. 5. The current diagnostic protocols and regimes are using a poorly understood TSH level as a guide to normal thyroid functioning. 6. There is desperate need for the current treatment protocols to be revised and updated. There has been too strong a reliance on the 'normal' TSH range as a sole diagnostic tool to identify all thyroid dysfunction. The term 'subclinical' has clouded judgement as doctors seem unwilling to consider treatment options until overt thyroid dysfunction can be confirmed, biologically, in accordance with the [misleading] TSH ranges, irrespective of clinical symptoms. ITT feels that the reasons for inadequate diagnosis, as outlined above, result in significant treatment delay (often for years and decades) and reflect poor management of thyrotoxicosis, and thyroid disease in general. This in turn results in greater health risks. Patients have reported to ITT that they endure delays in treatment, as they are misdiagnosed as menopausal or as having mental conditions, often because the relevant testing is being omitted. Sadly, this un/misdiagnosis and poor management, due to lack of understanding is affecting the mental health and wellbeing of patients and there are reports of patients being driven to consider suicide.	
Improve Thyroid Treatment Campaign Group	5	116	*"Non-surgical treatment"* ITT recommends that the scope should include guidance that the cause of enlargement be identified. ITT believes that full blood panels should be requested alongside antibody testing and scans if deemed necessary. Non-surgical treatment should be considered before invasive surgical treatment offered. Treatment should be defined by the underlying cause, be it injury, viral, hyperthyroidism or hypothyroidism. If injury or viral are the cause and blood tests are at acceptable levels then the goitre should be monitored for evidence that it is self-limiting. However, if the enlargement persists and/or	Thank you for your comment. The guideline will seek to address the role of surgery and non-surgical treatments for non-malignant thyroid enlargement as well as how thyroid dysfunction should be investigated.

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			further symptoms develop, more detailed investigation is required. If hyperthyroidism is evident, antithyroid drugs may be needed independently or in conjunction with thyroid hormone to reduce and control the enlargement. If hypothyroidism is suspected a trial of levothyroxine [L-T4] should be initiated and monitored for effectiveness. If euthyroid status is not achieved T3 blood results should be considered and thyroid hormone treatment options such as levothyroxine and liothyronine [L-T4 & L-T3], liothyronine [L-T3] or natural desiccated thyroid [NDT] should be considered. Any administration of medications should be closely monitored for reactions, efficacy and safety.	
Improve Thyroid Treatment Campaign Group	5	119	*"Management of primary hypothyroidism" - Treatment options: T4; T3 combination of both* The draft scope refers to T4:T3, combination of both, as treatment options. ITT believes that Natural Desiccated Thyroid (NDT) or T3 only treatment should also be included in the Scope. Conventional Hypothyroidism guideline approved treatment in the United Kingdom is with monotherapy of a synthetic form of the thyroid hormone thyroxine (L-T4) known generically as Levothyroxine. Thyroxine, an inert pro -hormone is deiodinated to T3, a biochemically active hormone and Reverse T3, an inert storage hormone in a ratio depending on the current needs of the patient. In most patients this process is unhindered, and T4 monotherapy is acceptable. Increasing evidence shows that some patients do not respond well to the use of T4 monotherapy. TSH (Thyroid Stimulating Hormone) and T3 and T4 are synergistically aligned in a feedback loop that keeps all the hormone levels balanced. In a healthy person, TSH stimulates the thyroid gland to produce T4 and T3 in a ratio of approximately 80:20%. T4 deiodinates to T3 mainly in the liver.	Thank you for your comment. T3 alone and thyroid extract will be covered by the guideline: this has been clarified in the scope.

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			• TSH rises when either T4 or T3 levels are too low. • TSH lowers when T4 or T3 levels rise. This helps to keep T3 at healthy levels • T4 only therapy creates an imbalance as T4 levels rise. TSH then falls, so less T4 is available to be converted to T3. This creates a more variable T4/T3 ratio than found in healthy people. • TSH may be normal even though T3 levels are low. • T4 only protocol results in lower T3 levels when compared to the same T4 levels found in people not on thyroid medication. A high TSH is an indicator of hypothyroidism, though there is some controversy about the true level of TSH that indicates when treatment should be started. ITT believe that this TSH treatment start level should be 3 **mIU/L.** TSH is very sensitive to supplemented thyroid hormone and its production will decline when thyroid hormone is taken. This decline in TSH also affects production of T4 and consequential deiodination and availability of T3. Multiple studies report the same results. TSH has it's limitations in diagnosing thyroid disease but a low TSH below 0.4 does indicate that the pituitary itself needs investigation and not that it is 'suppressed' as a result of thyroid medication. T4 monotherapy does not replicate normal thyroid gland output and creates a T3 deficiency, which in turn creates a lower free T3/free T4 ratio. Adding T3 to compensate for this deficiency will cause a decline in TSH that is not consistent with the TSH found in healthy people with the same T4 and T3 levels. Therefore, TSH cannot be used as a gauge in patients when supplementing with thyroid medication. A patient cannot have a normal TSH and healthy FT3 levels while taking T4 monotherapy. Most patients, given a choice of a healthy T3 level or a normal TSH would choose a healthy T3 level.	

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			Patients with the defective DIO2 gene, high/low cortisol, liver disease, Hashimoto's and certain medications that inhibit T4 to T3 conversion need supplemental T3 or NDT to function normally and lead a healthy life without the risk of heart, brain and kidney complications. Natural Desiccated Thyroid Extract was the first treatment for thyroid patients and has been safely used by doctors and patients for decades. The US Food and Drug Administration support its use in humans with thyroid illness. Synthetic T4 or T3 replacement do not contain all the thyroid hormones and exclude T2, T1, T0 and calcitonin. It has been assumed that natural body processes will produce these via deiodination of T4 and T3. NDT is supported as a treatment option in increasing research evidence relating to deiodination, polymorphisms and due to individual variation. It is also positively reported in accounts of patient experience. 30-50% of individuals on T4 (levothyroxine) are either over-treated or under-treated and others remain dissatisfied with treatment, despite achieving thyroid hormone concentrations within the standard laboratory reference ranges. Clinical trials support the patient story, and survey evidence available to ITT indicates that many hypothyroid patients prefer natural, full-spectrum thyroid extract to T4-only preparations. In one trial 49% of the volunteers preferred desiccated thyroid extract (DTE) while only 19% preferred the T4 hormone (33% had no preference). An analysis of those who preferred DTE found that they lost an average of four pounds while on DTE, and reported better concentration, memory, and sleep, and greater happiness and energy. The consideration of T4 and T4/T3 as the only treatment options will exclude many patients who are currently disenfranchised from the primary care system and self-medicate using T3 or NDT. This is	

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			evidenced through the number of patient stories and forums where patients are obtaining support rather than through the primary care system. This exclusion from the Scope will result in a poor patient treatment outcome and has implications for patient health and quality of life. While many tens of thousands of people around the globe pay testimony to their good health because of T3 and NDT, the implications are that while UK patients are also doing well self - treating on these therapies currently outside the Guidelines, primary and secondary care givers will increasingly lose the ability to care for these patients when the therapies once again come within the Guidelines because of an inability to update their personal knowledge base while currently operating within the T4 monotherapy Guideline. I. Thyroxine replacement: a clinical endocrinologist's viewpoint. Eligar V, et al. Ann Clin Biochem. 2016. https://www.ncbi.nlm.nih.gov/m/pubmed/27126268/?i=80&from=/28336049/related II. Stability, Effectiveness, and Safety of Desiccated Thyroid vs Levothyroxine: A Rebuttal to the British Thyroid Association. Dr. John C. Lowe. Thyroid Science 4(3):C1-12, 2009 III. Natural Desiccated Thyroid: Dr. Richard Guttler's False Claim about It. Natural Desiccated Thyroid. Dr John C Lowe. Thyroid Science 4(9):C1-6, 2009. http://www.thyroidscience.com/Criticism/lowe.9.24.09/lowe.guttler.9.22.09.pdf IV. Remarkable study comparing Armour Thyroid and levothyroxine. http://www.goodhormonehealth.com/articles/RemarkablestudycomparingArmourthyroidandlevothyroxine.pdf V. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. J Clin Invest. doi:10.1172/JCI77588. Published January 2, 2015 Joao Pedro Werneck de Castro	

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			VI. Conversion to Armour Thyroid from Levothyroxine Improved Patient Satisfaction in the Treatment of Hypothyroidism. Journal of Endocrinology, Diabetes & Obesity Volume 2, Issue 3 July-September 2014 Gary M. Pepper* and Paul Y. Casanova-Romero. www.jscimedcentral.com/Endocrinology/endocrinology-2-1055.pdf VII. The pharmacodynamic equivalence of levothyroxine and liothyronine. A randomized, double blind, crossover study in thyroidectomized patients. Clin Endocrinol (Oxf). 2010 May; Francesco S. Celi, Marina Zemskova, Joyce D. Linderman, Nabeel I. Babar, Monica C. Skarulis, Gyorgy Csako, Robert Wesley, Rene Costello, Scott R. Penzak5, and Frank Pucino. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2888764/pdf/nihms146786.pdf VIII. Only the combined treatment with thyroxine and triiodothyronine ensures euthyroidism in all tissues of the thyroidectomized rat. Endocrinology. 1996 Jun;137(6):2490-502. Escobar-Morreale HF1, del Rey FE, Obregón MJ, de Escobar GM. http://www.ncbi.nlm.nih.gov/pubmed/8641203 IX. Combination Treatment with T4 and T3: Toward Personalized Replacement Therapy in Hypothyroidism? Bernadette Biondi, and Leonard Wartofsky X. DOI: http://dx.doi.org/10.1210/jc.2011-3399. http://www.thyroiduk.org.uk/tuk/research/personalised-combination-therapy.pdf XI. Improvements in quality of Life in Hypothyroid Patients taking Armour Thyroid Abstract taken from: http://www.endocrine-abstracts.org. Endocrine Abstracts (2008) 15 P359 DH Lewis, J Kumar, P Goulden & DJ Barnes XII. Desiccated Thyroid Extract Compared with Levothyroxine in the Treatment of Hypothyroidism: A	

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			Randomized, Double-Blind, Crossover Study. Thanh D. Hoang, Cara H. Olsen, Vinh Q. Mai, Patrick W. Clyde, and Mohamed K. M. Shakir http://press.endocrine.org/doi/full/10.1210/jc.2012-4107 XIII. https://stopthethyroidmadness.com/uk-doctors/ XIV. https://www.thyroid.org/wp-content/uploads/publications/clinthy/volume25/issue6/clinthy_v256_122_124.pdf	
Improve Thyroid Treatment Campaign Group	5	120	*"Management of primary hypothyroidism"* **-** *Monitoring* ITT believes a patient-centred approach is required and signs and symptoms are as, or more important, than clinical tests. Patient signs and symptoms are very important to the management of thyroid disease. Recognition of the expertise that the patient brings as well as test evidence base form a stronger diagnostic methodology and would engage patients in shared decision-making. We believe that routine evaluation of patients' signs and symptoms (which can include, but are not exclusive to, weight gain, generalized weakness, tiredness or fatigue, infertility, depression, mood changes) would improve the diagnosis of this chronic illness and patients would be more likely to seek and obtain the right treatment in primary care. The scope should include recommendations that signs and symptoms are treated as more important than clinical tests and patients who present symptoms associated with thyroid disorders are routinely checked for thyroid dysfunction.	Thank you for your comment. The guideline seeks to address appropriate monitoring of thyroid disease.
Improve Thyroid Treatment Campaign Group	5	120	*"Management of primary hypothyroidism"* **-** *Monitoring* The draft scope recognises that about 90% of hypothyroidism is caused by autoimmune (Hashimoto) thyroiditis. The draft scope does not set out the tests that are in scope to manage autoimmune thyroiditis. Autoimmune attacks cause instability in the thyroid hormone levels and result in patients being symptomatic, visiting their GP and possibly undergoing other clinical/blood numerous tests and changing hormone replacement doses. That instability is not in	Thank you for your comment. The guideline seeks to address appropriate investigation and monitoring of thyroid disease.

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			the patient or primary care best interest. Secondly, understanding the antibody levels allows the patient to make an informed and shared decision on lifestyle changes that could minimise autoimmune attacks.	
Improve Thyroid Treatment Campaign Group	5	120	*"Management of primary hypothyroidism"* **-** *Monitoring* The draft scope considers the use of thyroid testing for monitoring. ITT believes thyroid tests should be extended from the sole use of TSH to a full thyroid panel including Free T4, Total T4, Free T3, Total T3 and reverse T3. Clinical research supports new perspectives on the interpretation of thyroid function tests and minimizes the diagnostic use of TSH. The use of TSH has been demonstrated to wrongly assume a level of diagnostic certainty that is inherently lacking in TSH, which is an indirect, conditional, and highly individual measure of thyroid function (Hoermann/Midgely). TSH is neither a precise marker of normal thyroid function, nor is it optimal for the fine-tuning of thyroid control. TSH levels defined for optimum health may not apply in many patients under hormone replacement treatment. Further, clinical research supports the view that there is a discernible disjoint between FT3 and TSH concentrations in patients with a thyroid dysfunction, which can result in an inability of synthetic T4 monotherapy to adequately address patient therapeutic needs. This is because FT3 levels become dependent on exogenous synthetic T4 supply. Furthermore, the T4-related conversion inefficiency may outweigh the benefits of escalating the synthetic T4 dose in some patients. The evidence points now to multivariate reference limits, personalised analysis, and the additional value of Free T3 for understanding thyroid status and assessing adequacy in thyroid hormone replacement treatment levels. There are patient health outcome consequences and long-term risks of an unphysiological Free T3–Free T4 ratio, Free T3–TSH disjoint. Measurement of Free T3 and Total T3 and calculation of conversion efficiency to Free T4 and Total T4 will help identify patients with	Thank you for your comment. The guideline seeks to address appropriate investigation of thyroid disease.

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			impaired biochemistry (e.g. methylentetrahydrofolate reductase) or deiodinase gene defects and a resulting lack of symptomatic control. Commonly inherited variation in the DIO2 gene is associated both with impaired baseline psychological well being on synthetic T4 hormone replacement, but enhanced response to combination T4/T3 therapy. Inclusion of this problem in the scope is especially important, because up to 20% of hypothyroid patients do not convert T4 hormone replacement into the active thyroid hormone T3, and remain symptomatic. This has consequences for the patient treatment option. Identification of the most suitable treatment option early will improve patient and primary care management outcomes. The use of a full thyroid panel of tests will promote both a more personalised approach and lead to better patient treatment outcomes. I. Homeostatic control of the thyroid-pituitary axis: Perspective for diagnosis and treatment. Prof Hoermann, J Midgley et al Front Endocrinol (Lausanne) 2015 Nov 20;6:177 https://www.frontiersin.org/articles/10.3389/fendo.2015.00177/full II. Dietrich JW, et al Calculated Parameters of Thyroid Homeostasis: Emerging Tools for Differential Diagnosis and Clinical Research https://www.frontiersin.org/articles/10.3389/fendo.2016.00057/full III. Rudolf Hoermann, John E. M. Midgley, Johannes W. Dietrich, and Rolf Larisch. Dual control of pituitary thyroid stimulating hormone secretion by thyroxine and triiodothyronine in athyreotic patients. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5524252/ IV. Endocr Connect. 2015 Dec;4(4):196-205. doi: 10.1530/EC-150056. Variation in the biochemical response to l-thyroxine therapy and relationship with peripheral thyroid hormone conversion efficiency. Midgley JE1, Larisch R1, Dietrich JW2, Hoermann R3.	

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			https://www.ncbi.nlm.nih.gov/pubmed/26335522 V. Tran, H A. Difficulties in diagnosing and managing coexisting primary hypothyroidism and resistance to thyroid hormone. https://www.ncbi.nlm.nih.gov/m/pubmed/16772202/?i=6&from=/28336049/related VI. Olympia Koulouri, MRCP, NIHR Academic Clinical Fellow, Pitfalls in the measurement and interpretation of thyroid function tests. 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3857600/#!po=60.9890 VII. Brijesh K. Singh and Paul M. Yen. A clinician's guide to understanding resistance to thyroid hormone due to receptor mutations in the TRα and TRβ isoforms. 2017. https://www.ncbi.nlm.nih.gov/pubmed/28932413 VIII. Bianco AC, et al. Deiodinases: implications of the local control of thyroid hormone action. https://www.ncbi.nlm.nih.gov/m/pubmed/17016550/ IX. Hall, JA and Bianco, AC. Triumphs of the Thyroid Despite Lesser Conversion. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5393300/ X. Bianco AC. Minireview: cracking the metabolic code for thyroid hormone signaling. https://www.ncbi.nlm.nih.gov/m/pubmed/21712363/ XI. Werneck de Castro JP, Fonseca TL, Ueta CB, McAninch EA, Abdalla S, Wittmann G, Lechan RM, Gereben B, Bianco AC. Differences in hypothalamic type 2 deiodinase ubiquitination explain localized sensitivity to thyroxine. https://www.jci.org/articles/view/77588	
Improve Thyroid Treatment Campaign Group	5	120	*"Management of primary hypothyroidism"* **-** *Monitoring* ITT believes the scope should consider the implications on the thyroid testing results, especially TSH, of the type of thyroid hormone replacement treatment a patient is undergoing. Clinical evidence indicates that thyroid hormones test results are adjusted by	Thank you for your comment. The guideline seeks to address appropriate treatment and monitoring of thyroid disease.

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			synthetic hormone replacement. Evidence supports the view that use of the TSH level is not an optimal measure of adequate thyroid hormone replacement therapy in all hypothyroid patients. The use of other more specific tests of thyroid hormone action at tissue levels will personalise the treatment of thyroid hormone deficiency. We ask that the monitoring of hypothyroidism include a testing of Free T4, Total T4, Free T3, Total T3 and reverse T3. 1. Biondi B, et al. Treatment with thyroid hormone. https://www.ncbi.nlm.nih.gov/m/pubmed/24433025/?i=31&from=/28336049/related 2. Birte Nygaard. Effect of combination therapy with thyroxine (T4) and 3,5,30-triiodothyronine versus T4 monotherapy in patients with hypothyroidism, a double-blind, randomised cross-over study. European Journal of Endocrinology (2009) 161 895–902. http://www.eje-online.org/content/161/6/895.full 3. Allan Carle. Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment – Data Using a Blind, Randomized, Clinical Study. https://www.researchgate.net/publication/316469677_Hypothyroid_Patients_Encoding_Combined_MCT10_and_DIO2_Gene_Polymorphisms_May_Prefer_L-T3_L-T4_Combination_Treatment_-_Data_Using_a_Blind_Randomized_Clinical_Study	
Improve Thyroid Treatment Campaign Group	5	120	*"Management of primary hypothyroidism"* **-** *Monitoring* ITT believes the management of hypothyroidism should consider whether the thyroidal status is unstable. This can happen in the first months of a thyroid treatment, with changes in thyroid hormone replacement, with autoimmune thyroiditis, or when the hypothalamic-pituitary function is disturbed (central hypothyroidism). In these	Thank you for your comment. The guideline seeks to address appropriate investigation and monitoring of thyroid disease.

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			circumstances, the use of TSH determination alone is diagnostically misleading and testing should include patient signs and symptoms and full thyroid hormone testing. We believe this would improve the patient treatment plan and shared treatment outcome decisions. 1. Sapin R1, Schlienger JL. 2003. Thyroxine (T4) and tri-iodothyronine (T3) determinations: techniques and value in the assessment of thyroid function. https://www.ncbi.nlm.nih.gov/pubmed/12915350	
Improve Thyroid Treatment Campaign Group	5	122	*"Treatment options"* ITT recommends that treatment options be included in the scope and review. Treatment of thyrotoxicosis will depend on the underlying cause. In the first instance, blood panels should include full thyroid function testing in which, thyroid antibody blood tests should be assessed. The underlying cause needs to be sought, to secure diagnosis. Subacute thyroiditis may cause hyperthyroidism in the initial stages. Subacute thyroiditis is likely to be detected as, unlike other thyroid inflammation, it does cause pain, which may present in the neck, jaw or ear areas. The gland may be tender and swollen. This may present with other symptoms of hyperthyroidism, such as fatigue, intolerance to heat, weight loss, and weakness and is likely to be preceded by an upper respiratory inflammation. Fever is also likely to be present. Unfortunately, subacute thyroiditis is likely to progress to hypothyroidism. The condition may resolve within a year to 18 months, however, the hypothyroidism can become permanent. [Hennessey: 2015] ITT understands that the main treatments offered for the differing forms of thyrotoxicosis are those set out below. 'Beta-blockers' and Anti-thyroid drugs [ATD] - such as Carbimazole	Thank you for your comment. The guideline seeks to address treatment options and monitoring of thyroid disease.

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			and Propranolol, may be used in the first instance. Sometimes in a bid to 'balance 'hormone production levothyroxine may be used in conjunction with the anti-thyroid drug. • RA and ultrasound scans may be deemed necessary to rule out cancerous growths. • FNB may be required if cancer is suspected. • Radioactive iodine. [RAI] may be recommended if ATD are not tolerated or successful. • Surgery should be considered where immediate and/or progressive danger is suspected. ITT asks that the scope should include recommendations that in situations which result in the total destruction or removal of the thyroid gland, leaving patients dependant on hormone replacement, a combination of Levothyroxine [L-T4] and liothyronine [L-T3] or Natural Desiccated Thyroid [NDT] should be offered. ITT adds that where inability to convert is known or becomes apparent, T3 monotherapy should be considered for optimal health. Full monitoring should take place to ensure optimal levels of vitamins and minerals are being maintained to assist in the uptake of hormone replacement. ITT recommends that all patients should be monitored under secondary care, until medication is optimised and stable. Patients should be supported and confident that their follow-up needs will be met before making drastic choices to have their thyroid destroyed or removed. All options should be explained in detail to patients and diagnosis, treatments and aftercare defined: Causes of thyrotoxicosis: In the management of thyrotoxicosis, all options should be explained in detail to patients, and aftercare defined. Patients are being left with inadequate T4 monotherapy treatment when they are unable to convert this method of hormone replacement.	

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			ITT understands that antithyroid drugs [ADTs], such as Carbimazole have been thought to be inappropriate for long term use. Patients using ADTs should be monitored for adverse effects, and should remain on the medication, if possible, until euthyroid. If need be, an amount of L-T4 may be required to balance thyroid function and reduce the risk of heart problems. Periodic blood tests should inform the need for continued medications or alterations to dosage. Following a period of 18 months on medication patients should have their dose slowly reduced to assess if Graves' disease is in remission. At this stage if symptoms do not reoccur the patient should be weaned off the medication slowly. If symptoms persist discussion between patient and doctor should determine if another period of ADTs is advisable or if other treatment options should be considered. Patients tell ITT that they would have preferred to remain on the medication rather than undergo RAI or surgery. Most patient stories highlight that they feel less well following definitive treatment. This is likely to be due to the lack of physiological thyroid replacement when L-T4 mono therapy is offered. Many patients have self-sourced NDT and/or L-T3 in the hope of improving their health when L-T4 (synthetic T4) fails to support them. Some patients are doing so with the support of their doctors, others find their doctors feel unable to support, and even refuse to monitor them. Sadly, many patients have no choice other than to remain on L-T4 and become increasingly ill. For some, the addition of L-T3 to L-T4 or even NDT, which also includes the missing T2 & T1, does not allow them to fully recover health and they feel they were better on Carbimazole. Whilst cost implications may be implicit in the preference of approach for RAI treatment over long term ATD treatment, the consequences of unnecessary definitive treatment can be devastating. Many patients are being left with such inadequate treatment they are too ill to function properly, they are left unable to work, dependent, and some are even bedridden. ITT recommends	

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			that the scope recognise that patients should not be asked to undergo definitive treatments unless the replacement therapy is physiologically sound, medication options available for those known to have defective conversion processes, and an agreed willingness and plan to issue the required medication in ongoing follow-up care. ITT believes that RAI should be used with caution, following careful and full consideration of the consequences. It is not a suitable treatment option for patients with thyroid eye disease [TED], as it is known to worsen symptoms. Nor should RAI be considered for patients with Graves' disease without careful consideration to the likelihood of the development of TED, and full discussion of the risks. It is estimated that 30 -50% of patients with Graves' disease will suffer with TED. RAI should be avoided if there is any possibility of pregnancy, or if pregnancy is planned within six months of treatment. Furthermore, the risk of developing some cancers is significantly increased, by up to 53%, following RAI treatment. Patients report to ITT that these risks are rarely discussed and the risk of cancer is impacting on the preference for RAI treatment. During both surgery and RAI treatments it is possible for the parathyroid glands and the larynx to be injured or damaged in the process. This can leave the patient with parathyroidism and/or changes in voice. Following RAI or thyroidectomy the function of the parathyroid glands should be assessed. Calcium level should be monitored to determine function. Voice assessments should be made prior to, and following, any surgical or RAI treatments to assess any changes and identify damage. I. Hyperparathyroidism after radioactive iodine therapy for Graves' disease. Esselstyn CB Jr, Schumacher OP, Eversman J, Sheeler L, Levy WJ. [1982] https://www.ncbi.nlm.nih.gov/pubmed/6897129	

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			II. Subacute Thyroiditis James V Hennessey, M.D., FACP [2015] https://www.ncbi.nlm.nih.gov/books/NBK279084/ [accessed 09/11/17] III. http://breastcancer.org/ IV. Radioactive Iodine Treatment Increases Cancer Risk. http://www.breastcancer.org/research-news/20070604-2	
Improve Thyroid Treatment Campaign Group	5	123	*Monitoring Thyrotoxicosis* Monitoring requirements will depend on the nature and cause of thyrotoxicosis. Some self-limiting thyrotoxicosis may just need to be observed and periodically assessed until the patient returns to the euthyroid state. The euthyroid state being determined as 'wellbeing' rather than meaning the biological testing returning to 'current' normal ranges. Monitoring of subacute thyroiditis needs to be carried out to ensure that symptoms do regress, and for indicators that the condition is converting to hypothyroidism, when hormone replacement will be required. For other types of thyrotoxicosis, monitoring will depend on the treatment option and patient need. Patients should undergo liver function testing prior to commencing treatment on Anti thyroid drugs [ATDs]. They should be monitored regularly to ensure that medication levels are appropriate, for improvement and that medication is correctly tolerated by the patient. Thyroid function blood tests will help to define the correct dosage of ATDs. A need for the addition of thyroid hormone may be identified and patients should be closely monitored until a stable level is reached. Liver and heart monitoring is also advisable.	Thank you for this information. The guideline seeks to address the investigation, treatment and monitoring of thyroid disease.

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			There is evidence that the use of Carbimazole can, on rare occasions, cause reduced white blood cells. Patients and carers should be advised to report signs of sore throat, fever and or mouth ulcers. Following RAI treatment patients may need to avoid 'vulnerable' contacts to avoid radiation contamination. e.g. young children and pregnant women. They should not become pregnant within six months of treatment. A large proportion of patients are expected to become hypothyroid following treatment. So all patients should be monitored at regular intervals for signs and symptoms of hypothyroidism. Clinical symptoms alongside full thyroid blood test, including free T3 levels, should denote the need for and type of hormone replacement. It is possible for the surgical treatment of thyroidectomy, sub, or full, to damage the recurrent laryngeal nerve, which can affect the patient's voice. Voice assessment should be conducted prior to, and following surgery. As the parathyroid glands are attached to the thyroid gland it is possible that one or both can be removed with the thyroid. Calcium levels of patients should be monitored to ensure hypoparathyroidism is not present. In the case of both RAI and thyroidectomy, there is a strong chance of the patient becoming hypothyroid. However, in the process of destroying the thyroid, over a number of days, the thyroid may 'dump' it's remaining hormones and this may cause confusion following treatment. 1. **Conversion issues**. Levothyroxine is not physiologically equal to the natural thyroid hormones. All patients opting for Radioactive Iodine treatments or surgery should be offered a 2. **The management of thyrotoxicosis**. All options should be	

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			explained in detail to patients, and aftercare defined. Patients are being left with inadequate T4 monotherapy treatment when they are unable to convert this hormone replacement, due to gene fault or other conversion issues. Levothyroxine is not physiologically equal to the natural thyroid hormones. All patients opting for Radioactive Iodine treatments or surgery should be offered a combination of Levothyroxine [L-T4] and Liothyronine [L-T3], increased to a therapeutic dose to suit the individual. (3-4:1) Alternatively Natural desiccated thyroid replacement should be an option. Where inability to convert becomes apparent T3 monotherapy should be considered and all options monitored under secondary care until optimisation is stable. Alternatively Natural desiccated thyroid replacement should also be an option, as some patients will have the inability to process synthetics. Patients deserve to be fully informed of all options and consequences and should have the confidence that their follow up needs will be met before making drastic choices to have their thyroid destroyed or removed.	
Improve Thyroid Treatment Campaign Group	5	124	*"Management of subclinical thyroid dysfunction"* The draft scope comments on subclinical hypothyroidism. Subclinical hypothyroidism is a condition associated with a raised serum concentration of thyroid stimulating hormone (TSH) but a within range serum free thyroxine (FT4). Both hypothyroidism and subclinical hypothyroidism share the same symptoms. Because hypothyroid symptoms appear on a spectrum, those with subclinical hypothyroidism will likely experience hypothyroid symptoms of reduced intensity. It is common, affecting about 10% of women above the age of 55 years. Autoimmunity is the commonest cause of subclinical hypothyroidism. About 2.5% of patients with subclinical hypothyroidism progress to clinically overt hypothyroidism each year; the rate of progression is higher in patients with thyroid antibodies	Thank you for your comment. The guideline seeks to cover how subclinical hypothyroidism should be managed.

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			and higher thyroid stimulating hormone levels. ITT believes the scope should treat subclinical forms of thyroid disorder as simply a grade of hypothyroidism. Subclinical hypothyroidism has the same health consequences for patients as hypothyroidism. ITT believes a patient-centred approach is required and signs and symptoms are as important as the clinical tests. Outcomes will be improved through a shared patient and primary care approach. Using meta-analysis Madariaga, Palacios, Guillén-Grima and Galofré [2014], looked at the prevalence of Thyroid Dysfunction in Europe to find 11% of Europeans as having thyroid dysfunction. However, half of them were unaware of their condition. Two thirds were thought to have subclinical thyroid disease. It is concerning that "In recent years, there has been an increasing amount of data suggesting that any degree (clinical and subclinical) of thyroid dysfunction is associated with deleterious health effects." This would support the need for universal screening for thyroid disease. The objective of thyroid screening should be to identify and treat patients with thyroid dysfunction. Early diagnosis would prevent the development of complications e.g. heart problems (line 27). Hoermann and Midgely [2012] highlight the changing focus of TSH "from its reactive and interactive role with thyroid hormones to an exclusive statistical parameter whose value is assumed to define the functional state of the subject" [2012] In the link below, Hoermann and Midgely [2012] discuss inadequacies, misunderstandings and misinterpretations of the current TSH. This test was never meant to be a diagnostic tool in its own right. It was meant to be used in conjunction with clinical observations and a range of other tools. One major problem is the nonexistence of agreed reference limits. There is strong suggestion that the term and diagnostic of 'subclinical' in thyroid dysfunction is clouding judgement as treatment is avoided until biochemistry shows 'overt' dysfunction. In doing so patients are being left clinically unwell and at greater risk of further health complications.	

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			The doctor-patient relationship should be a collaboration following discussion and full evaluation of the presenting symptoms. Patients are their own best judges of what is happening to them. Patients need to be listened to and taken seriously. Too many patients are being dismissed as psychosomatic or depressed through dismissal of diagnosis based solely on the TSH blood level. Full thyroid function testing is important but patient experience along with clinical observations has to be paramount. I. Redford C, et al Subclinical hypothyroidism: Should we treat? Redford C, et al. Post Reprod Health. 2017 https://www.ncbi.nlm.nih.gov/m/pubmed/28406057/?i=40&from=/28336049/related II. Ross DS. Bone density is not reduced during the short-term administration of levothyroxine to postmenopausal women with subclinical hypothyroidism: a randomized, prospective study. Ross DS. Am J Med. 1993. https://www.ncbi.nlm.nih.gov/m/pubmed/8213870/?i=86&from=/28336049/related III. Singh S, et al. Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality: a meta-analysis. 2008. https://www.ncbi.nlm.nih.gov/pubmed/17434631 IV. Duggal A, et al. Cardiovascular risk with subclinical hyperthyroidism and hypothyroidism: pathophysiology and management. 2007. https://www.ncbi.nlm.nih.gov/pubmed/17786084 V. Walsh JP, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. 2005. https://www.ncbi.nlm.nih.gov/pubmed/16314542 VI. Rodondi N, et al. Subclinical hypothyroidism and the risk of heart failure, other cardiovascular events, and death. 2005. https://www.ncbi.nlm.nih.gov/pubmed/16314541 VII. Biondi B, et al. 2002. Effects of subclinical thyroid dysfunction on the heart.	

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			https://www.ncbi.nlm.nih.gov/pubmed/12458990 VIII. Relationship between Subclinical Thyroid Dysfunction and the Risk of Cardiovascular Outcomes: A Systematic Review and Meta-Analysis of Prospective Cohort Studies. Sun J, Yao L, Fang Y, Yang R, Chen Y, Yang K, Tian L. 2017. https://www.ncbi.nlm.nih.gov/pubmed/29081800 IX. TSH Measurement and Its Implications for Personalised Clinical Decision-Making. Rudolf Hoermann and John E. M. Midgley [2012] https://www.hindawi.com/journals/jtr/2012/438037/ accessed 08/11/17 X. The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis Ane Garmendia Madariaga Silvia Santos Palacios Francisco Guillén-Grima Juan C. Galofré https://academic.oup.com/jcem/article/99/3/923/2537300/The-Incidence-and-Prevalence-of-Thyroid [Accessed 9/11/17]	
Improve Thyroid Treatment Campaign Group	5	125	*"Management of subclinical thyroid dysfunction – Treating subclinical hypothyroidism"* ITT advocates that the scope should include guidance that the decision whether to treat, or not to treat subclinical hypothyroidism, should be made after careful consideration of the patient's age, symptoms, the presence of thyroid antibodies and other risk factors such as cardiovascular disease. ITT recommends that the use of a single TSH test result is not sufficient to manage subclinical thyroid function. ITT also recommend that the current TSH test range of >10mIU/l is too high and there are long-term health consequences of a patient experiencing higher than 3.0mIU/l TSH levels. Both hypothyroidism and subclinical hypothyroidism share the same symptoms on a spectrum. Evidence supports that many cases with subclinical hypothyroidism are actually already mildly hypothyroid. Patient evidence shows that many have experienced symptoms for many years before diagnosis, but the clinical tests have not met the threshold for treatment, with detrimental effects on their quality of	Thank you for your comment. The guideline seeks to cover how subclinical hypothyroidism should be managed.

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			life. A consideration of patient treatment should not be made without understanding the impact of a lack of treatment on the personal circumstances of the patient. Patient stories and surveys (from around the world) evidence that many patients reduce work hours, stop working or struggle with family commitments prior to diagnosis. Patient signs and symptoms should be used in conjunction with a broad range of thyroid hormone tests to decide if thyroid hormone replacement should be considered. I. Wartofsky L, et al. Overt and 'subclinical' hypothyroidism in women. 2006. https://www.ncbi.nlm.nih.gov/m/pubmed/16842634/?i=22&from=/28336049/related II. Demartini B, et al. 2014. Depressive symptoms and major depressive disorder in patients affected by subclinical hypothyroidism: a cross-sectional study. https://www.ncbi.nlm.nih.gov/pubmed/25010109 III. Pacchiarotti A, Martino E, Bartalena L, Aghini Lombardi F, Grasso L, Buratti L, Falcone M, Pinchera A (1986). Serum free thyroid hormones in subclinical hypothyroidism. Journal of Endocrinological Investigation. 1986 Aug;9(4):315-9. IV. Skinner GR, Thomas R, Taylor M, Sellarajah M, Bolt S, Krett S, Wright A. (1997). Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients. *British Medical Journal*: June 14; 314(7096). V. Subclinical Hypothyroidism Is Mild Thyroid Failure and Should be Treated. October 2001. Michael T. McDermott E. Chester Ridgway. https://academic.oup.com/jcem/article/86/10/4585/2848862 VI. Levothyroxine Treatment of Subclinical Hypothyroidism, Fatal and Nonfatal Cardiovascular Events, and Mortality. Salman Razvi, MD, FRCP; Jolanta U. Weaver, PhD, FRCP; Timothy J. Butler, MRCGP; et al. 2012. https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/1149639	

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Improve Thyroid Treatment Campaign Group	5	125	*Treating subclinical hypothyroidism* One common symptom in hypothyroid disease is temperature intolerance. In hypothyroidism this generally means that the patient has a tendency to feel the cold more keenly than those around them. Though this can also mean that they are also unable to tolerate higher temperatures too. The importance of body temperature control in hypothyroidism is currently undermined. Dr Broda Barnes noticed that hypothyroid patients tend to have a much lower body temperature than the expected norm. He and other doctors since have acknowledged that a low body temperature tends to reflect the extent of the disease, and can reflect recovery. Unfortunately conventional doctors tend not to accept this. Patients confirm that their body temperature changes in line with their health state. It seems odd to patients that a raised body temperature can cause alarm, yet a significantly lowered one is largely ignored. Dr E. Denis Wilson also recognises that low body temperature is linked to low thyroid function and advocates the use of body temperature to determine the rate of metabolism and the need for T3. This, he has named Wisons Temperature Syndrome, also know as Wilson's Thyroid Syndrome. The Broda Barnes Self Test for Thyroid Deficiency by Melissa, Lead Cellulite Investigator [2010] http://www.celluliteinvestigation.com/2010/08/broda-barnes-self-test-for-thyroid.html Wilson's Temperature Syndrome http://www.wilsonssyndrome.com/identify/wts-overview/	Thank you for this information.

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Improve Thyroid Treatment Campaign Group	5	126	*"Management of subclinical thyroid dysfunction – thyrotoxicosis".* Research shows that patients with subclinical hyperthyroidism had a 30% increased risk of arterial fibrillation, and patents with high normal thyroid function had a 12% increased risk of arterial fibrillation. Selmer et al [2014] and Parle et al [2001] both report an increase in cardio vascular mortality with, long-term untreated subclinical hyperthyroidism. This would indicate that subclinical hyperthyroidism requires equal care and consideration to overt hyperthyroidism. Evidence also shows correlations between subclinical hyperthyroidism and cognitive decline in dementia progression. [Wijsman et al: 2013] In the interest of prevention and reducing health risks, such as heart dysfunction and thyroid eye disease the term 'subclinical' needs to be viewed as meaning 'onset of', as currently 'subclinical' seems to mean 'negative'. This in turn largely equates to inaction, non-diagnosis and non-treatment. This need for a distinction between overt and subclinical is questionable and should be reviewed, as research is proving that subclinical thyroid dysfunction, can present with debilitating symptoms and patients would benefit from treatment. ITT feels it is imperative that patient symptoms are accounted for when clinicians assess for treatment. We believe that a persistently, and otherwise unexplained low TSH of = 0.4 or less, with T4 and T3 levels at top of range or higher, should warrant carefully monitored treatment. With particular consideration for treatment in patients over 65, to protect patients from cardio-vascular complications. I. Subclinical Thyroid Dysfunction and Cognitive Decline in Old Age II. Liselotte W. Wijsman, Anton J. M. de Craen, Stella Trompet, Jacobijn Gussekloo, David J. Stott, Nicolas Rodondi, Paul	Thank you for your comment. The guideline seeks to address who should be investigated for thyroid disease and the appropriate management of subclinical thyrotoxicosis.

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			Welsh, J. Wouter Jukema, Rudi G. J. Westendorp, Simon P. Mooijaarthttp://journals.plos.org/plosone/article?id=10.1371/journal.pone.0059199 III. Thyroid function and the risk of coronary heart disease: 12-year follow-up of the HUNT study in Norway. Asvold BO1, Bjøro T, Platou C, Vatten LJ. [2012] https://www.ncbi.nlm.nih.gov/pubmed/22724581?dopt=Abstract IV. The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study. Christian Selmer, et al [2012] http://www.bmj.com/content/345/bmj.e7895 *BMJ* 2012;345:e7895 V. Subclinical and overt thyroid dysfunction and risk of all-cause mortality and cardiovascular events: a large population study. Selmer C, Olesen JB, Hansen ML, von Kappelgaard LM, Madsen JC, Hansen PR, Pedersen OD, Faber J, Torp-Pedersen C, Gislason GH. https://www.ncbi.nlm.nih.gov/pubmed/24654753?dopt=Abstract VI. Prediction of all-cause and cardiovascular mortality in elderly people from one low serum thyrotropin result: a 10-year cohort study. Parle JV, Maisonneuve P, Sheppard MC, Boyle P, Franklyn JA https://www.ncbi.nlm.nih.gov/pubmed/11567699?dopt=Abstract VII. https://www.ncbi.nlm.nih.gov/pubmed/24654753?dopt=Abstract VIII. https://www.ncbi.nlm.nih.gov/pubmed/11567699?dopt=Abstract IX. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0059199	
Improve Thyroid Treatment	5	127	*"Monitoring subclinical thyroid dysfunction"* As with the management of hypothyroidism the monitoring of	Thank you for your comment. The guideline seeks to address appropriate monitoring of subclinical thyroid dysfunction.

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Campaign Group			subclinical thyroid dysfunction should be conducted routinely. Patient signs and symptoms and circumstances should be used in conjunction with a broad range of thyroid hormone tests to decide if thyroid hormone replacement should be considered. Comments at lines 119, 120, 124, 125 apply. As the scope recognises, most thyroid dysfunction is caused by autoimmune disease. Untreated subclinical hypothyroid thyroid dysfunction, caused by autoimmunity will lead to further thyroid damage, increased symptoms and increased patient dissatisfaction along with decreased life quality and chances. ITT considers that it is particularly worrying that patients are not aware of health problems that are leaving them with increased risk of further more serious complications. This fact calls for consideration of screening as a routine and regular aspect of health care. I. The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis. Ane Garmendia Madariaga Silvia Santos Palacios Francisco Guillén-Grima Juan C. Galofré https://academic.oup.com/jcem/article/99/3/923/2537300/The-Incidence-and-Prevalence-of-Thyroid	
Improve Thyroid Treatment Campaign Group	5	127	*Monitoring of subclinical thyroid dysfunction.* It is imperative that subclinical thyroid dysfunction is reviewed. Consideration should be given to the distinction and labelling of 'subclinical' as equating to 'no need for treatment', when this is not always the case. The need for treatment or not is very much dependent on the cause. Which in itself is an issue, as many primary care providers are not adequately trained in the varying aspects of thyroid disease. Most thyroid dysfunction is caused by autoimmune disease. Untreated subclinical hypothyroid dysfunction, caused by autoimmunity will lead to further thyroid damage, increased	Thank you for your comment. The guideline seeks to address appropriate monitoring of subclinical thyroid dysfunction.

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			symptoms and increased patient dissatisfaction along with decreased life quality and chances. Subclinical hyperthyroid disease can instigate and/or worsen thyroid eye disease. Initially monitoring of any subclinical thyroid dysfunction should include careful monitoring of full thyroid function blood tests. Autoimmune testing is vital to diagnosis and monitoring of thyroid dysfunction. It is particularly important to establish the need for monitoring thyroid eye disease and for informing patients about nutritional choices that may help control the levels of antibodies. As noted in line 126 subclinical hyperthyroidism, promotes the risk of cardio-vascular disease. Madariaga et al [2014] conducted a 'Meta-Analysis' of the prevalence of thyroid dysfunction in Europe. Their findings suggest that the figure is likely to be 11% but they acknowledge that half of these are unaware they have thyroid disease. This is particularly worrying as individuals are not aware of health problems that are leaving them with increased risk of further more serious complications. This fact calls for consideration for screening to be a routine and regular aspect of health care. The Incidence and Prevalence of Thyroid Dysfunction in Europe: A Meta-Analysis Ane Garmendia Madariaga Silvia Santos Palacios Francisco Guillén-Grima Juan C. Galofré https://academic.oup.com/jcem/article/99/3/923/2537300/The-Incidence-and-Prevalence-of-Thyroid	
Improve Thyroid Treatment	5	128	*"Information for people with thyroid disease their families and carers".*	Thank you for your comment. The guideline seeks to address what the most important information is to provide to people with

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Campaign Group			ITT welcomes this inclusion. We also believe that the scope should extend to primary care professionals. We believe that information supports a shared decision culture. Information should extend to the test results, different treatment options, explanations of autoimmunity, and how lifestyle and diet changes could support the treatment received. Information needs to be better defined, more comprehensive, and more inclusive of all current knowledge. It is particularly important that all options and subsequent consequences of treatment are made clear and understood, by patients. Consideration for ongoing research should be included and made available to patients before treatment decisions are made. ITT recommendations on the information are at line 212 – 214.	thyroid disease, their families and carers. Primary care professionals will be a key audience for the guideline when it is published.
Improve Thyroid Treatment Campaign Group	5	130	*"Management of thyroid eye disease*." [TED] Also known as Graves' Ophthalmology [GO]. ITT believes that this area should be considered for inclusion within this scope, which in turn should feed into relevant, secondary/multidisciplinary care. Inclusion in this guidance is necessary as the patient is likely to be assessed, in the first instance, by their general practitioner. "*Management of GO is often suboptimal, largely because available treatments do not target pathogenic mechanisms of the disease." (Bartalina et al: 2016)* Patients reported to ITT that they are told that their 'dry and gritty' eye problems are not thyroid-related. Often because patients are deemed to be unaffected by TED as they are hypothyroid, as opposed to hyperthyroid. They are offered artificial tears, antibiotic drops and corticosteroids. Many people, with thyroid disease, seem to be suffering repeatedly with some elements of TED, yet are unable to be properly diagnosed. Few are referred to ophthalmology. TED can cause facial changes and even disfigurement, keratitis and diplopia along with optic nerve depression. Reduced visual activity, visual fields deficits and colour deficits, are some of the possible symptoms of TED. General practitioners need to be aware of the importance and urgency in early diagnosis.	Thank you for your comment. The scope specifically excludes the management of thyroid eye disease (TED) as it was not prioritised for inclusion and would not be possible to cover in appropriate depth; however, TED is likely to be a topic that features in the section on "information for people with the thyroid disease" to reflect the importance of recognition.

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			I. "*The ultimate goal is early identification of TED, with effective halting and reversal of the active inflammatory process."* (Bricerio et al 2014) II. "*The acute progression of the disease is an ocular emergency." (McAlinden: 2014)* TED is generally associated with Graves' disease, with 25-50% of Graves' patients presenting with TED. However, it is also associated with Hashimoto's Thyroiditis, thyroid carcinoma and both primary hyperthyroidism and hypothyroidism. These conditions should not rule out TED diagnosis or treatment. The pathogeny of TED is currently poorly understood. Sibini et al concluded that complete disappearance of TED is rare. Identification and diagnosis is equally lacking. Consideration should be given to family history/genetics of thyroid disease, and with the first signs of Graves' or TED indicators, it is imperative that immediate investigation through antibody testing and eye screening be undertaken. Bhatti & Dutton, 2014, highlight the importance of attaining a euthyroid state in the management of TED. III. Advances in the Management of Thyroid Eye Disease. César A. Briceño, MD,a Shivani Gupta, MD, MPH,a and Raymond S. Douglas, MD, PhDa a. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3711216/ [Accessed 10/11/7] IV. An Overview of thyroid eye disease. Colm McAlinden: 2014. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4655452/ [Accessed 10/11/17] V. Thyroid eye disease: therapy in the active phase. Bhatti MT, Dutton JJ 2014. https://www.ncbi.nlm.nih.gov/pubmed/24821102 VI. Does Graves' Orbitopathy Ever Disappear? Answers to an Old Question. Sabini E, Leo M, Mazzi B, Rocchi R, Latrofa F, Nardi M, Vitti P, Marcocci C, Marinò M. 2017	

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			https://www.ncbi.nlm.nih.gov/pubmed/29071239 [Accessed 10/11/17] VII. The 2016 European Thyroid Association/European Group on Graves' Orbitopathy Guidelines for the Management of Graves' Orbitopathy Bartalena L.a · Baldeschi L.b · Boboridis K.c · Eckstein A.d · Kahaly G.J.e · Marcocci C.f · Perros P.g · Salvi M.h · Wiersinga W.M. · on behalf of the European Group on Graves" Orbitopathy (EUGOGO) https://www.karger.com/Article/FullText/443828 [Accessed 10/11/17]	
Improve Thyroid Treatment Campaign Group	5	132	*"Screening for congenital hypothyroidism."* ITT believe congenital hypothyroidism should be given further considered within this scope. There is growing interest in the genetic factors influencing disease. Thyroid disease is largely genetic and this is recognised in the NHS Guide to newborn screening. I. A Laboratory Guide to Newborn Screening in the UK for Congenital Hypothyroidism. https://www.bsped.org.uk/clinical/docs/CHTLabGuideFebruary2014.pdf	Thank you for your comment. Recommendations on screening are outside the remit of NICE guidelines.
Improve Thyroid Treatment Campaign Group	5	133	*"Acute Thyroid disease"* Whilst it is understood that Acute Thyroid Dysfunction is likely to be dealt with in an emergency situation. ITT feels that because it forms part of the remit of 'Thyroid Disease', that it warrants inclusion in some part of the guidelines scope, as it is possible that these conditions may present in primary care or secondary endocrine care situations, and need to be recognised. The two ends of the thyroid disease spectrum may result in acute thyroid dysfunction. Untreated or sub-optimally treated hypothyroidism can lead to myxoedema. This is a crisis state of severe hypothyroidism, which	Thank you for your comment. This was not raised as a high priority issue during scope development and stakeholder meetings.

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			can lead, to what is called a myxoedema crisis, a medical emergency, which can lead to coma and death. Myxoedema is termed from the presence of mucin in the tissue, which may cause swelling and thickening skin. However, it may only affect internal organs and might not affect the skin itself. Patients may present with any number of hypothyroid symptoms. Body temperature may be very low and the patient very lethargic. Untreated, coma will ensue. At the other end of the spectrum is Thyroid storm. Thyroid storm, also known as thyrotoxic crisis, is a rare complication of thyrotoxicosis and can happen after, trauma, childbirth, surgery, infection and stroke. [Vaidya & Pearse: 2014 in NICE CKS 2016] Congestive heart failure and diabetic ketoacidosis may also contribute to thyroid storm. Thyroid storm may occur following thyroidectomy, or more likely after, Radioactive Iodine treatment [RAI] usually if this is happening it will occur between two and eight days following treatment. Common but extreme severity of symptoms such as: Racing heart >140bpm; high fever; persistent sweating: shaking; agitation; restlessness; confusion; diarrhoea and possible unconsciousness, are likely to be evident I. Diagnosis and management of thyrotoxicosis Bijay Vaidya, Simon H S Pearce [2014] http://www.bmj.com/content/349/bmj.g5128 II. NICE Hyperthyroidism. Clinical Knowledge Summary [2016] http://cks.nice.org.uk/hyperthyroidims#!backgroundsub:1	
Improve Thyroid	5	134	*"Thyroid disease in pregnant women"*	Thank you for your comment. Given the breadth of the current guideline scope and

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Treatment Campaign Group			ITT strongly advocates that thyroid disease in pregnancy should be in scope. Other than rare exceptions primary maternal hypothyroidism is defined as the presence of an elevated TSH concentration during gestation. Hypothyroidism affects 4-10% of women, which includes a substantial proportion of women of reproductive age. In pregnancy, the prevalence of overt and subclinical hypothyroidism is estimated at 0.5 and 4-8% respectively although higher rates are reported when the gestational upper TSH limits recommended by International guidelines are applied. Overt Hypothyroidism in pregnancy has been shown to be associated with adverse pregnancy complications and detrimental effects upon foetal neurocognitive development. Risks include premature birth, low birth weight and miscarriage, gestational hypertension and placental abruption. Abalovich et al. demonstrated that such patients carry an estimated 60% risk of foetal loss when Overt Hypothyroidism was not adequately detected and treated. Another study of interest in support of an adverse impact attributable to maternal hypothyroidism, data from a large case-control study demonstrated a seven-point reduction in IQ among children born to untreated overtly hypothyroid women compared to euthyroid controls. Findings also supported a delay in motor skill development, language development and attention at 7-9 years of age. https://www.ncbi.nlm.nih.gov/pubmed/10451459. We recommend that the scope includes guidance on the treatment of Overt Hypothyroidism and that it should always be treated in pregnancy with thyroid hormone. https://www.ncbi.nlm.nih.gov/pubmed/11838732 https://www.ncbi.nlm.nih.gov/pubmed/11126160 Subclinical hypothyroidism is associated with increased risk of adverse pregnancy complications including preterm delivery and placental abruption with an increased risk of neurocognitive deficits in the developing foetus. https://doi.org/10.1210/jc.2009-2009	the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			Studies suggest a relationship between higher levels of maternal TSH and pregnancy loss. https://www.ncbi.nlm.nih.gov/pubmed/20534758 The largest study investigating the association of maternal hypothyroidism and premature delivery was performed by Casey et al. https://www.ncbi.nlm.nih.gov/pubmed/17470594 Although this trial shows no benefit in obstetric outcomes, treatment did not start until 20 weeks, so, too late for treatment benefit although miscarriage rates are still lower in the treated group, just not statistically significant. If treatment had been started earlier, the benefit would have been shown to be far greater. These papers tell us that if you are going to treat, to do it early on in pregnancy. ITT recommend to the scope that subclinical hypothyroidism be treated in pregnancy if the TSH concentration is greater than 2.5 mU/L The most common cause of hypothyroidism is autoimmune thyroiditis or Hashimotos. Hypothyroidism can occur due to initial presentation of Hashimotos, inadequate treatment of a woman already known to have hypothyroidism, or over-treatment of a hyperthyroid woman with antithyroid medicine. 2.5%of women will have elevated TSH of greater than 6 and 0.4 a TSH of greater than 10. Thus risking miscarriage. https://www.ncbi.nlm.nih.gov/pubmed/2071868 https://www.ncbi.nlm.nih.gov/pubmed/25057882 ITT asks the scope to recommend checking TSH values when a pregnancy is being considered, or when first seen in surgery. Pregnant women with TSH concentrations >2.5mU/L should be evaluated for TPOAb status. According to the American Thyroid Association Pregnancy Guidelines, there is almost double the rate of miscarriage in women with Hashimotos disease who are sub-clinically hypothyroid, with TSH levels between 2.5 and 5.0 mIU/L versus women who have Hashimotos disease with TSH levels below 2.5 mIU/L. Untreated or inadequately treated hypothyroidism is associated with anaemia,	

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			myopathy, congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants and postpartum haemorrhage. Thyroid hormone is critical for the brain development of the baby. Babies born with hypothyroidism can have severe cognitive development and abnormalities if not treated properly. ITT asks the scope to consider screening all newborn babies for congenital hypothyroidism, so treatment with thyroid hormone can be started as soon as possible. ITT asks that the scope include guidance recommending that TSH be tested every 4 weeks during the first half of pregnancy. Thyroid hormone requirements increase in pregnancy so an adjustment in the need of Levothyroxine dose should be monitored. An increase by 25-50% is normal. Following adjustment, 92% of abnormal maternal TSH values were detected when blood testing was performed every 4 weeks through mid-pregnancy. In comparison, a strategy assessing thyroid function every 6 weeks detected only 73% of abnormal values. Leila Yassa, Ellen Marqusee, Rachel Fawcett and Eric K. Alexander Thyroid Hormone Early Adjustment in Pregnancy (The THERAPY) Trial https://www.ncbi.nlm.nih.gov/pubmed/20463094 Once birth has occurred the woman may go back to her pre-pregnancy LT4 dose with monitoring. However, a study demonstrated that more than 50% of women with Hashimotos thyroiditis required an increase in the pregestational thyroid hormone dose in the postpartum period. In women started on LT4 during pregnancy for thyroid autoimmunity in the absence of TSH elevation, LT4 can be stopped at delivery, with serum TSH assessment at 6 weeks postpartum along with antibody checks. A fascinating new study by Tim I M Korevaar et al June 2017 has found evidence that levels of human chorionic gonadotropin (hCG) levels are linked with the risk of miscarriage and that an additional measurement of hCG may improve thyroid-related risk assessments during pregnancy. ITT asks that the scope include guidance to consider routine	

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			checking of hCG levels. Human chorionic gonadotropin (hCG) stimulates thyroid function during pregnancy. Thyroid autoimmunity severely attenuates the thyroidal response to hCG stimulation and this may underlie the higher risk of premature delivery in thyroperoxidase antibody (TPOAb)-positive women. One study hypothesized that a lower thyroidal response to hCG stimulation in TPOAb-negative women is also associated with a higher risk of premature delivery and preterm premature rupture of membranes (pPROM). The results showed that women with high TSH and low hCG concentrations did not have a higher risk of premature delivery or pPROM, with protective effect estimates. In contrast, women with a high TSH concentration despite a high hCG concentration had twofold to 10-fold higher risk of premature delivery ($P_{difference}$ = 0.022) and an up to fourfold higher risk of pPROM ($P_{difference}$ = 0.079). hCG concentrations were not associated with premature delivery or pPROM. It concluded that in TPOAb-negative women with high-normal TSH concentrations, only women with high hCG concentrations had a higher risk of premature delivery or pPROM. These results suggest that a lower thyroidal response to hCG stimulation is also associated with premature delivery in TPOAb-negative women and that an additional measurement of hCG may improve thyroid-related risk assessments during pregnancy. Thyroid Function and Premature Delivery in TPO Antibody−Negative Women: The Added Value of hCG Tim I M Korevaar**,** Eric A P Steegers, Layal Chaker, Marco Medici, Vincent W V, JaddoeTheo, J Visser, Yolanda B de Rijke, Robin P Peeters https://academic.oup.com/jcem/article/102/9/3360/3882602/Thyroid-Function-and-Premature-Delivery-in-TPO It is believed the rise in autism and ADHD is due to maternal hypothyroidism. "Pregnant women who don't make nearly enough thyroid hormone are nearly 4 times likelier to produce autistic children than healthy women", report scientists from the Houston Methodist Neurological Institute and Erasmus Medical Centre in an upcoming *Annals of Neurology.* The association emerged from a	

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			study of more than 4,000 Dutch mothers and their children, and it supports a growing view that autism spectrum disorders can be caused by a lack of maternal thyroid hormone, which past studies have shown is crucial to the migration of fetal brain cells during embryo development. "It is increasingly apparent to us that autism is caused by environmental factors in most cases, not by genetics," said lead author Gustavo Román, M.D., a neurologist and neuroepidemiologist who directs the Nantz National Alzheimer Center. "That gives me hope that prevention is possible." The researchers also found that autistic children had more pronounced symptoms if their mothers were severely deficient for T4, also called thyroxine. Mild T4 deficiencies in mothers produced an insignificant increase in autistic children's symptoms. The most common cause of thyroid hormone deficiency is a lack of dietary iodine -- because both the thyroid hormones, T3 and T4, contain that element. In an article in Sciencedaily.com it was reported: Maternal thyroid hormone insufficiency during pregnancy can affect children's cognitive development. Nevertheless, the behavioural outcomes of children exposed prenatally to mild thyroid hormone insufficiency are understudied. Children exposed to maternal hypothyroxinaemia in early pregnancy had more ADHD symptoms, independent of confounders. This finding suggests that intrauterine exposure to insufficient thyroid hormone levels influences neurodevelopment in offspring. Maternal Mild Thyroid Hormone Insufficiency in Early Pregnancy and Attention-Deficit/Hyperactivity Disorder Symptoms in Children. Modesto T, Tiemeier H, Peeters RP, Jaddoe VW, Hofman A, Verhulst FC, Ghassabian A. https://www.ncbi.nlm.nih.gov/pubmed/26146876 https://www.ncbi.nlm.nih.gov/pubmed/20463094 Hyperthyroidism is less common than hypothyroidism occurring in approximately 0.1-1.0% of pregnancies. Graves' disease accounts for at least 80% of these cases while other causes include solitary or	

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			multiple autonomous nodules. Overt hyperthyroidism (high FT4 and low TSH in pregnancy is a serious condition, resulting in increased risk of adverse obstetric outcomes including miscarriage, stillbirth, pre-term birth and intra-uterine growth restriction. Fetal hyperthyroidism with fetal tachycardia, goitre and hydrops is a potential cause of pregnancy loss. Furthermore, 1-5% of neonates born to mothers with Graves' disease develop neonatal hyperthyroidism due to the trans-placental transfer of thyroid-stimulating TSH receptor antibodies from the mother's circulation to the newborn. Although this condition is typically self-limiting it may cause significant neonatal morbidity and is occasionally fatal. In the absence of thyroid testing, recognition of neonatal hyperthyroidism may prove challenging, especially in the infants of mothers with undiagnosed hyperthyroidism. Estrogen mediated increases in thyroid binding globulins together with the weak thyroid-stimulating actions of human chorionic gonadotrophins (hCG) lead to a rise in total thyroid hormones, which is accompanied by a corresponding fall in TSH. While biochemically similar to Graves, there are no antibodies against the TSH receptor, goitre, abnormal thyroid texture on ultrasound or the presence of ophthalmopathy. This transient thyrotoxicosis presents in the first trimester of pregnancy at the time of peak levels of hCG and occurs in 1.7–3.0% of pregnant women. It is not associated with adverse obstetric or offspring outcomes probably because the fetus is protected from marginal excess FT4 through the inactivating effect of placental type 3 deiodinase. Thus, specific therapy is not indicated for this condition. Peter N Taylor, Onyebuchi E Okosieme, Lakdasa Premawardhana and John H Lazarus. Thyroid Research Group, Institute of Molecular & Experimental Medicine, Cardiff University School of Medicine, Should all women be screened for thyroid dysfunction in pregnancy? file:///C:/Users/Mark/Downloads/15%20Should%20all%20women%20be%20screened%20in%20pregnancy.pdf ITT recommends that the scope include guidance that all women	

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			who are hyperthyroid to ensure their thyroid levels are optimized before trying to conceive. Any babies that are born to hypothyroid/hyperthyroid mothers should be screened for neonatal hyperthyroidism. Isolated Hypothyroxinaemia. Offspring born to mothers with FT4 indices in the lowest 10th percentile despite having normal serum TSH concentrations have adverse outcomes, these include; reduction in IQ, worsened motor function, language delay, smaller head circumference and increased risk of autism and ADHD. https://www.ncbi.nlm.nih.gov/pubmed/23600900 http://www.nejm.org/doi/full/10.1056/NEJMc1202720#t=article https://www.ncbi.nlm.nih.gov/pubmed/25057882 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3879664/ Hypothyroxinaemia can be due to relative iodine deficiency where the thyroid produces triiodothyronine instead of thyroxine to preserve iodine as raw material but it is a condition also observed in populations with iodine sufficiency. ITT asks that the scope set out guidance on tests for adequacy of iodine in women with isolated hypothyroxinaemia. Initially, thyroidologists considered hypothyroxinaemia a pregnancy-specific disease that reflects a state of mild iodine deficiency; however, hypothyroxinaemia also occurs in iodine-sufficient areas, and concentrations of free T4 and T4 typically do not increase following iodine supplementation. Interestingly, the largest study on iodine and thyroid disease entities performed to date, found that a subset of women with low urinary iodine concentrations (<100 or 100-149ug/l) were not at higher risk of hypothyroxinaemia compared with women with normal urinary iodine concentrations. Women with high urinary iodine concentrations (>500ug/l), however, had a 2.9-fold higher risk of hypothyroxinaemia than women with normal urinary iodine concentrations. Taken together this suggests that not	

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			only iodine deficiency, but a multifactorial and pregnancy specific pathophysiology underlies the development of hypothyroxinaemia. This concept is also in line with the various newly identified risk factors for gestational hypothyroxinaemia, including iron status, placental angiogenic factors and patient characteristics, such as BMI and age. In accordance with the general notion that hypothyroxinaemia is a pregnancy-specific disease, in 2017, we reported that the concentration of hCG is a determinant of hypothyroxinaemia. We also demonstrated that the thyroidal response to hCG in women with hypothyroxinaemia was similar to that in euthyroid women, which indicates that hypothyroxinaemia could be a reflection of increased thyroid hormone sensitivity rather than a shortage of thyroid hormone availability. Further studies will help identify the mechanisms underlying hypothyroxinaemia. Thyroid disease in pregnancy: new insights in diagnosis and clinical management Tim I. M. Korevaar, Marco Medici,Theo J. Visser, and Robin P. Peeters.	
Improve Thyroid Treatment Campaign Group	5	134	*"Thyroid disease in pregnant women"* ITT believes that the scope should include consideration of Infertility. Infertility affects 1 in 5 couples and most patients undergo extensive, costly diagnostic treatments and interventions. ITT believes cost and infertility and miscarriage rates would be reduced by screening for autoimmunity and thyroid disease in the first instance. If a universal programme were started it would pick up problems that could be treated early. • **Blood Tests** - A full thyroid assessment TSH, T4, T3, rT3 & Thyroid Antibodies. TRH may also be required. For optimum fertility, the TSH level should be between 1 and 2 mIU/L • **Urinary Iodine** - Iodine is a key component of thyroid hormone. Excessive iodine as well as a deficiency of iodine can result in low thyroid function.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			• **A lack of vitamin D** causes oxidative stress to the ovaries which results in them malfunctioning, it's essential to have a test done. Vitamin D is also essential for the developing foetus. Oxidative stress can also be due to a lack of other antioxidants. This is particularly common if processed foods are eaten as these lack antioxidants. Vitamin D deficiency is seen often in the United Kingdom but especially is related to thyroid disease. • A manganese deficient diet can lead to defective ovulation, testicular degeneration and infant mortality. Also, a lack of zinc in men is common in thyroid disease. • **Autoimmune thyroid disease** can lead to hypothyroidism or hyperthyroidism, both of which can impact fertility. In cases that are associated with gluten-related autoimmunity, we would ask the draft scope to advise an elimination of gluten and casein to reduce inflammatory response. Autoimmune infertility treatments include anti-coagulants, corticosteroids, intravenous immunoglobulin IVIG, tumour necrosis factor-alpha blockers and lymphocyte immunisation therapy. Naturopathic treatment would include N-Acetyl Cysteine, which reduces inflammatory cytokines and improves autoimmune thyroid disease, and L-Selenomethionine, helpful for thyroid antibodies if hypothyroid. Use of bioidentical hormone therapy may be indicated to prevent miscarriage. Thyroid protomorphogen may be useful for patients with antithyroid antibodies to act as a decoy. Probiotics, 20 billion CFU's daily to repair gut lining are advised. • PCOS, or polycystic ovaries is an increasing problem worldwide and one of the most common signs of infertility. Linked frequently to thyroid disease. Anovulation is a	

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			frequent occurrence, leading to potential problems in conceiving and carrying a child. Oxidative stress is behind PCOS, the antioxidants are essential, in particular vitamin D. This has successfully reversed PCOS in a number of women. A healthy thyroid is essential. Both hyperthyroidism and hypothyroidism can have a direct effect on ovarian function. Often, a malfunctioning thyroid is a sign of vitamin D deficiency and/or a lack of iodine. This is essential, as a lack of iodine can lead to goitre formation in the mother and neuropsycho-intellectual impairment in the child. Polycystic Ovary Syndrome has autoimmune components and Premature Ovarian Insufficiency. 50% of cases have autoimmune factors. Thyroid disorders and polycystic ovary syndrome (PCOS) are two of the most common endocrine disorders in the general population. Although the etiopathogenesis of hypothyroidism and PCOS is completely different, these two entities have many features in common. An increase in ovarian volume and cystic changes in ovaries have been reported in primary hypothyroidism. In the other direction, it is increasingly realized that thyroid disorders are more common in women with PCOS as compared to the normal population. Thyroid disorders and polycystic ovary syndrome: An emerging relationship. Rajiv Singla, Yashdeep Gupta, Manju Khemani, and Sameer Aggarwal https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4287775/ • **Progesterone -** One of the least known but commonest signs of infertility is a lack of progesterone during the second half of the monthly cycle. This is known as a 'defective luteal phase'. During the first half of the Menstruation Cycle, oestrogen stimulates the lining of the uterus to develop. This is known as the follicular or proliferative stage. Once ovulation has taken place, and progesterone is being	

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			secreted by the corpus luteum, it causes the lining to thicken ready for the fertilised egg. The second half of the menstrual cycle is known as the luteal or differentiation phase, and should last 12 to 14 days. Progesterone is vital for pregnancy, but if the interval between ovulation and menstruation is too short (less than 12 days) it means inadequate progesterone has been produced. Research into the causes and signs of infertility has shown that often conception occurs in a fertile woman, to be followed by failure of the egg to embed itself in the lining. This could result in a miscarriage as early as the next menstruation. So, fertility could be high, but with low progesterone it appears as if the woman is infertile. Low progesterone is common in thyroid disease. Excess stress raises cortisol levels and drops progesterone levels (both potential signs of infertility). The adrenals produce progesterone before converting it into cortisol. If the adrenals are exhausted, they will steal other sources of progesterone, notably ovarian. This impacts on the reproductive cycle. Stress can cause anovulation and miscarriages. Stress is also known to inhibit the release of FSH and LH, leading to impaired development of an egg/s. Because synthesis of progesterone is increased after ovulation, stress induced impairment of egg development could potentially alter progesterone synthesis and release. Progesterone is excellent for stress, as it activates the GABA receptor sites. GABA is one of the most calming neurotransmitters. Often the cause behind anovulation is oxidative stress. Stress, adrenal fatigue and high cortisol can all be linked to the thyroid especially in autoimmune thyroid disease Endometriosis is caused by oxidative stress and excess oestrogen, leading to severe inflammation, a clear sign of	

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			infertility. This poses major problems to any egg trying to embed in the endometrium. High levels of progesterone are needed to reverse it. If the thyroid and adrenals are not working properly progesterone levels will not be optimal. Prolactin, although originally known as the hormone of lactogenisis, has now been found to be an inflammatory hormone. A lack of protein can lead to hyperprolactinemia, due to insufficient tyrosine in the diet. This amino acid is the precursor to dopamine. Prolactin increases with high oestrogen levels and low dopamine levels. Like oestrogen, it also suppresses progesterone if in excess. Supplemental progesterone suppresses both oestrogen and prolactin. Supplemental tyrosine will increase dopamine levels. Another of the signs of infertility, hypopituitarism, although a rare problem, can lead to low FSH and LH. This is turn will prevent follicles maturing and ovulating. The possible anovulation means no progesterone will be produced. Progesterone is needed for the acrosome reaction in sperm. Low progesterone levels would stop this occurring and would prevent the sperm entering the egg and fertilising it. There is strong evidence that progesterone is involved in the sexual response in males. It also increases libido, and can correct erectile dysfunction. Another problem that may be a sign of infertility is adrenal disease, which is commonly linked with the thyroid. http://www.progesteronetherapy.com/signs-of-infertility.html **MTHFR Gene Mutation**. Another factor for infertility is the MTHFR Gene Mutation. MTHFR is a very common genetic defect that affects approximately 1 in 4 people seriously and nearly 1 in 2 people mildly. Currently, there are over 5,000 studies on it. Those with the	

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			variant of MTHFR called C667T have a 40% to 60% decreased ability to produce the body's most active form of folate called methylfolate. Methylfolate is a critical nutrient affecting neurotransmitter production, DNA regulation, immunity and the cardiovascular system. Indirectly, methylfolate affects hormone levels and detoxification. This gene resides in each and every cell of the body producing the end product, methylfolate. Methylfolate is the nutrient that starts a series of countless critical enzymatic reactions. https://www.bellybelly.com.au/pregnancy/mthfr-mutation/ Methyl tetrahydrofolate reductase (MTHFR) is the name of both the gene and the enzyme that the gene produces. The enzyme is used to convert folic acid and folate into a form that the body can use, i.e. methylfolate, which is important for numerous biological processes. MTHFR composition is dependent upon the two genes inherited from parents. Depending on whether you inherited zero, one or two MTHFR SNPs (pronounced "snips"), functioning may be reduced by as much as 30 or 70 percent. Methylation is also required for: • Repairing damaged cells, as well as ensuring optimal protein and DNA cell function. • Coenzyme Q10, creatine, melatonin, phosphatidylcholine and carnitine synthesis. Since mitochondria depend on these compounds, energy and immune processes are also impacted. • Glutathione, the body's primary antioxidant. • Metabolizing (breaking down) chemicals and toxins. • Metabolizing B-vitamins, neurotransmitters, and hormones. • Regulating dopamine, serotonin, and norepinephrine, which influence sleep, behaviour and cognitive abilities. • Detoxification and Thyroid Glutathione, methylation and folate are all integrated cycles associated with MTHFR function, and are also linked to thyroid related conditions. Glutathione is the most abundant detoxifier in the body. It keeps inflammation low, acting as armour against disease	

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			processes. Individuals with MTHFR mutations are more vulnerable to stress, toxins, and illness, due to diminished glutathione levels. Research studies show a direct correlation between a breakdown in the glutathione system and autoimmune disease, such as Hashimoto's. Autoimmune disease is linked to leaky gut, yet in order to have a healthy gut, maintenance of glutathione levels is necessary. **Methylation, B-Vitamins and Thyroid** Nutritional and pharmaceutical recommendations are generally based on the assumption that all systems are functioning at optimal levels. The topic of MTHFR is a good example of how this thinking can falter, and why some people are more sensitive. Folate, B6 and B12 are revered as the most important vitamin "co-factors" in the methylation process, however, riboflavin also plays a key role. To elucidate: **Folate:** Folic acid is the synthetic form of folate used to fortify foods, yet it requires MTHFR for the conversion to a useable form. With the abundance of folic acid in processed foods and vitamin supplements, some are concerned. Without MTHFR, folic acid can pile up potentially resulting in the following: • Masking a B12 deficiency. As a result, consequences of low B12 (energy, nerve and brain functions) continue to go untreated, and causing anaemia. • B12 deficiency is found in approximately 40% of hypothyroid patients. • Low B12 also means build -up of homocysteine, which is an amino acid that needs B12 to convert it to methionine. • Homocysteine is a marker for inflammation such that high levels are associated with high risk of disease, i.e. thyroid disorders and cardiovascular disease. • Impaired methylation and high homocysteine negatively affect production of glutathione. Inflammation and oxidative stress are increased under these conditions.	

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			Riboflavin: Riboflavin (vitamin B2) is a cofactor in the conversion of MTHFR. First, the body must convert riboflavin to its useable form, FAD, and the thyroid hormone thyroxine is necessary for this to occur. **Thyroid:** Thyroxine (T4) is the hormone the thyroid releases into the bloodstream, where it travels to organs such as the liver and kidneys. The hormone then converts to its active form, T3, which is used by the cells. Thyroxine has important roles in digestion, brain, heart, muscle and bone health, making it one of the most important hormones we have. The body is designed to tightly regulate levels of thyroxine in the bloodstream. However, it often becomes derailed and conditions such as hyperthyroidism (overactive thyroid) or hypothyroidism (underactive) can result. When thyroxine is low, less is available to convert riboflavin, to a form needed for MTHFR. Therefore, folate metabolism, methylation, and everything within its sphere of influence are affected. Should defective MTHFR functioning exist due to a genetic mutation, the consequences may potentially be exaggerated further. https://www.holtorfmed.com/mthfr-gene-thyroid-connection/ ITT asks that the scope include guidance to test for the MTHFR gene defect, or for all prenatal medicines to contain methylfolate as standard. **Endometriosis.** Of interest, autoimmune thyroid disease may also occur in patients with endometriosis, which has a frequent association with infertility. In the study of Poppe et al., involving 197 women with a female cause of infertility, they found 11% were attributed to endometriosis. Of these 11%, 29% were TPO Ab+, which was a significantly higher prevalence compared to controls. Endometriosis has also been associated with immunological changes, including possible endometrial autoantibodies and deposition of complement, cytotoxic effects on the endometrium, and	

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			declining levels or functional defects in natural killer (NK) cells. Such NK cell dysregulation may activate Graves' disease or Hashimoto's thyroiditis. Thyroid and infertility. Poppe K, Velkeniers B. https://www.ncbi.nlm.nih.gov/pubmed/12649931 **Influence of Thyroid Antibodies on IVF Failure.** It was Geva et al. that first described the possible correlation of in vitro fertilization (IVF) and thyroid antibodies in a study examining organ-specific autoimmune antibodies arguing for its possible role in predicting poor success for IVF, in such patients. The pregnancy rate in women with thyroid antibodies, in their study, was only 13.6%. In a prospective cohort study, 234 women were screened for TPOAb, serum TSH, and Free T4 prior to the first cycle of IVF, and there was a 50% miscarriage rate in females with thyroid antibody positivity but only a 23% rate of loss in those who did not. The hypotheses that have been suggested for this relationship are similar to those of miscarriage in normal pregnancy discussed earlier. However, one study of the use of levothyroxine in IVF in euthyroid women did not show any differences in the frequency of miscarriages compared to untreated controls suggesting a different pathophysiology, but a recent meta-analysis of 220 patients in 3 randomized control trials showed improvement in the rate of delivery and embryo implantation in LT4 supplemented patients versus placebo treated patients and a decreased rate of miscarriage. **Thyroid Autoantibodies in Pregnancy: Their Role, Regulation and Clinical Relevance** Francis S. Balucan, Syed A. Morshed, and Terry F. Davies https://www.hindawi.com/journals/jtr/2013/182472/ Autoimmune premature ovarian failure. Beata Komorowska https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5327623/ This study shows a very high correlation of autoimmunity and infertility. In the 193 women with Graves' Disease and the 66 with Hashimoto's Thyroiditis enrolled in this study, the prevalence of infertility was 52.3% and 47.0% respectively. I. High Prevalence of Infertility among Women with Graves'	

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			Disease and Hashimoto's Thyroiditis Alessandra Quintino-Moro, Denise E. Zantut-Wittmann, Marcos Tambascia, Helymar da Costa Machado, and Arlete Fernandes https://www.hindawi.com/journals/ije/2014/982705/	
Improve Thyroid Treatment Campaign Group	5	134	*"Thyroid disease in pregnant women"* ITT recommends that pregnant women be included within the scope because of the impact of "Natural Killer Cells" ("NK"). Natural Killer (NK) Cells represent one of the three subsets of lymphocytes, besides T- and B- cells. In comparison to the latter, NK cells belong to the innate immune system and form a first line of defence against a wide variety of pathological challenges. Particularly, they provide protection against viral and bacterial infections and they help to detect and limit the development of cancer. In this regard, NK cells were first described as cells that have the ability to kill tumour cells without any priming or prior activation (remember that e.g. cytotoxic T cells need priming by antigen presenting cells) and their name is ultimately connected to this 'natural' ability to kill. Additionally, NK cells secrete cytokines, as for example INFg and TNFa, which constitute a second important defence mechanism during an immune reaction. Cells that display a natural ability to kill need to be controlled very strictly to protect healthy cells from attack. Therefore, in addition to a variety of different activating receptors, NK cells express inhibitory receptors that recognize cognate MHC class I (this is also referred to as recognition of 'self'). This is a very efficient mechanism of control as almost all 'normal' cells express MHC class I and are therefore protected from unwanted attack. Philipp Eissmann, Imperial College, London, UK When NK cells in the blood stream (not uterine NK cells) reach the site of inflammation in the uterus or pelvic cavity, the uterine killer	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			cells that are protecting the embryo move out of the way to let the NK cells do their work. Unfortunately, sometimes an embryo is recognised as a foreign organism and is attacked and killed off. This is where the issues surrounding recurrent miscarriage come in. This is also a reason why any inflammation in the uterus or pelvic cavity needs to be addressed to help fix this issue, and one of the reasons why any woman having fertility issues needs to have a laparoscopy prior to any further fertility treatment. A laparoscopy is the gold standard for the addressing and treatment of issues in the uterine and pelvic cavity. As mentioned earlier, these naturally occurring immune mediated cells can occur due to an overactive immune system and inflammation in the body. This is why autoimmune or immune disorders such as thyroid issues need to be screened as well. When screening for thyroid issues, it is important not to just screen for TSH (Thyroid Stimulating Hormone) levels but to also screen free T3 and T4 levels, and more importantly to screen for thyroid antibodies. Many women with the beginnings of thyroid disease can have normal TSH levels but can have very high antibody levels. If any inflammation is present in the pelvic cavity or the endometrial lining (endometriosis, PCOS, tubal inflammation etc.), the immune system responds by sending NK cells in the blood stream to attack and kill off the inflammation. https://www.bellybelly.com.au/conception/natural-killer-cells-miscarriage/ "In the present study, we clearly found that in subjects with Graves' and Hashimoto's disease NKCC is depressed and that the secretion by NK of the inflammatory cytokine TNF-α is reduced under stimulation with LPS and IL-2. The defect of NK cells can affect both cytotoxic function and the ability of NK to produce cytokines. The depression of NK cells is, therefore, related to all of the functional aspects linked to the immune activity expressed by these cells (i.e. cytolytic and secretory functions). Defect of a subpopulation of natural killer immune cells in Graves' disease and Hashimoto's thyroiditis: normalizing effect of dehydroepiandrosterone sulfate"	

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			SebastianoBrunoSolerte et al.2005 http://www.eje-online.org/content/152/5/703.full I. Natural killer cell activity in patients with Graves' disease and Hashimoto's thyroiditis. Wenzel BE[1], Chow A, Baur R, Schleusener H, Wall JR. https://www.ncbi.nlm.nih.gov/pubmed/9848716 There is a special class of NK cells (CD16-, CD56+) in the placenta that promotes fetus survival. Opposing is another group of NK cells (CD16+, CD56+) that, if active, are toxic to the placenta and hence may cause a miscarriage. The same cells secrete tumor necrosis factor (TNF), which can destroy the placenta. Implantation of embryos into the mother's womb is a complex process involving several factors including the local systemic immune responses. Pregnancy may fail when these events are not well synchronized. Therapy aimed at calming these immune activating factors should, theoretically at least, encourage fetal viability. CD69 is a functional triggering molecule on activated NK cells and is one of the earliest cell surface activation markers expressed and is capable of inducing toxicity. CD94 is an inhibitory marker of NK cell function. In 1999, a study demonstrated that NK cell toxicity could be blocked by the CD94 inhibitory receptor. Previous studies have shown that imbalances in CD69 and CD94 expression could result in infertility of unknown aetiology or recurrent miscarriage. The NK cell is the most abundant immune cell infiltrating the womb implantation site. In a previous study, an elevated percentage of peripheral blood NK cells were associated with recurrent failed IVF-ET treatment cycles. Another study showed that increased peripheral blood NK cell toxicity was associated with an increased rate of recurrent failed implantation after IVF-ET treatment. More recent studies have confirmed elevated NK cell CD69 expression as being associated with recurrent miscarriage and infertility of unknown aetiology. Finally, a recent small non-randomised study	

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			has also suggested elevated NK cell CD69 expression may be related to failed implantation of the embryo. "We recently conducted a study to evaluate the effect of steroid therapy in women (who have positive peripheral blood NK cells CD16/56) on implantation and miscarriage rates after IVF-ET treatment. Our results are very encouraging with success rate exceeding 80%." http://www.miscarriageclinic.co.uk/causes-side-effects?quicktabs_causes=1 ITT asks the scope to include consideration of screening for natural killer cells for patients with recurring miscarriage and also advise patients that there is screening and treatment for natural killer cells in the private sector.	
Improve Thyroid Treatment Campaign Group	5	134	*"Thyroid disease in pregnant women"* THYROID FUNCTION TESTS IN PREGNANCY If a woman suffers from thyroid disease that is not detected before or during pregnancy there are risks to the mother and the foetus. The pregnancy could be at risk of miscarriage during the early stages or developing pre-eclampsia and placenta abruptio. If thyroid disease is left untreated there can be risks to the baby's brain development during the pregnancy that may affect development in childhood. *British Thyroid Foundation, 2017* Advances in understanding the physiology of thyroid function in normal pregnancy have highlighted the importance of the consequences of abnormal function on obstetric outcome and foetal well-being. *John H Lazarus, Thyroid Function in Pregnancy, British Medical Bulletin 2011; 97:137-146* Current guidelines recommend a targeted approach to screening all	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.

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			women in early pregnancy for thyroid dysfunction but studies have demonstrated that such a strategy may exclude 30-50% of women with significant dysfunction. *Vaidya B, Anthony S, Bilous M et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high risk case finding. J Clin Endocrinol Metab 2007;92:203-07* Gestational narrative reference ranges for thyroid function tests are required for proper interpretation of any abnormalities. It is essential to have reliable accurate tests of thyroid function in pregnancy as maternal thyroid dysfunction may affect maternal health, foetal health and obstetric outcome. Gestational thyroid physiology affects thyroid tests and it is becoming clear that normative gestational related reference ranges for thyroid hormones are required for diagnosis. *Lazurus JH, Soldin OP, Evans C, Assessing thyroid Function in pregnancy. In Brent GA (ed.).Thyroid function testing New York:Springer, 2010,209-33* Measurement of thyroid stimulating antibodies and antithyroid peroxidase antibodies is useful for diagnosis of thyroid disease in pregnancy. Uncorrected thyroid dysfunction in pregnancy has adverse effects on foetal and maternal well-being. The deleterious effects of thyroid dysfunction also extend beyond pregnancy and delivery to affect neurointellectual development in the early life of the child. *John H Lazarus, Thyroid Function in Pregnancy, British Medical Bulletin 2011; 97:137-146* The strength of evidence relating maternal hyperthyroidism to low IQ in children suggests strongly that screening thyroid function in early gestation with L-thyroxine intervention in appropriate women would be cost effective. *Thung SF, Funai EF, Grobman WA, The cost effectiveness of universal screening in pregnancy for subclinical hypothyroidism. Am*	

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			J Obstet Gynecol 2009;200:267.e1-7 *Dosiou C, Sanders GD, Araki SS et al. Screen pregnant women for autoimmune thyroid disease: a cost effectiveness analysis. Eur J Endocrinol 2008;158:841-51* Higher maternal TSH levels even within the normal reference range are associated with an increased risk of miscarriage, foetal and neonatal distress *Benhadi N. Wiersinga WM, Reitsma JB et al Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, foetal or neonatal death. Eur J Endocrinol 2009;160:985-91* as well as pre-term delivery. *Stagnaro-Green A, Chen X, Bogdenn JD et al. The thyroid and pregnancy: a novel risk factor for very preterm delivery. Thyroid 2005;15:351-7* There is a detrimental effect of gestational maternal hypothyroidism on foetal brain development. The availability of thyroxine to the developing foetal neurones is vital for their maturation and proper function. *Williams GR. Neurodevelopmental and neurophysiological actions of thyroid hormone. J Neuroendocrinol 2008;20:784-94* Hypothyroidism usually subclinical is common and should be treated with L-thyroxine to reduce obstetric and foetal complications. Women already receiving thyroxine require an increase in dose during gestation *Yass L. Marquese E, Fawcett R et al Thyroid hormone early adjustment in pregnancy. The Therapy Trial. J Clin Endocrinol Metab 2010;95:3234-241.* Due to the changes in serum concentrations in pregnancy gestation-specific reference intervals for total thyroid hormones need to be defined and used. However in most clinical laboratories total T4	

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			testing has been replaced with free hormone assays. It is therefore essential to have reliable accurate tests of thyroid function in pregnancy. In early gestation TSH is supressed by 20-50% by week 10. So it is essential to rely on T3 & T4 to assess thyroid status in early gestation. TSH will be significantly elevated in overt hypothyroidism. From 16 weeks on approximately TSH is more reflective of thyroid status. *Lazurus JH, Soldin OP, Evans C, Assessing thyroid Function in pregnancy. In Brent GA (ed.). Thyroid function testing New York:Springer, 2010,209-33* Early diagnosis and good management of maternal thyroid dysfunction is essential to ensure minimal adverse affects on foetal development. *Haddow JE, Palomaki GE, Allan WC et al. Maternal Thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. NEJM 1999;341:549-55* Maternal FT3 and FT4 must be measured in pregnancy. TT3 and TT4 increase in pregnancy due to increased serum concentrations of thyroid hormone binding proteins. Only the free not bound fraction can enter the cells. Trimester specific reference ranges for FT3 and FT4 need to be applied for diagnosis. *Demmer LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol 2003;58:138-140* *Alexander EK, Marqusee E, Lawrence J et al. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. NEJM 2004;351:241-9* The fetus relies on maternal thyroxine until 12 weeks gestation when its own thyroid gland develops. The offspring of women whose free throxine levels are in the lowest 10% of the reference range in the first trimester of pregnancy have significant neurodevelopmental delays at the age of two years.	

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			There is an increase in FT4 levels in women early in normal pregnancy but in women with hypothyroidism this increase does not occur. It is therefore very important to ensure adequate T4 replacement from as early as 5 weeks gestation. Ideally women with hypothyroidism should be euthyroid pre pregnancy and have their thyroxine dose increased immediately they become pregnant and have their TSH and FT4 monitored regularly. Patients with established hypothyroidism should have their daily dose of T4 increased by 25 micrograms once pregnancy is confirmed and should have thyroid function tests re-checked after approximately 2 weeks to ensure a satisfactory FT4 level has been achieved. (FT4 16-21 pmol/L with ideally a TSH of less than @m U/L) A further increase in T4 dose may be required to achieve this ideal thyroid function test profile. Patients newly diagnosed with hypothyroidism whilst pregnant should have the treatment commenced immediately with a starting dose of 100 micrograms daily. A further assessment of thyroid function tests should be performed after 2 weeks to ensure FT4 is ideally 16-21 pmol/L. TSH should be less than 2m U/L. Further changes in the T4 dose followed by repeat thyroid function tests may be required to achieve this ideal biochemical profile. As a minimum, patients should have thyroid function tests, once in each trimester. If TFTs are unstable referral to a specialist as early as possible as growth scans may be required. T4 treatment should be reduced to pre-pregnancy dose at 2-6 weeks post partum and rechecked TSH and FT4 6-8 weeks later. *Toft A. 2004 Increased levothyroxine requirements in pregnancy – why, when and how much? NEJM;351(3):292-3* *Demmer LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol 2003;58:138-140* *Alexander EK, Marqusee E, Lawrence J et al. Timing and*	

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			magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. NEJM 2004;351:241-9 *Pop VJ, Brouwers EP, Vader HL et al. Maternal hypothroxinaemia during early pregnancy and subsequent child development: a 3 year follow-up study. Clin Endocrinol 2003;59:282-8* Given the high percentage of pregnant women who are not diagnosed with a thyroid dysfunction due to a lack of simple tests, and the risks to both the mother and the pregnancy we would like to see all pregnant women to be included in the test regimes currently offered to targeted groups only. The mother and pregnancy should not be jeopardised in their total ignorance on the basis of cost given the screening of all pregnant women for autoimmune thyroid disease in the first trimester has been evidenced to being cost-effective compared to not screening. *European Journal of Endocrinology 158 841-851*	
Improve Thyroid Treatment Campaign Group	5	135	*"Management of thyroid diseases with iodine and selenium supplementation"* ITT recommends that iodine deficiency and the link to miscarriage, stillbirth, mental impairment, increase of perinatal and infant mortality should be included in the scope. The thyroid gland increases 10% in size during pregnancy in iodine-replete countries and 20-40% in areas of iodine deficiency. Dr Vanderpump told a meeting of the Society for Endocrinology 'Our data suggests the UK is now iodine deficient' warranting a full investigation of the UK iodine status. In fact, a study involving 700 teenage girls at nine UK centres found more than two thirds had an iodine deficiency. http://astutehealthcare.co.uk/iodine-aqua/pdf/2011-bbcnews-Worrying-levels-of-iodine-deficiency-in-the-uk.pdf Production of thyroxine (T4) and triiodothyronine (T3) increases by 50% along with a 50% increase in the daily iodine requirement. These physiological changes may result in hypothyroidism in the later stages of pregnancy in iodine deficient women who were	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline. Outside of the context of pregnancy, the role of iodine supplementation in managing hypothyroidism will be considered.

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			euthyroid in their first trimester. Even a mild deficiency can damage a baby's developing brain and in areas of severe iodine deficiency thyroid nodules can be present in as many as 30% of pregnant women. Maternal dietary iodine deficiency results in impaired maternal and fetal thyroid hormone synthesis. Low thyroid hormone values stimulate increased pituitary TSH production and the increased TSH stimulates thyroid growth, resulting in maternal and fetal goitre. I. Berghout A, Wiersinga W, 1998 Thyroid size and thyroid function during pregnancy: an analysis. European Journal of Endocrinology 138: 536-542 https://www.researchgate.net/publication/13659885_Thyroid_size_and_thyroid_function_during_pregnancy_An_analysis Iodine deficiency in pregnant women has been associated with pregnancy loss, stillbirth and increased perinatal and infant mortality. Delange FM, Dunn JT 2005 Iodine Deficiency. In Braverman LE, Utiger RD (eds) Werner and Ingbars The Thyroid: A Fundamental and Clinical Text. Ninth edition. Lippincott, Williams and Wilkins, Philadelphia, pp 264-288. Iodine deficiency is the leading cause of preventable intellectual deficits worldwide according to The Deficiency Disorders/Children's World Health Organisation/ International Council for the Control of Iodine Fund (WHO/ICCIDD/UNICEF) 2007 Assessment of the Iodine Deficiency Disorders and monitoring their elimination. WHO, Geneva. https://apps.who.int/iris/bitstream/10665/43781/9789241595827_eng.pdf In Iodine, deficient areas iodine supplementation of mothers prior to conception or in early pregnancy results in children with improved cognitive performance. Decreased rates of stillbirth and neonatal and infant mortality are also seen. II. Chaouki ML, Benmiloud M, 1994 Prevention of Iodine Deficiency Disorders by Oral Administration of Lipidol during	

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			Pregnancy. European Journal of Endocrinology 130: 547-551 https://www.ncbi.nlm.nih.gov/m/pubmed/8205252 Adequate supplies of maternal thyroid hormone and iodide are essential for normal fetal brain development, with thyroid hormone critical in the first trimester and iodide from the second trimester on. It is increasingly apparent that even very mildly reduced maternal T4 levels may impair the offspring's neuro-cognitive function. Impaired maternal thyroid function from iodine deficiency or autoimmune thyroid disease is common and may represent a major public health issue. Kelly Richard et al 2012 Placental Transport of Thyroid Hormone and Iodide Royal Brisbane and Women's Hospital and The University of Queensland, Australia https://researchgate.net/publication/221927567 It is probable that, in mild to moderate iodine deficient countries, iodine supplementation during pregnancy and lactation may have substantial obstetric and offspring benefits and is economically advantageous. Recently a study involving 1040 mother and child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) showed a mild to moderate iodine deficiency (defined by urinary iodine to creatinine ratio <150 mcg/g) in the first trimester of pregnancy is associated with increased odds of offspring IQ being in the lowest quartile (OR=1.43; 95%CI 1.04, 1.98; P=0.03) with the greatest impact observed on verbal IQ. This study implies that there are potentially substantial benefits from correcting/preventing even mild iodine deficiency in pregnancy. I. P.N Taylor and B. Vaidya Iodine supplementation in pregnancy – is it time? II. file:///C:/Users/Mark/Downloads/23%20Iodine%20supplementation%20in%20pregnancy.pdf The World Health Organisation recommends daily intake of 250ug/d of iodine during pregnancy and lactation along with several other	

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			societies. Iodine, required for infant nutrition is secreted in to breast milk. Therefore, lactating women also have increased dietary iodine requirements. ITT recommends that iodine levels be checked as standard in patients displaying thyroid disease symptoms. Iodine should be checked as standard when a pregnancy is being planned, supplementing three months prior to pregnancy would be the ideal or as soon as pregnancy is discovered. The easiest way to be sufficient in iodine is through food, most countries use iodized salt and in Australia they fortify bread with very successful results. We ask the scope to consider these methods and to discuss with the Department of Health. However, excessive doses of iodine intake from diet and dietary supplements exceeding 500 ug/d should be avoided during pregnancy due to concerns about the potential for fetal thyroid dysfunction.	
Improve Thyroid Treatment Campaign Group	5	135	*Management with thyroid disease with iodine and selenium.* ITT would ask for reconsideration in this area also as selenium is shown to be of therapeutic benefit to those with thyroid disease and thyroid eye disease [TED], including the benefit of reducing TSHR-Ab and TPO-Ab. The thyroid gland requires a steady flow of selenium for metabolism. There is no definitive agreement as to the optimal dose, or length of treatment required. However, there has been a significant reduction in the level of antibodies with a daily selenium dose of 200µg Combining selenium with antithyroid drugs has been shown to have maximum benefit to those who are hyperthyroid. Reducing and controlling antibodies and obtaining euthyroidism is the main aim of treatment. If taking selenium can result in Euthyroidism being obtained faster for patients with TED, this should be included in the Thyroid Disease guidance. It is also accepted that there is greater benefit when selenium is started early in the disease process.	Thank you for your comment. The scope has been amended and the appropriate role of supplementation of iodine and selenium will be considered.

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			Selenium supplementation in thyroid associated ophthalmopathy: an update Dharmasena A. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4003098/ The use of Iodine is also controversial and not generally considered in the UK for treatment of thyroid disease. However, in conjunction with selenium it is being used by some to treat autoimmune thyroiditis. Selenium is used to protect the gland prior to supplementation with iodine. Hashimotos, Selenium and Iodine, Part Two J Dach. http://jeffreydachmd.com/hashimotos-selenium-and-iodine-part-two/ With the increases in costs of some thyroid medication, and in some individual cases, where conventional medication is not able to optimise health, it is important for patients to have other options available. However, it is also crucial that the patient and doctor maintain a working and respectful relationship. Patients do not wish to be left to self medicate without supervision and if doctors could see a way to support patients for whom conventional medication is failing, this in itself will increase the level of wellbeing.	
Improve Thyroid Treatment Campaign Group	5	137	*"Drug induced thyroid dysfunction"* ITT believes that this area is relevant within the Thyroid Disease guidance and should be included. Whilst accounting for only a small percentage of hyperthyroid patients, the ITT patient stories indicate that many of the symptoms they endure are being caused by thyroid medication, and levothyroxine in particular. Thyroid dysfunction may be drug induced. Facticious Thyrotoxicosis may be caused by interferon, molecular-targeted agents, amiodarone, iodine, thyroid hormone and other drugs. Antithyroid	Thank you for your comment. This was not raised as a high priority area for guidance; however, the importance of people and their healthcare professionals being aware of the impact of medication on thyroid function may feature in the information for people with thyroid disease, should the underlying evidence reviews and committee suggest this is appropriate.

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			drugs, lithium and iodine inhibit thyroid hormone production, and dopamine and similar drugs block TSH secretion. There is patient evidence that inadequate thyroid replacement, in the form of L-T4 monotherapy for those who have impeded conversion, is leading to L-T4 toxicity, which is causing worsening and increasingly debilitating symptoms. Dependent on the circumstances, it may be necessary to continue with the dysfunction inducing medication, and/or balancing it out with other medication. Drugs such as Carbimazole may not solely reduce the effects of thyrotoxicosis and T3/T4 replacement hormone drugs may be required to balance out effects of over blockage, and to reduce the likelihood of permanent hypothyroidism. Over medication, can lead to dysfunction. Too little or ineffective medication can leave a patient symptomatic and/or with drug toxicity. Too much L-T4 or L-T3 can result in high levels of Reverse T3 in the system, or T3/T4 toxicity. Both can result in palpitations, and more serious heart problems. It is thought that long-term toxicity may cause osteoporosis. Patients who have failed to obtain optimal thyroid health using L-T4 mono therapy reported a variety of symptoms that were clearly evident when on L-T4 monotherapy, which dissipated when L-T3 or NDT was added or substituted. These symptoms include: Fatigue, fibromyalgia, migraine and dryness and hair loss along with metabolic changes such as weight and body temperature change. I. [Drug-induced thyroid dysfunction]. Nishikawa M1, Toyoda N, Nomura E [2012] https://www.ncbi.nlm.nih.gov/pubmed/23214068	
Improve Thyroid Treatment Campaign Group	5	138	*"Management of thyroid diseases with dietary and lifestyle interventions"* ITT believes dietary and lifestyle interventions should be included within the scope of the review. Exclusion of these will materially limit the impact primary care can have on patient health. Thyroid disease,	Thank you for your comment. The scope excludes consideration of the management of thyroid diseases with dietary and lifestyle interventions; however, the scope does not seek to exclude any consideration of the role of diet and lifestyle in thyroid disease as a

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			as noted in the draft scope, is commonly autoimmune which is often improved through diet or vitamin and mineral supplementation interventions. People with Hashimoto's and other autoimmune conditions will often present with intolerances to multiple proteins, such as gluten, dairy, soy, and eggs. These proteins are not broken down properly and result in inflammation of the intestinal tract. This inflammation perpetuates the autoimmune attack on the thyroid and prevents the absorption of many nutrients. Autoimmune thyroiditis, not effectively managed, will result in instability of the thyroid leading to patients remaining symptomatic and requiring primary care support. ITT recommends its inclusion because diet and lifestyle interventions are not expensive, can be managed in primary care, are consistent with primary care guidance remit and allow patients to have a shared ownership in their care. Finally, clinical studies by the American Thyroid Association have shown that dietary changes resulted in a reduction in the thyroid medication required. I. http://drflannery.com/study-confirms-autoimmune-paleo-aip-diet-works/ II. https://thyroidpharmacist.com III. http://www.nutritionist-resource.org.uk/articles/hypothyroidism.html IV. Mazokopakis EE, Papadomanolaki MG, Tsekouras KC, Evangelopoulos AD, Kotsiris DA, Tzortzinis AA. 2015. Is vitamin D related to pathogenesis and treatment of Hashimoto's thyroiditis? https://www.ncbi.nlm.nih.gov/pubmed/26637501 V. THYROID HORMONE THERAPY. ATA 2012. The effect of celiac disease on the absorption of levothyroxine tablets. https://www.thyroid.org/patient-thyroid-information/ct-for-patients/vol-5-issue-6/vol-5-issue-6-p-3-4/ VI. Food Intolerances to multiple Proteins https://holtorfmed.com/gerd-and-thyroid-disease-does-your-thyroid-doctor-know VII. Nomura, M. Association of Symptoms of Gastroesophageal	whole and it is anticipated that this may feature under the question on information for people with thyroid disease, although this will depend on the evidence identified and committee discussions.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			Reflux with Metabolic Syndrome Parameters in Patients with Endocrine Disease. ISRN Gastroenterol. 2014; 2014: 863206. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3929142/	
Improve Thyroid Treatment Campaign Group	5	138	*The management of thyroid disease with dietary and lifestyle interventions.* There is growing evidence that dietary changes such as moving to an autoimmune protocol diet, gluten and dairy free diets or such, promote control and reduction of antibodies. For this reason, ITT feels there is need for inclusion of this aspect of thyroid disease, if only to inform and direct the patient to further investigation and self-help in this area. This would prove to be more productive and positive than the current advice, which is usually to lose weight and exercise. This current advice is not helpful when dieting and exercising with a failing metabolism will only exasperate the problems of weight gain and fatigue. Reducing thyroid antibodies is crucial for achieving euthyroidism in the control of thyroid eye disease. Patient evidence suggests that, for some at least, antibodies can be reduced by limiting or removing certain food types such as gluten, dairy foods and/or other food groups. Testing for Coeliac disease and allergens may be required.	Thank you for your comment. The scope excludes consideration of the management of thyroid diseases with dietary and lifestyle interventions; however, the scope does not seek to exclude any consideration of the role of diet and lifestyle in thyroid disease as a whole and it is anticipated that this may feature under the question on information for people with thyroid disease, although this will depend on the evidence identified and committee discussions.
Improve Thyroid Treatment Campaign Group	6	144	*"Coeliac disease: recognition, assessment and management (2015) NICE guideline NG20."* ITT supports the inclusion in the scope. Evidence from recent studies indicates that there is a strong clinical association between	Thank you for your comment.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			autoimmune thyroid disease and adult coeliac disease. Where levothyroxine dose requirements are much higher than expected, evaluation for gastrointestinal disorders or coeliac disease should be considered. Furthermore, if such disorders are detected and effectively treated, re-evaluation of thyroid function and thyroid hormone replacement dosage is recommended. Studies have documented higher thyroid medication or different medication treatment where coeliac disease is present. I. International Journal of Celiac Disease, 2016, Vol. 4, No. 4, xx Available online at http://pubs.sciepub.com/ijcd/4/4/6 ©Science and Education Publishing DOI10.12691/ijcd-4 http://pubs.sciepub.com/articleinpress/ijcd/ijcd-4-4-6.pdf II. Prevalence of Celiac Disease in Patients with Autoimmune Thyroid Disease: A Meta-Analysis. Roy Abhik, Laszkowska Monika, Sundström Johan, Lebwohl Benjamin, Green Peter H.R., Kämpe Olle, and Ludvigsson Jonas F. Thyroid. July 2016, 26(7): 880-890. http://online.liebertpub.com/doi/10.1089/thy.2016.0108 III. A large variety of clinical features and concomitant disorders in celiac disease – A cohort study in the Netherlands. MarleenSpijkerman. http://www.sciencedirect.com/science/article/pii/S1590865815300281 IV. Research shows that people with celiac diseases, gluten intolerance are more likely to have thyroid disease and vice versa (1-10) by Jordan Fallis https://www.dovepress.com/effects-of-low-carbohydrate-diet-therapy-in-overweight-subject-with-au-peer-reviewed-article- V. THYROID HORMONE THERAPY. ATA 2012. The effect of celiac disease on the absorption of levothyroxine tablets. https://www.thyroid.org/patient-thyroid-information/ct-for-patients/vol-5-issue-6/vol-5-issue-6-p-3-4/	
Improve Thyroid	6	156	*"Medicines Optimisation NG5 "*	Thank you for your comment. The guideline will seek to address the most appropriate

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
Treatment Campaign Group			ITT is supportive of the Francis Report (2013) which emphasised the need to put patients first at all times, and posited that they must be protected from avoidable harm. The Berwick report (2013) recommended 4 guiding principles for improving patient safety, including: • placing the quality and safety of patient care above all other aims for the NHS • engaging, empowering, and hearing patients and carers throughout the entire system, and at all times. Unfortunately, the recent action by many CCGs to withdraw liothyronine T3 has left many patients believing that the primary care system is not based on these principles. ITT encourage NICE to ensure there is a range of treatment options for patients because "a one size fits all" approach is incompatible with recognition of patients as individuals, and the complexity of the biochemistry of the endocrine system.	management of primary hypothyroidism and the role of T3 will be considered in this area.
Improve Thyroid Treatment Campaign Group	6	156	*Medicines Optimisation* - This is of utmost importance to patients as optimal medication is proving impossible for many to achieve, with the current levothyroxine [L-T4] monotherapy treatment protocols. For patients with conversion problems, such as the defective DIO2 gene, or liver disease, who are unable to achieve euthyroid state with L-T4, there is an obvious and imperative need for other medications to be made more readily available. Likewise for patients who have undergone definitive thyroid removal or destruction, L-T4 is rarely, if ever adequate, as it is not physiologically equal to the natural thyroid hormone production. Inadequate and inappropriate medication means patients remain ill, living substandard lives and missing out on life opportunities.	Thank you for your comment. The guideline will seek to address the most appropriate management of primary hypothyroidism and the role of T3 and thyroid extract will be considered in this area.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			For medicine optimisation to be achieved liothyronine [L-T3] and Natural Desiccated Thyroid [NDT] must be made available for those who need them. Refer to lines 118/119	
Improve Thyroid Treatment Campaign Group	6	157	*"Patient experience in adult NHS services (2012) NICE guideline CG138."* The guideline states that, "*Patients wish to be seen as an individual within the healthcare system. This requires healthcare professionals to recognise the individual, and for services to be tailored to respond to the needs, preferences and values of the patient. Advice on treatments and care, including risks and benefits, should be individualised as much as possible"* ITT supports the inclusion and setting of guidelines based on the experience of patients. ITT believes that a patient based approach is not the current treatment experience of the majority of patients with thyroid disorders. Thyroid disorders present many different symptoms and impact patients in various ways. Patients should be treated as individuals and treatments tailored according to individual circumstances. ITT fully supports the aim that services be tailored to respond to the needs, preferences and values of the patient. ITT observes that this section of the draft scope is about how the profession sees the patients' responsibility. ITT would encourage the use of patient centric guidance and incorporation into the guidance the responsibility towards the patients. ITT patient stories evidence that NICE guidance on valuing, respecting and listening to patients (1.2 Essential Requirements of Care in (2012) NICE guideline CG138) is often not followed by clinicians. ITT, unfortunately, has examples in the patient stories submitted to us of belittling, arrogance, anger, lack of sympathy, cruelty, inhumane, neglectful, condescending, dismissive and patronising language and attitudes used by professionals to patients. We recognise that thyroid disease	Thank you for your comment. As with all NICE guidelines, this guideline will seek to include the views of patients as much as possible alongside published evidence on the clinical and cost effectiveness of any potential recommendations.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			can be more complex for non-specialists and this is in part due to the lack of professionals' knowledge of thyroid disease or the oversimplification, which has been given in training. The GMC curriculum simplifies the problems that many patients with thyroid problems encounter. NICE guidance should include emphasis on treating the person as a whole and not just as a gland, which can be fixed in isolation. There is considerable evidence from social media and patient stories that a significant number of patients with thyroid related conditions do not feel that they are seen as individuals within the healthcare system. These patients do not feel that their treatment is adequate, or that they are able to have a positive working relationship with their healthcare professional regarding their treatment. Patients who choose to explore other treatment options often find themselves unsupported by the healthcare system and do not feel respected and supported in their choice of treatment. There are a large number of disenfranchised patients who do not use the NHS for thyroid treatment. Instead they self-medicate and use private blood testing services. ITT does not feel that advice on treatments and care, including risks and benefits are individualised as much as possible. One area of specific patient concern is that treatment options are not explored with them. No mention is made of NDT, T4/T3 combination or T3 only therapy options. The experience of patients is that their concerns are largely dismissed, they are not given the opportunity or time to discuss management of this chronic condition, and as current treatment is dominated by the results of the TSH test, ongoing unresolved symptoms are largely dismissed as unrelated to a thyroid condition if the TSH lies within UK reference ranges. ITT believes a patient-centred approach is required and signs and symptoms are as, or more, important than clinical tests. ITT recommends that NICE use patient surveys and feedback to inform the patient experience outcome of the thyroid disease review.	
Improve Thyroid	6	158	*"Medicines adherence (2009) NICE guideline CG76 "*	Thank you for your comment. The guideline will seek to address the most useful

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Treatment Campaign Group			ITT is supportive of involving patients in decisions about prescribed medicines and supporting adherence. ITT patient stories evidence that an emphasis on patient-centred care is missing when it comes to Thyroid disease (see lines 157, 212 - 214). Guidance frequently revolves around use of TSH only results, which may not be appropriate for many patients. This may lead to a misunderstanding that the patient is not compliant with medication. Primary care professionals require information on why TSH testing may not be appropriate, and the importance of listening to patients' symptoms. Many patients report learning later that other medication they take may result in lower absorption of their thyroid hormone replacement. We encourage the scope to recommend provision of better information to professionals and patients to aid adherence. Other medication types that cause absorption complications include: • Sucralfate; contains a considerable amount of aluminium, and this probably accounts for its ability to reduce levothyroxine absorption. In one study, giving the sucralfate 8 hours after the levothyroxine circumvented the interaction. • Phosphate Binders; patients on haemodialysis may need treatment with drugs that can bind phosphate in the gut, thus reducing their phosphate load. The phosphate binder sevelamer (Renagel) has been shown to increase thyrotropin concentrations in patients on levothyroxine; hypothyroid symptoms have been reported. Calcium carbonate also can be used as a phosphate binder and it also interacts with levothyroxine, but limited clinical evidence suggests that calcium acetate may not affect levothyroxine absorption. • Iron; evidence from case reports and clinical studies suggests that iron preparations can inhibit levothyroxine absorption and can result in clinical evidence of hypothyroidism. It seems likely that all iron salts would inhibit levothyroxine absorption, although the magnitude may vary among the various preparations.	information to be provided to people with thyroid disease.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			• Binding Resins; cholestyramine is known to bind to a number of drugs, and has been shown to reduce levothyroxine absorption as well. The effect of other binding resins such as colestipol (Colestid), colesevelam (Welchol), and ezetimibe (Zetia) on thyroid absorption is not as well established, but be alert for the possibility. • Other drugs that have been reported to reduce levothyroxine absorption include ciprofloxacin (Cipro), raloxifene (Evista), and caffeine in coffee. More study is needed to establish whether these interactions are likely to be clinically important	
Improve Thyroid Treatment Campaign Group	6	171	*" 1.1 Who should be investigated for thyroid disease?"* Patient signs and symptoms are especially important in the consideration for investigations. Clinical testing only may not adequately identify thyroid disorder especially where there are elevated antibodies. We believe the scope should include consideration of routine testing of women over the age of 16. 1. Given Thyroid disorders are more common (90% are women) ITT advocates that women over the age of 16 routinely be screened. Many patients, especially females, report signs and symptoms throughout childhood and adolescence that were not recognised as thyroid based, yet diagnosis was made much later in life, often after decades of struggling with increasingly growing and worsening symptoms. 2. Thyroid disorder is common during pregnancy; 3. People with other autoimmune diseases are more likely to develop autoimmune thyroid disease. The opposite is also true, people with autoimmune thyroid disease are more likely to develop other autoimmune diseases. 4. Coeliac disorders 5. Diabetes 6. Pernicious anaemia 7. Genetic predisposition exists	Thank you for this information. The guideline will seek to address the most appropriate ways of investigating thyroid dysfunction.

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			8. Patients exhibiting unexplained weight gain or loss, tiredness, fatigue, insomnia, bowel issues, temperature intolerance, weakness, blood pressure irregularities, raised cholesterol, or other thyroid related symptoms 9. Anyone with obvious biological blood results, which indicate thyroid disease. With consideration for the necessary review of the TSH 'normal' range levels. 10. Consideration for borderline negative at neonatal to be retested throughout childhood, along with children with family history of the disease. https://healthunlocked.com/thyroiduk/posts/private/136451970/tsh-levels-in-healthy-people-with-no-known-thyroid-disease	
Improve Thyroid Treatment Campaign Group	6	172	*" 1.2 Which thyroid function tests should be requested? "* ITT believes that the present approach to testing only TSH (a pituitary test) does not adequately capture the complexities of thyroid disorder. Clinical studies (referenced below) sufficiently demonstrate that TSH is a poor marker for the body's overall thyroid level. Tests to analyse serum levels of TSH, free T4, TotalT4, free T3, Total T3, reverse T3, anti-TG antibodies, and anti-TPO antibodies to assess central and peripheral thyroid function, as well as thyroid auto-immunity. Evidence from Thyroid associations around the world support broader testing than TSH and T4. ITT believes, given 90% of thyroid disorders are autoimmune related, thyroid antibodies should be tested routinely. This will allow earlier intervention and facilitate, with appropriate guidance, patients to make informed choices and take control to manage their own health. The thyroid function tests should routinely be comprehensive. Thyroid biochemistry is complex and tests to provide a thorough analysis of thyroid hormone metabolism should be conducted. Tests should include those for thyroid gland regulation and activity, thyroid production and secretion, peripheral thyroid conversion, and thyroid autoimmunity to allow a primary practitioner to identify thyroid	Thank you for your comment. The guideline will seek to address the most appropriate ways of investigating thyroid dysfunction.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			disorders. ITT advocates that where TSH is used the reference range should be updated and lowered. ITT recommends 2.0mIU/l should be used to indicate a potential to progress to hypothyroidism, which requires a patient to consider thyroid hormone treatment. I. Hu S, Rayman MP Multiple Nutritional Factors and the Risk of Hashimoto's Thyroiditis. https://www.ncbi.nlm.nih.gov/pubmed/28290237 II. Alevizaki, M., Mantzou, E., Cimponeriu, A. T., Alevizaki, C. C., & Koutras, D. A. (2005). TSH may not be a good marker for adequate thyroid hormone replacement therapy. Wiener Klinische Wochenschrift, 117(18), 636-640. III. Becker DV, Bigos ST, Gaitan E, Morris JC, Rallison ML, Spencer CA, Sugarawa M, Van Middlesworth L, Wartofsky L. (1993). Optimal use of blood tests for assessment of thyroid function. Journal of the American Medical Association. 1993 Jun 2; 269: 273. IV. De Los Santos ET, Mazzaferri EL (1988). Sensitive thyroid-stimulating hormone assays: Clinical applications and limitations. Comprehensive Therapy.1988; 14(9): 26-33. V. Després N, Grant A. (1998). Antibody interference in thyroid assays: a potential for clinical misinformation. Clinical Chemistry March 1998 vol. 44 no. 3 440-454. VI. Dickey RA, Wartofsky L, Feld S. (2005). Optimal thyrotropin level: normal ranges and reference intervals are not equivalent. Thyroid. 2005 Sep;15(9):1035-9 VII. Goldberg A, Tirona R, Schwarz U, Kim RB, Van Uum SHM. (2001). Hypothyroidism with Very Low Free T3/Free T4 Ratio May Represent Decreased Peripheral Conversion of T4 to T3: Case Report and Differential Diagnosis. Endocrine Reviews. Vol. 32: P3-616. VIII. Hoermann, R., Midgley, J. E., Giacobino, A., Eckl, W. A., Wahl, H. G., Dietrich, J. W., & Larisch, R. (2014). Homeostatic equilibria between free thyroid	

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			hormones and pituitary thyrotropin are modulated by various influences including age, body mass index and treatment. Clinical endocrinology. IX. Holtorf, K. (2014). Thyroid Hormone Transport into Cellular Tissue. Journal of Restorative Medicine, 3(1), 53-68. Chicago. . X. Holtorf, K. (2014). Peripheral Thyroid Hormone Conversion and Its Impact on TSH and Metabolic Activity. Journal of Restorative Medicine, 3(1), 30-52. XI. Holtorf, K. (2012). Hormone Replacement Therapy in the Geriatric Patient: Current State of the Evidence and Questions for the Future. Estrogen, Progesterone, Testosterone, and Thyroid Hormone Augmentation in Geriatric Clinical Practice. XII. Kalra S, Khandelwal, SK (2011). Why are our hypothyroid patients unhappy? Is tissue hypothyroidism the answer? Indian Journal of Endocrinology and Metabolism. 2011 July; 15(Suppl2): S95–S98. XIII. Pritchard, E.K. (2013). Reducing the Scope of Guidelines and Policy Statements in Hypothyroidism. Journal of Orthomolecular Medicine. Volume 28, Number 2, 2013. XIV. Rowsemitt, C. and Najarian, T. (2011) TSH is Not the Answer: Rationale for a New Paradigm to Evaluate and Treat Hypothyroidism, Particularly Associated with Weight Loss. Thyroid Science; 6(4): H1-16. XV. Rudolf Hoermann1*, John E. M. Midgley2, Rolf Larisch1 and Johannes W. Dietrich3,4,5. (2016). Relational Stability in the Expression of Normality, Variation, and Control of Thyroid Function. Front. Endocrinol, 07 November 2016 | http://dx.doi.org/10.3389/fendo.2016.00142. XVI. Ruhla, S., Arafat, A. M., Weickert, M. O., Osterhoff, M., Isken, F., Spranger, J., & Möhlig, M. (2011). T3/rT3-ratio is associated with insulin resistance independent of TSH. Hormone and metabolic research, 43(02), 130-134. XVII. Sesmilo G, Simó O, Choque L, Casamitjana R, Puig-	

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			Domingo M (2011). Serum free triiodothyronine (T3) to free thyroxine (T4) ratio in treated central hypothyroidism compared with primary hypothyroidism and euthyroidism. Endocrinología y Nutrición. 2011 Jan;58(1):9-15 XVIII. Skinner GRB, Holmes D, Ahmad A, Davies JA, Benitez J (2000). Clinical Response to Thyroxine Sodium in Clinically Hypothyroid but Biochemically Euthyroid Patients. Journal of Nutritional and Environmental Medicine. Vol. 10, No. 2 , Pages 115-124. XIX. Skinner GR, Thomas R, Taylor M, Sellarajah M, Bolt S, Krett S, Wright A. (1997). Thyroxine should be tried in clinically hypothyroid but biochemically euthyroid patients. British Medical Journal: June 14; 314(7096). XX. van den Beld, A.W., Visser, T., Feelders, R., Grobbee, R., Lamberts, W.J., (2005) Effect of Exogenous Thyroid Hormone Intake on the Interpretation of Serum TSH Results. The Journal of Clinical Endocrinology & Metabolism; 90 (12): 6403-6409. XXI. Welsh, Dr Kerry J & Soldin, Steven J (2016). DIAGNOSIS OF ENDOCRINE DISEASE: How reliable are free thyroid and total T3 hormone assays? doi: 10.1530/EJE-16-0193. Eur J Endocrinol December 1, 2016 175 R255-R263. XXII. Woeber, K. A. (2002). Levothyroxine therapy and serum free thyroxine and free triiodothyronine concentrations. Journal of endocrinological investigation, 25(2), 106-109. XIII. TSH - role in patients on replacement therapy, by Thyroid UK advisors Rudolf Hoermann, John E.M. Midgley and Johannes W. Dietrich. (2014). Retrieved August 2014 from: http://www.thyroiduk.org.uk/tuk/research/TSH.html. The full article is published in: © 2014 John Wiley & Sons Ltd, Clinical Endocrinology (2014), 0, 1–9. AND the original article is in: Clinical Endocrinology (2014), doi: 10.1111/cen.12527	

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Improve Thyroid Treatment Campaign Group	6	172	*" 1.2 Which thyroid function tests should be requested? "* Thyroid disorders, especially associated with autoimmune conditions, are also often associated with vitamin deficiencies. Vitamin and mineral deficiencies, other hormones, certain viruses, food and chemical sensitivities/allergies and intolerance also influence thyroid health. Many vitamin and mineral symptoms are similar to thyroid disorder symptoms e.g. vitamin D and B deficiencies. ITT recommends that these be considered within the scope of the tests conducted. I. Bozkurt NC, Karbek, B., Ucan B, Sahin M, Cakal E, Ozbek M, Delibasi T (2013). The Association Between Severity of Vitamin D Deficiency and Hashimoto's Thyroiditis. Endocrine Practice; 2013 Jan 21:1-14. II. Camurdan OM, Döğer E, Bideci A, Celik N, Cinaz P. (2012). Vitamin D status in children with Hashimoto thyroiditis. Journal of Pediatric Endocrinology & Metabolism. 2012;25(5-6):467-70.. III. Kivity S, Agmon-Levin N, Zisappl M, Shapira Y, Nagy EV, Dankó K, Szekanecz Z, Langevitz P, Shoenfeld Y. (2011). Vitamin D and autoimmune thyroid diseases. Cellular & Molecular Immunology; 8(3): 243-7. IV. McDonnell, DP, Pike, JW, O'Malley, BW (1988). The Vitamin D receptor: A primitive steroid receptor related to thyroid hormone receptor. Journal of Steroid Biochemistry, Volume 30, Issues 1–6, Pages 41–46. V. Tetsuyuki Yasuda, Yasuyuki Okamoto, Noboru Hamada, Kazuyuki Miyashita, Mitsuyoshi Takahara, Fumie Sakamoto, Takeshi Miyatsuka, Tetsuhiro Kitamura, Naoto Katakami, Dan Kawamori, Michio Otsuki, Taka-aki Matsuoka, Hideaki Kaneto, and Iichiro Shimomura (2012). Serum vitamin D levels are decreased and associated with thyroid volume in female patients with newly onset Graves' disease. Endocrine. 2012 December; 42(3): 739–741.	Thank you for your comment. The guideline will seek to address the most appropriate ways of investigating thyroid dysfunction.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			VI. Carmel, R, Spencer, CA (1982). Clinical and Subclinical Thyroid Disorders Associated with Pernicious Anemia. Archives of Internal Medicine 1982;142(8):1465-1469. VII. Jabbar A, Yawar A, Waseem S, Islam N, Ul Haque N, Zuberi L, Khan A, Akhter J. (2008). Vitamin B12 deficiency common in primary hypothyroidism. Journal of Pakistan Medical Association. May;58(5):258-61. VIII. Ness-Abramof, Rosane MD; Nabriski, Dan A. MD; Braverman, Lewis E. MD; Shilo, Lotan MD; Weiss, Eliahu MSc; Reshef, Tamar MSc; Shapiro, Menachem S. MD; Shenkman, Louis MD (2006). Prevalence and Evaluation of B12 Deficiency in Patients with Autoimmune Thyroid Disease. American Journal of the Medical Sciences: Volume 332 - Issue 3; pp 119-122. IX. Okuda, K., Chow, B. (1961). The Thyroid and Absorption of Vitamin B12 in Rats. Endocrinology April 1, 1961 vol. 68 no. 4 607-615. X. Perros, P., Singh, RK, Ludlam, CA, Frier, BM (2000). Prevalence of pernicious anaemia in patients with Type 1 diabetes mellitus and autoimmune thyroid disease. Diabetic Medicine. Volume 17, Issue 10, pages 749-751. XI. Beard, JL, Borel, MJ, Derr, J. (1996). Impaired thermoregulation and thyroid function in iron-deficiency anemia. The Journal of Biological Chemistry; May 1996, 271, 12017-12023. XII. Hess S, Zimmermann MB, Arnold M, Langhans, W, Hurrell, R (2002). Iron Deficiency Anemia Reduces Thyroid Peroxidase Activity in Rats. The Journal of Nutrition. vol. 132 no. 7 1951-1955. XIII. Zimmermann, MB, Köhrle, J (2002). The Impact of Iron and Selenium Deficiencies on Iodine and Thyroid Metabolism: Biochemistry and Relevance to Public Health. Thyroid. October 2002, 12(10): 867-878. XIV. Watts, D. L. (1989). The nutritional relationships of the thyroid. Journal of Orthomolecular Medicine, 4(3).	

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			XV. Effects of low-carbohydrate diet therapy in overweight subject with autoimmune thyroiditis: possible synergism with ChREBP I.Authors Esposito T, Lobaccaro JM, Esposito MG, Monda V, Messina A, Paolisso G, Varriale B, Monda M, Messina G Received 15 February 2016 Accepted for publication 11 May 2016 Published 14 September 2016 Volume 2016:10 Pages 2939—2946 DOI https://doi.org/10.2147/DDDT.S106440	
Improve Thyroid Treatment Campaign Group	6	173	*"1.3 When should thyroid antibodies be tested?"* ITT believes that early diagnosis of autoimmune thyroid disorders is essential. The scope recognises that 90% of thyroid disease is autoimmune related. It allows informed patients to be more engaged in treatment options and manage their own health. Earlier intervention to identify antibodies will assist both patients and primary care in management of the progression of thyroid, or other, autoimmune disease. ITT believes that the current diagnosis of hypothyroidism is limited because it does not routinely test for thyroid antibodies. The presence of antibodies is a predictor of thyroid dysfunction, thyroid nodules and thyroid cancer. Testing should be conducted and used in the diagnosis of thyroid disease. Autoimmune attacks cause instability in the thyroid hormone levels and result in patients being symptomatic, visiting their GP and possibly undergoing tests and changing doses. That instability is not in the patient or primary care best interest. Secondly, understanding the antibody levels allows the patient to make an informed and shared decision on lifestyle changes that could minimise autoimmune attacks. These include gluten free and/or dairy free or autoimmune diets. Thirdly, autoantibodies are positively associated with the risk of developing thyroid nodules and goitres. Earlier intervention by understanding the antibody levels may prevent surgery. The most common cause of hypothyroidism is autoimmune thyroiditis or Hashimotos. Hypothyroidism can occur due to initial	Thank you for your comment. The guideline will seek to address the most appropriate ways of investigating thyroid dysfunction.

Organisation name	Page no.	Line no.	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
			presentation of Hashimotos, inadequate treatment of a woman already known to have hypothyroidism or over-treatment of a hyperthyroid woman with antithyroid medicine. 2.5%of women will have elevated TSH of greater than 6 and 0.4 a TSH of greater than 10. Thus, risking miscarriage. https://www.ncbi.nlm.nih.gov/pubmed/2071868 https://www.ncbi.nlm.nih.gov/pubmed/25057882 ITT recommends that the scope include checking of TSH values when a pregnancy is being considered or when first seen in surgery. Pregnant women with TSH concentrations >2.5mU/L should be evaluated for TPOAb status. According to the American Thyroid Association Pregnancy Guidelines, there is almost double the rate of miscarriage in women with Hashimotos disease who are subclinically hypothyroid, with TSH levels between 2.5 and 5.0 mIU/L versus women who have Hashimotos disease with TSH levels below 2.5 mIU/L. Untreated or inadequately treated hypothyroidism is associated with anaemia, myopathy, congestive heart failure, pre-eclampsia, placental abnormalities, low birth weight infants and postpartum haemorrhage. I. Spencer CA1, Hollowell JG, Kazarosyan M, Braverman LE. National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. 2007. https://www.ncbi.nlm.nih.gov/pubmed/17684054 II. Weimin Xu,Liangliang Huo,Zexin Chen,Yangmei Huang, Xingyi Jin, Jing Deng, Sujuan Zhu,1and Yunxian Yu. 2017. The Relationship of TPOAb and TGAb with Risk of Thyroid Nodules: A Large Epidemiological Study. https://www.ncbi.nlm.nih.gov/pubmed/28678169 III. Panudda Srichomkwun, Neal H. Scherberg, Jasminka Jakšić, and Samuel Refetoff. 2017. Diagnostic Dilemma in Discordant Thyroid Function Tests Due to Thyroid Hormone	

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			Autoantibodies. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5286684/ IV. Boelaert K, et al. 2010. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. https://www.ncbi.nlm.nih.gov/pubmed/20103030	
Improve Thyroid Treatment Campaign Group	7	191 - 201	*"4.4 When radioactive iodine is used, what is the most clinical and cost effective way of using this treatment to treat thyrotoxicosis (for example different dosing strategies)?"* ITT considers that consideration of cost effectiveness of radioactive iodine treatments without including the correct replacement medication can be false economy. If patients are left with inadequate hormone replacement they will remain ill and in constant need of health care, investigations and treatments.	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of treatment options for thyrotoxicosis including radioactive iodine.
Improve Thyroid Treatment Campaign Group	7	191 - 193	*"4.1 What is the clinical and cost effectiveness of using radioactive iodine vs antithyroid drugs vs surgery to treat thyrotoxicosis secondary to Graves' disease?"* ITT believes the scope should reflect that individual cases should be treated as such. Consideration should be given to the previous health history and patient circumstances. Patients should have full information of the implications of all of the treatment options and follow-up procedures before making decisions as to the appropriate treatment for them. The use of radioactive iodine [RAI] is controversial and is thought/known to be instrumental in worsening and even instigating thyroid eye disease. Antithyroid drugs do not suit all. Sometimes a combination of both antithyroid drugs and levothyroxine is required to find the right balance of thyroid function. However, this may not be an option for those with the defect DIO2 gene. Meaning that the options are then reduced to radioactive iodine or surgery. Patient stories evidence that following RAI and surgery they are	Thank you for your comment. The guideline will seek to address the most appropriate management of thyrotoxicosis. It will also seek to address patient information needs.

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			issued with thyroid replacement medication in the form of levothyroxine [L-T4]. This is not always adequate and leaves many unwell. RAI and surgery can impact on the parathyroid glands through inadvertent damage, and on the larynx. The aftercare of patients following RAI and/or surgery is paramount to patient outcome and cost effectiveness. If patients are not receiving the correct medication to replace the thyroid hormones they will not be well and able to function on any normal level.	
Improve Thyroid Treatment Campaign Group	7	196 - 198	*"4.3 When anti-thyroid drugs are used, what is the most clinical and cost effective way of using these drugs to treat thyrotoxicosis (for example choice of drugs, different treatment regimens)?"* Initial treatment for Hyperthyroidism and/or Graves tends to be beta-blockers or antithyroid drugs [ATDs], Carbimozole in particular. Most patients respond well to this treatment with low instances of side effects (only 3 -5 %). Historically It has been suggested that the long-term use of ATDs is not advisable as usage is likely to cause adverse side effects. However, more recent clinical evidence suggests that this is no longer true. For a number of patients on Carbimazole the addition of levothyroxine, (or other thyroid drug, L-T3 or NDT) may be an option used to balance the blocking effect. Alternatively, a change of medication to propylthiouracil may be warranted. If propylthiouracil is administered the patient will need regular checks for liver problems. If propylthiouracil is prescribed, patients should undergo a liver function test prior to start of medication with regular assessments throughout treatment. Patients who cannot tolerate Carbimozole will need to discuss this with their physician and agree a long-term treatment option. Carbimazole is not recommended in the first trimester of pregnancy. Propylthiouracil is usually issued instead. When ATDs work, duration of treatment is undefined and can vary widely. One study showed that 46% of patients went into remission after an average treatment period of eighteen months. Another study	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of thyrotoxicosis management options.

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			showed that a second course of treatment with ATD could also be effective, putting 75.78% of patients into 'permanent' remission. Many patients remain on ADTs, PTU aside, for many years, without adverse effects. However, remission is not achievable for all Graves' sufferers. Their long-term treatment must be considered carefully. For these patient RAI and/or surgery may be the only options. Neither of these options guarantees optimal health. Marcocci et al [1990] discuss a retrospective evaluation of "The outcome of radioiodine therapy of Graves' hyperthyroidism" in respect of patients treated between 1975 and 1984. After 1 year 36.9% of patients were considered to be permanently hypothyroid. Only 42% of patients achieve euthyroid state following RAI treatment. 4% would be expected to remain hyperthyroid. The other 54% would remain hypothyroid. It must be recognized that most patients rendered hypothyroid, by either RAI or surgery, never feel that they fully regain their health, even when a biochemical euthyroid state is achieved. This fact, and the life long cost, to the NHS, of a patient being hypothyroid, raises the question of the cost effectiveness of RAI treatments. ITT feels clinicians must fully inform their patients of the risks of becoming hypothyroid and not belittle the health consequences of reliance on thyroid hormone replacement. Patient stories evidence that in post RAI or surgery treatment they have been met with blasé statements such as, "it will be fine, hypothyroidism is easily treated with one little pill every day and you will be back to your old self". This lack of recovery is thought by patients to be the consequence of inadequate replacement therapy with the use of levothyroxine [L-T4] monotherapy. The evidence from patient stories is that few patients find their way back to health. The thyroid produces approximately 80% T4 and 20% T3 hormone. L-T4 is not physiologically equivalent to natural thyroid hormone production, as it does not contain T3. The T4 produced by the thyroid has to convert to T3 to be used at the	

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			cellular level. Where patients have no thyroid or conversion inability L-T4 will not be processed correctly. Therefore L-T3 is required. Patients need to have their T3 levels tested, along with TSH and T4, following RAI or total thyroidectomy, to check and correctly treat the deficit due to their lack of natural thyroid. ITT recommends that a range of treatment options be available to those patients who have RAI or surgery. When balancing the complexities of follow up care, after RAI or Surgery, the cost of treatments: long term ATDs vs RAI/surgery and the likelihood of long term hypothyroid treatment, it may prove to be more cost effective to treat Graves' disease with long term ATD plus regular monitoring. ITT feels that patients are being neglected and mistreated. When L-T4 proves unsuccessful patients must have alternative treatment options available. This has to be L-T3 and NDT. T3 levels must be sought and considered, and replacement to the upper quartile issued where necessary. I. You have Graves' disease and had Radioactive Iodine (RAI) or a Thyroidectomy. Now What? Dana Trentini [2014] http://hypothyroidmom.com/you-have-graves-disease-and-had-radioactive-iodine-rai-or-a-thyroidectomy-now-what/ II. Combination Treatment with T4 and T3: Toward Personalized Replacement Therapy in Hypothyroidism? Bernadette Biondi Leonard Wartofsky [2011] https://academic.oup.com/jcem/article/97/7/2256/2833962/Combination-Treatment-with-T4-and-T3-Toward III. A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism. Claudio Marcocci, D. GianchecchiI. MasiniF. Golia C. CeccarelliE. Bracci G. F. FenziA. Pinchera [1990]	

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			https://link.springer.com/article/10.1007/BF03348615 IV. Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. Azizi F1, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami F [2005] https://www.ncbi.nlm.nih.gov/pubmed/15879354 V. Propylthiouracil-induced liver failure and artificial liver support systems: a case report and review of the literature. Dong-Bo Wu, En-Qiang Chen, Lang Bai, and Hong Tang [2017] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5238756/ VI. Predicting relapse of Graves' disease following treatment with antithyroid drugs. LIN LIU, HONGWEN LU, YANG LIU, CHANGSHAN LIU, and CHU XUN [2016] [Accessed 10/11/7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4812122/ VII. A second course of antithyroid drug therapy for recurrent Graves' disease: an experience in endocrine practice. Xiaomei Liu, * Wei Qiang, * Xingjun Liu, Lianye Liu, Shu Liu, Aibo Gao, Shan Gao, and Bingyin Shi [2015] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4321192/	
Improve Thyroid Treatment Campaign Group	7	199 - 201	*"4.4 When radioactive iodine is used, what is the most clinical and cost effective way of using this treatment to treat thyrotoxicosis (for example different dosing strategies)?"* ITT believes that consideration of cost effectiveness of radioactive iodine treatments without including the correct replacement medication can be false economy. If patients are left with inadequate hormone replacement they will remain ill and in constant need of health care, investigations and treatments.	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of thyrotoxicosis management options.
Improve Thyroid Treatment Campaign Group	7	194 - 195	*"4.2 What is the clinical and cost effectiveness of using radioactive iodine vs surgery to treat thyrotoxicosis secondary to toxic nodular goitre? RAI is the first line recommended treatment of toxic nodular goitre due the unreliability of remission."*	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of thyrotoxicosis management options.

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			Because many patients with toxic nodule goitre may not have elevated levels of radioactive iodine uptake, RAI treatment can prove challenging, Therefore, more than one course of treatment is often necessary. Although, in the retrospective study by Hatch et al, [2015] study, the cure rate was 93.9% six months after RAI treatment, hypothyroidism was observed in 74 (31.7%) patients, and euthyroidism was achieved in 145 (62.2%) patients while 14 (6%) patients remained in hyperthyroid state. As noted in line 191, consideration of risk to the parathyroid must be given due consideration, particularly in elderly patients. As total thyroidectomy surgery renders all patients hypothyroid, RAI must be the first choice in the treatment toxic multi nodular goitre, as it offers the patient the chance of avoiding the life long condition hypothyroidism. I. Effectiveness of Radioiodine Treatment for Toxic Nodular Goiter. Hatice Şakı, Arzu Cengiz, and Yakup Yürekli [2015] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4745401/	
Improve Thyroid Treatment Campaign Group	7	174	*"Which imaging tests should be requested?"* ITT recommends that where goitre is present and nodules are obvious the patient should be offered scans to identify the nature of the goitre, and rule out thyroid cancer. The decision as to the type of scan will be determined by the symptoms present. Generally, when a patients presents with goitre together with hyperthyroid symptoms, Radioactive Iodine Uptake [RAIU] testing would be recommended, as this will reliably image thyroid blood flow. RAIU is also able to identify other causes of raised thyroid hormone levels, e.g. homogenous thyroid without nodules. RAIU should not be conducted if there is any possibility of pregnancy. ITT ask that the scope recognise that thyroid nodules do not reflect a single disease but are the clinical manifestation of a wide spectrum of different thyroid diseases. In a normal gland or a diffuse goitre, thyroid nodules may be solitary or multiple. Among multinodular goitres, one nodule may become clinically dominant in terms of growth, dimension, and	Thank you for your comment. The guideline will seek to address which imaging tests should be used in each relevant context. There is also existing NICE guidance on investigation of an unexplained lump on the thyroid in the suspected cancer guideline (NG12).

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			functional characteristic. The risk of malignancy is similar among hypofunctioning solitary nodules and multinodular goitre. Non-tumoral nodules may be found in patients with thyroid hyperplasia, and with inflammatory or autoimmune thyroid diseases. The aim of the diagnostic approach to thyroid nodules is the differential diagnosis between benign and malignant nodules and, in the event of malignancy, the selection of an appropriate surgical procedure. For patients with singular or multi nodular thyroid, an ultrasound scan would be appropriate. This will be able to distinguish more accurately between the types of nodules. The malignancy or benignity of nodules, singular or in multiples must be assessed accurately through fine needle aspirations biopsy. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323759/	
Improve Thyroid Treatment Campaign Group	7	175	*"Which people with structural thyroid abnormalities should have a fine needle aspiration biopsy and should this be under ultrasound guidance."* The European Thyroid association [ETA] recommends the use of Fine needle aspirations [FNA] also known as Fine Needle biopsy [FNB] following the identification of nodules, through clinical examination and history, ultrasound of the neck, and/or full thyroid function blood tests, including antibody and calcitonin testing. Should the nodules prove to be greater in diameter than 1cm, or less than 1cm but suspicious. Where the TSH was deemed to be low, or there was multi-nodular evidence, the ETA would recommend a thyroid scan, and if cold nodules found a FNA would be recommended. Polyzos and Anastasialakis state that complications of FNA are rare, they do acknowledge the reluctance of performers to publicise complications they encounter. Whilst most complications are rare and considered minor, "*On the contrary, anaphylactic reaction or thromboembolism may be life-threatening. The performers of thyroid FNB are hereby encouraged to publish these complications, if they ever occur, because awareness of them could render FNB even safer."* All factors that raise the risk of a singular or multi-nodular thyroid being malignant should be assessed with care. ITT	Thank you for your comment. The guideline will seek to address which abnormalities should be biopsied and whether this should be under ultrasound guidance. Any recommendations will rely on the clinical and cost effectiveness evidence identified. We are not aiming to cover people with suspected thyroid cancer as there will be another NICE guideline covering this. However, the guideline seeks to determine whether an abnormality indicates presence of thyroid disease, be that benign enlargement, thyroid cancer, or thyroid dysfunction.

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			recommends that the scope consider factors such as male gender, younger in age, fewer and smaller nodules and, of course, the singular nodule. If an ultrasound scan shows the singular nodule is not a cyst. If it is deemed to be tissue and not fluid, a FNA biopsy should be undertaken, preferably under guidance of ultrasound. I. Rare potential complications of thyroid fine needle biopsy. S A Polyzos and A D Anastasilakis. 2011. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3209672/ II. Are there predictors of malignancy in patients with multinodular goitre? Jie Luo, B.S., Catherine McManus, B.S., Herbert Chen, M.D., and Rebecca S. Sippel, M.D. [2012] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3323759/ [Accessed III. Ultrasound of thyroid cancer. K T Wong and Anil T Ahuja [2005]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1665239/ [Accessed]	
Improve Thyroid Treatment Campaign Group	7	180	*"2.1 Which people with non-malignant thyroid enlargement should be referred for surgery?"* If hypothyroidism is present, Levothyroxine [L-T4] may be required, at a dose dependent on the patients TSH level to reduce the size of goitre. Liothyronine [L-T3] or Natural Desiccated thyroid [NDT] may be necessary if the patient has conversion blockage or other conversion factors. Beta-blockers or Antithyroid Drugs [ATDs] may reduce goitre. ITT considers that, unless the patient is in immediate danger, such as restricted breathing or swallowing, or the enlargement is negatively impacting on the patient psychologically, surgery should be a last resort. It should only be considered when all other options have been considered and ruled out. Surgery and the implications	Thank you for your comment. The guideline will seek to address the appropriate criteria for referral for surgery, taking into account the evidence of the benefits, harms and costs of such an intervention.

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			should be discussed with the patient, including the implications of post-operative treatment. Patients where Betablocker, ATD's and RAI treatments are ruled our as ineffective or not recommended treatments, and where possible self-limitation of the condition has been reasoned and rejected.	
Improve Thyroid Treatment Campaign Group	7	182	*"2.2 What is the clinical and cost effectiveness of non-surgical treatments for non-malignant thyroid enlargement?"* ITT recommends that the scope consider clinical effectiveness of non-surgical treatments for non-malignant thyroid enlargement over cost effectiveness. Thyroid enlargement is a sign that there is thyroid dysfunction, temporarily or otherwise. Thyroid cancer should be ruled out initially and the circumstances should then inform other treatment options. If the enlargement is due to hypothyroidism, the use of levothyroxine [L-T4] (liothyronine [L-T3] or Natural Desiccated Thyroid [NDT] if conversion or allergen issues are prevalent) to help reduce the size of goitre is very cost effective and easily managed in primary care. The use of thyroid panel tests including, TSH, T4 & T3 should be used to determine and monitor progression and dosage. Although not as common in the UK as it is in the US, hyperthyroidism due to excessive iodine can cause thyroid enlargement. The blood tests as specified above should be used to determine the cause of the goitre, alongside a urinary test for iodine levels. In the case of excessive iodine reducing it in the diet may help reduce the size of the goitre and the symptoms of hyperthyroidism if present. ATD drugs can also be used to control any hyperthyroid symptoms, however subclinical and help reduce the size of the goitre. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3976240/ More common in the UK is iodine deficiency. ITT recommends for the scope that a test for iodine deficiency be carried out. Iodine deficiency can cause goitres to grow and supplementation at an early stage has been known to eliminate them completely.	Thank you for your comment and for the information provided. The guideline committee considers both clinical and cost effectiveness in order to ensure that the care provided to the patients represent the best use healthcare resources.

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			It must be noted that either levothyroxine treatment or iodine supplementation must be initialized as soon as possible. If no treatment or supplementation is administered within the first few years, the thyroid will be permanently damaged and never reduce in size. https://www.spectracell.com/media/uploaded/1/0e2035135_142fullpaper2000ajcngoiter-and-iron-deficiency.pdf	
Improve Thyroid Treatment Campaign Group	7	184	*"2.3 How should non-malignant thyroid enlargement be monitored?"* ITT asks that the scope recognise that, when serious malignancy has been ruled out, all relevant blood levels should be examined, including antibodies. Even if treatment is not deemed to be necessary, initially, enlargement should be monitored. If enlargement persists or is reoccurring this should warrant further investigations and regular monitoring to assess the effects on the thyroid gland, including follow up blood testing. Again, it is important to check antibodies, even if this was negative in previous test. Follow-up testing should be considered wherever there is known family history of thyroid disease. ITT has received feedback from patients that doctors do not always listen. Time pressure on both doctor and patient is often the issue. Surgery time is limited. Patients are often expected to discuss one symptom only, within the allotted appointment time, yet thyroid patients are likely to have any number of related health issues. Patients are the best judges as to how they feel and the symptoms they are enduring. They are perhaps better placed to advise of the changes in goitre, size and action. ITT considers that patient experience should be of equal value to the biological testing and practitioner observations.	Thank you for your comment. The guideline will seek to address appropriate monitoring of people with thyroid disease. As with all NICE guidelines, the views of patients will be considered alongside evidence on clinical and cost effectiveness when recommendations are made and the committee will include lay members.
Improve Thyroid Treatment	7	186	*" 3.1 What is the clinical and cost effectiveness of using levothyroxine [L- T4], liothyronine [L-T3], combination of L-T4 and L-T3 and thyroid extracts to treat primary hypothyroidism? "*	Thank you for your comment. The economic implications of alternative interventions will be considered in the guideline, taking into

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Campaign Group			ITT recommends that the cost effectiveness review should consider more than the cost of the medication. The cost to patients due to reducing working hours, being prevented from working, their ability to support and care for families or impact on primary and secondary care of remaining symptomatic, require equal consideration. The cost of misdiagnosed patients, patients going undiagnosed and doctors and endocrinologists diagnosing thyroid illness but not prescribing treatment that provides symptom relief lead to the following costs on our public health system that could be avoided. Examples of avoidable public health spend include: • Consultations, laboratory tests and hospital visits that do not result in an accurate diagnosis of the patient's thyroid health. • Thyroid treatments prescribed that do not provide symptom relief. • Other medications prescribed that do not work because thyroid disorder has been misdiagnosed as something else; plus the associated doctors visits, tests and hopsital visits associated with the prescrbing of these medications • Undiagnosed/untreated/undertreated patients on DWP payments because they are too sick to work • Patients go on to develop other illnesses because their thyroid is left untreated/undertreated/misdiagnosed as something else. For example some clinical studies show that 'subclinical hypothyroidism' has been linked to infertility, pregnancy complications, psychiatric illness, neuromuscular symptoms, cardiac dysfunction and mortality. Resulting in unnecessary extra tests and investigations such as colonoscopy, sleep apnoea, allergy testing, referrals for psychotherapy and treatment of high cholesterol. • Patient experience has shown that prescriptions for various different antidepressants and anxiety meds, propranolol,	account both costs and savings. We will adopt an NHS and Personal and Social Services perspective when assessing the cost effectiveness of interventions; however, we do not include productivity costs. If these costs are considered in NICE Guidelines, those interventions aimed at the working population would be favoured and we would discriminate against older people, children, the unemployed and those who are unable to work.

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			HRT, testosterone, antihistamines, epipen, steroids, painkillers, diuretics etc. could be finished once alternative thyroid treatment instead of just Levothyroxine, was commenced and optimal. • Many thyroid patients with low T3 are usually suffering from 'gastric acid' and prescribed PPI's (proton pump inhibitors) such as Omeprazole and Lanzaprazole or Ranitidine (an H2-Receptor-Blocker). As hypothyroidism slows the metabolism down, without adequate thyroid therapy medication, this means that the body's ability to generate enough bile acid to digest food also slows down. So 'gastric acid' could mean that hypothyroid patients have low stomach acid and not as most doctors assume, too much stomach acid. PPIs have various side effects and once a diagnosis of low stomach acid is confirmed, PPIs can be reduced or completely eliminated. ITT would like the scope to recognise that the current medical guidelines that advise doctors to only prescribe enough thyroid hormone to maintain a normal TSH are wrong and outdated and leaves many patients deficient in T3, who then cannot lead a normal functioning life. ITT agrees that the scope should extend to consideration of other treatment options including T3 only and thyroid extracts/natural desiccated thyroid (NDT). • There is clinical evidence to support T4/T3 combination and T3 only therapies and that natural desiccated thyroid is safer and more effective than T4 only products. • Substantial evidence shows that enormous numbers of hypothyroid patients are disappointed with their T4-replacement therapy. The experience of hypothyroid patients feeling better when they switched from a T4 only treatment to a treatment containing T3 is supported by patient stories and patient survey data evidence in other parts of the world. • The Thyroid Foundation of America conducted a survey of	

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			patients whose thyroid glands had been removed. The majority were dissatisfied with their treatment. • One of the advantages frequently reported through patient stories is that NDT does not contain ingredients they react to. Given the majority of thyroid dysfunction is autoimmune related this is especially important to many patients. For instance, many synthetic T4 (L-T4) ingredients include acacia, confectioners' sugar, lactose, magnesium stearate, povidone, talc and colour additives. Most of the synthetic thyroid medications contain more other ingredients than NDTs e.g. lactose, and some of these are problematic for our members. (8 line 223). Doctors often prescribe thyroid medications without mentioning what other ingredients they contain and considering the impact these might have on the patient's health. • Sensitivity to 'other ingredients' in other medications and supplements that support thyroid health is an issue for many thyroid patient I. Treating Thyroid patients like children. Dr Malcolm Kendrick https://drmalcolmkendrick.org/2015/05/01/treating-thyroid-patients-like-children/ II. Gautam Das, Shweta Anand & Parijat De. Does synthetic thyroid extract work for everybody? Endocrine Abstracts (2007) P316 III. The T4/T3 Thyroid Drug Controversy Mary Shomon. https://www.verywell.com/the-t4t3-thyroid-drug-controversy-3233185 IV. Alan R. Gaby, MD. Sub-laboratory Hypothyroidism and the Empirical use of Armour Thyroid. (Altern Med Rev 2004;9(2):157-179) V. Thyroid Insufficiency: Is Thyroxine the Only Valuable Drug? Baisier, W.V., Hertoghe, J., and Eeckhaut, W. Journal of Nutritional and Environmental Medicine, 11:159-166, 2001. http://www.tandfonline.com/doi/abs/10.1080/135908401200	

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			83376 VI. Taylor, S., Kapur, M., and Adie, R.: Combined thyroxine and triiodothyronine for thyroid replacement therapy. Brit. Med. J., 2:270-271, 1970. http://www.nejm.org/doi/full/10.1056/NEJM199902113400603#t=article VII. Tigas,S.,Idiculla,J.,Beckett,G., et al. :Is excessive weight gain after ablative treatment of hyperthyroidism due to inadequate thyroid hormone therapy? Thyroid, 10(12):1107-1111, 2000. https://www.ncbi.nlm.nih.gov/pubmed/11201857 VIII. Combination Treatment with T4 and T3: Toward Personalized Replacement. Therapy in Hypothyroidism? Bernadette Biondi, and Leonard Wartofsky J Clin Endocrinol Metab. 2012 Jul;97(7):2256-71. https://www.ncbi.nlm.nih.gov/pubmed/22593590 IX. Paradigm shifts in thyroid hormone replacement therapies for hypothyroidism. Wilmar M Wiersinga. Nature Reviews Endocrinology 10, 164-174 (2014) www.nature.com/nrendo/journal/v10/n3/abs/nrendo.2013.258.html X. Effects of thyroxine (T4) as compared with thyroxine (T4) plus triiodothyronine (T3) in patients with hypothyroidism. Benevicius R, Kazanavicius G, Zalinkovicius R, Prange AJ New England Journal of Medicine.1999; 340: 424-9. http://www.nejm.org/doi/full/10.1056/NEJM199902113400603 XI. Peripheral markers of thyroid function: the effect of T4 monotherapy vs T4/T3 combination therapy in hypothyroid subjects in a randomized crossover study. Schmidt U. 2013. https://www.ncbi.nlm.nih.gov/pubmed/23781319 XII. Stability, Effectiveness, and Safety of Desiccated Thyroid vs Levothyroxine: A Rebuttal to the British Thyroid Association. Dr. John C. Lowe. 2009. http://www.thyroidscience.com/Criticism/lowe.3.16.09/lowe.bta.rebuttal.3.16.09.pdf	

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Improve Thyroid Treatment Campaign Group	7	189	*"3.2 How should hypothyroidism be monitored? "* ITT believes monitoring of hypothyroidism should be conducted using patient signs and symptoms and a broad set of clinical tests (see line 111). We recommend that the scope includes thyroid tests on diagnosis for all thyroid hormones; Free T4, Total T4, Free T3, Total T3, Reverse T3 and thyroid antibodies, vitamin and mineral levels. TSH is not an accurate measure of thyroid function and should not be used in isolation. The use of a broader set of tests will improve the accuracy of diagnosis and management, improving patient outcomes, and will reduce the number of repeat visits to primary care or onward referral to secondary care. Patient insight is invaluable in thyroid disorder where, because of the range of symptoms, no patient health impact is the same. Where TSH is used, ITT recommends the use of a lower reference range upper limit to trigger the consideration with the patient of thyroid hormone replacement. I. Patients' attitudes and perceptions towards treatment of hypothyroidism in general practice: an in-depth qualitative interview study Rosie Dew, PhD, Kathryn King, PhD, Onyebuchi E Okosieme, MD, FRCP, Simon Pearce, PhD, MD, FRCP, Gemma Donovan, MSc, Peter Taylor, MSc, MBChB, Graham Leese, MD, FRCP, Janis Hickey, BA,Salman Razvi, MD, FRCP, Colin Dayan, PhD, FRCP, Scott Wilkes, PhD, FRCGP. Journal of General Practice; DOI:10.3399/ bjgpopen17X100977 http://bjgpopen.org/content/bjgpoa/early/2017/06/26/bjgpopen17X100977.full.pdf	Thank you for your comment. The guideline will seek to address appropriate monitoring of people with thyroid disease.
Improve Thyroid Treatment Campaign	7	191	*What is the clinical and cost effectiveness of using radioactive iodine vs antithyroid drugs vs surgery to treat thyrotoxicosis secondary to Graves' disease*?	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of management options for thyrotoxicosis including RAI.

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Group			Initial treatment for Hyperthyroidism and/or Graves tends to be beta-blockers or antithyroid drugs [ATDs], Carbimozole in particular. Most patients respond well to this treatment with low instances of side effects of only 3 -5 % It has been suggested that the long term use of ATDs is not advisable as usage is likely to cause adverse side effects. There is evidence of this in our Patient stories. However, this is deemed no longer true. For a number of patients on Carbimazole the addition of levothyroxine, (or other thyroid drug, L-T3 or NDT) may be an option used to balance the blocking effect, and reduce the risk of heart dysfunction. Alternatively a change of medication to propylthiouracil may be warranted. If propylthiouracil is administered the patient will need regular checks for liver problems. Patients who cannot tolerate Carbimozole will need to discuss this with their physician and agree a long-term treatment option. Carbimazole is not recommended in the first trimester of pregnancy. Propylthiouracil is usually issued instead. So if propylthiouracil is prescribed, patients should undergo a liver function test prior to start of medication with regular assessments throughout treatments. When ATDs work, duration of treatment is undefined and can vary widely. One study showed that 46% of patients went into remission after an average treatment period of eighteen months. Another study showed that a second course of treatment with ATD could also be effective, putting 75.78% of patients into 'permanent' remission. Many patients remain on ADTs, PTU aside, for many years, without adverse effects. However remission is not achievable for all Graves' sufferers. Their long-term treatment must be considered carefully.	

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			For these patient RAI and/or surgery may be the only options. Neither of these options guarantees optimal health. Marcocci et al [1990] discuss a retrospective evaluation of "The outcome of radio iodine therapy of Graves' hyperthyroidism" in respect of patients treated between 1975 and 1984. After 1 year 36.9% of patients were considered to be permanently hypothyroid. Only 42% of patients achieve euthyroid state following RAI treatment. 4% would be expected to remain hyperthyroid, the other 54% remained hypothyroid. It must be recognized that most patients rendered hypothyroid, by either RAI or surgery, never feel that they fully regain their health, even when a biochemical euthyroid state is achieved. This fact, and the life long cost, to the NHS, of a patient being hypothyroid, raises the question of the cost effectiveness of RAI treatments. ITT feel clinicians must fully inform their patients of the risks of becoming hypothyroid and not brush this condition off with blasé statements such as, "it will be fine, hypothyroidism is easily treated with one little pill everyday and you will be back to your old self" as this is, very often in our experience as a patient group, proved not to be the case for post RAI. Post surgery patients are often told the same and again have similar unsuccessful recovery. This lack of recovery is thought, by patients, to be the consequence of inadequate replacement therapy, with the use of levothyroxine [L-T4] mono therapy. Few find their way back to health. The thyroid produces approximately 80% T4 and 20% T3 hormone. L-T4 is not physiologically equivalent to natural hormone replacement, as it does not contain T3. The T4 produced by the thyroid has to convert to T3 to be used at the cellular level. Where patients have no thyroid or conversion inability L-T4 will not be processed correctly. Therefore L-T3 is required.	

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			Patients need to have their T3 levels tested, along with TSH and T4, following RAI or total thyroidectomy, to check and correctly treat the deficit due to their lack of natural thyroid. Patients seem to be actively encouraged to have definitive treatment rather than long term ATD treatment. Carbimazole has been subject to price increases. Does this have bearing on the other options being suggested to patients? When balancing the complexities of follow up care, after RAI or Surgery, the cost of treatments: long term ATDs vs RAI/surgery + the likelihood of long term hypothyroid treatment, it may prove to be more cost effective to treat Graves' disease with long term ATD plus regular monitoring. Patients have submitted stories to ITT describing the horrendous health issues they have been left with following RAI or surgery, or both. Many are fending for themselves, as doctors refuse to issue anything but L-T4 treatment as hormone replacement. ITT feels patients are being neglected and mistreated. When L-T4 proves unsuccessful patients must have alternative treatment options available. This has to be L-T3 and NDT. T3 levels must be sought and considered, and replacement to the upper quartile issued where necessary. Patients must be fully informed of all possible consequences following RAI or surgery treatments. You have Graves' disease and had Radioactive Iodine (RAI) or a Thyroidectomy. Now What? Dana Trentini [2014] http://hypothyroidmom.com/you-have-graves-disease-and-had-radioactive-iodine-rai-or-a-thyroidectomy-now-what/	

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			Combination Treatment with T4 and T3: Toward Personalized Replacement Therapy in Hypothyroidism? Bernadette Biondi Leonard Wartofsky [2011] https://academic.oup.com/jcem/article/97/7/2256/2833962/Combination-Treatment-with-T4-and-T3-Toward A reappraisal of the role of methimazole and other factors on the efficacy and outcome of radioiodine therapy of Graves' hyperthyroidism Claudio Marcocci, D. GianchecchiI. MasiniF. Golia C. CeccarelliE. Bracci G. F. Fenzi A. Pinchera [1990] https://link.springer.com/article/10.1007/BF03348615 Effect of long-term continuous methimazole treatment of hyperthyroidism: comparison with radioiodine. Azizi F1, Ataie L, Hedayati M, Mehrabi Y, Sheikholeslami F [2005] https://www.ncbi.nlm.nih.gov/pubmed/15879354 Propylthiouracil-induced liver failure and artificial liver support systems: a case report and review of the literature Dong-Bo Wu, En-Qiang Chen, Lang Bai, and Hong Tang [2017] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5238756/ Predicting relapse of Graves' disease following treatment with antithyroid drugs LIN LIU, HONGWEN LU, YANG LIU, CHANGSHAN LIU, and CHU XUN [2016] [Accessed 10/11/7] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4812122/ A second course of antithyroid drug therapy for recurrent Graves' disease: an experience in endocrine practice Xiaomei Liu,* Wei Qiang,* Xingjun Liu, Lianye Liu, Shu Liu, Aibo Gao, Shan Gao, and Bingyin Shi [2015] https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4321192/	

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Improve Thyroid Treatment Campaign Group	7	202	*"When surgery is indicated what is the most clinical and cost-effective way of using surgery to treat thyrotoxicosis (e.g. total vs subtotal thyroidectomy)?"* When considering surgery, the primary concerns are to eliminate thyrotoxicosis and / or remove a goitre that is dangerously large. When considering surgery for thyrotoxicosis a primary concern must be to attempt to avoid hypothyroidism. There are many risk factors that need consideration when contemplating surgery. Complications including • infection, • bleeding in the neck, which tends to affect 1 in 30 patients and can need urgent surgery to rectify. • Seroma, a fluid collection under the incision which if doesn't self-correct needs draining. • Voice change, surgery can affect the recurrent laryngeal nerve and superior laryngeal nerve, which in nearly 2% of cases can cause voice loss or permanent damage. Although temporary changes to the voice are more common, affecting up to 10% of patients for up to 6 months. Damage is generally less pronounced in subtotal thyroidectomies. Although if initially a subtotal thyroidectomy is carried out, but the problems are not resolved / return, there are increased risks of surgery complications. • Hypoparathyroidism, also known as transient hypocalcaemia, is a common complication of surgery, although it is rare to affect the patient long term. In 70% of patients, within 2 months the parathyroid glands were functioning normally. Only 1.9% of patients are left with permanent symptoms and needing calcium supplementation. Following all thyroidectomy surgery, it is recommended that the patient supplement with calcium for the first 6 weeks. A blood test should be taken at the 2 months stage to check the function of the parathyroid.	Thank you for your comment. When considering the clinical and cost effectiveness of surgery, all relevant costs and consequences, in both the short and long term, will be considered including complications.

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			Views on best practice vary considerably with respect to what is most highly recommended. As stated in the following document, it is common to recommend total thyroidectomy for permanent resolution of thyrotoxicosis. Although, as noted, no consideration is given to the fact that total thyroidectomy always renders a patient hypothyroid. Whereas with subtotal thyroidectomy there is a chance that the patient may achieve euthyroid status. To dismiss this chance, due to probably cost effectiveness long term, is misguided. It is not acceptable to intentionally replace one chronic condition with another. ITT recommends that all options and outcomes are discussed at length with the patient and that a subtotal thyroidectomy should come most highly recommended. I. Safety and effectiveness of total thyroidectomy and its comparison subtotal thyroidectomy and other thyroid surgeries: a systematic review. Ashwini Aithal Padur 2016 II. https://www.hindawi.com/journals/jtr/2016/7594615/ III. A second course Subtotal and near total versus total thyroidectomy for the management of multinodular goitre. M Vaimen 2008. https://www.ncbi.nlm.nih.gov/pubmed/18340482 IV. Hypoparathyroidism after Total Thyroidectomy: Incidence and Resolution Kathryn Ritter BA BS 2015 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4466142/	
Improve Thyroid Treatment Campaign Group	7	205	*"4.6 How should thyrotoxicosis be monitored? "* Whatever treatment options are decided on, monitoring should continue until the patient is stabilised. Patients report that once they have had radioactive iodine treatment to destroy their thyroid, or surgery to remove their thyroid, they are typically given levothyroxine (L-T4) as a thyroid hormone replacement, and there is no further follow up to ensure that this treatment is adequate and optimising health. Many patients report that the consequences of treatments were not explained. They were told that all they would need would	Thank you for your comment. The guideline will seek to address appropriate monitoring of people with thyroid disease.

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			be one pill a day to replace the thyroid function, and do not understand the consequences of L-T4 monotherapy. There is no explanation provided to patients of the possibility of a non-conversion of L-T4 and there is usually no consideration of the need for T3. T3 is a vital addition for those who are unable to produce their own hormones. L-T4 is not physiologically equal to the naturally output thyroid hormones, being an inactive hormone. L-T3 or NDT is vital for those who cannot convert L-T4. Patients who have undergone radioactive iodine treatment need to be monitored to ensure that existing thyroid eye disease is kept under control, and where not present, to monitor for initiation.	
Improve Thyroid Treatment Campaign Group	8	212 -214	*"6.1 What information should people with thyroid disease, their family and carers receive?"* ITT advocates that the current information provided to patients, families and carers needs to be completely reviewed. Patient stories evidence the current complete lack of information and support in the primary care. ITT recommends that the information for patients that is designed for the thyroid disease review be informed by patients, through surveys and feedback. Many Thyroid patients have problems with their NHS treatment and over 67,000 consult Thyroid UK patient advocacy groups. This can be compared to diabetes patients where in contrast Health Unlocked diabetes group only has 8,000 members; Diabetics guidance and care in the system is much more comprehensive than that for Thyroid patients'. ITT recommends that the scope should incorporate the need for information to be comprehensive for both medical professionals and patients, sufficiently informative to encourage and enable patients to manage their own care, and allow patients to discuss their condition with family and work. Stories given to ITT by patients of their experiences with thyroid disease have demonstrate the lack of information provided; • On subclinical diagnosis	Thank you for your comment. The guideline will seek to address appropriate information to provide people with.

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			• On diagnosis • Before and after surgery and RAI. • At the beginning of pregnancy for RAI treated women to make aware of risk of hyperparathyroidism and need for screening • Over the duration of their disease • GP appointments do not allow enough time for adequate information on their condition to be provided • Patient access to paper or online thyroid blood tests and medical records is poor and does not allow patients to manage their condition ITT believes that the scope should incorporate the following; • Professionals in both primary and secondary care need training in the complexities of the thyroid so that they become knowledgeable about its physiology. The GMC curriculum simplifies the problems that many patients with thyroid problems encounter. • The GMC curriculum needs to be updated to take account of current knowledge so that students can recognise these symptoms alongside blood testing • More traditional or "Old-fashioned" methods such as palpation of the neck, lower than normal pulse and temperature and testing of the Achilles tendon should be brought back, to the benefit of patients • Thyroid patients should be invited to medical schools to give their experience of the disease and their treatment in the system • Persistent symptoms that patients experience should trigger further testing, FT3, FT4, RT3 - Vitamin D & B12 and thyroid antibodies, if not already addressed • Tests of FT3, FT4, Vitamin D & B12, ferritin and folate all need to be optimal to work effectively (line 172). A test of the DIO2 should be considered when patients remain symptomatic on a T4 based hormone replacement treatment	

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			option. • Alternative treatment options should be explained • Testing Laboratories should also receive the patient information to put their work into context. Many laboratories over rule GPs and do not complete thyroid tests requested • Patient experience is that subclinical diagnosis can leave patients in ill health for many years and GP's should be aware of the consequences and engage with the patient on treatment options at an early stage. Patients frequently do not have their subclinical status explained to them and they are left bewildered or worried by their undiagnosed symptoms or being sent for further clinical investigations. ITT supports earlier monitoring and treatment to ensure a better quality of life outcome for patients. • Patient expertise in their own signs and symptoms should be accepted when discussing diagnosis, monitoring and treatment. • The information given to patients should reflect the latest state of worldwide research on the thyroid. A mechanism to ensure the latest information is provided to both professionals and patients is essential. The scope should reflect there is now an abundance of information on the internet from Patient UK, Nice CKS guidelines and the Thyroid patient advocacy groups. GP's, Endocrinologists and Surgeons should all have resources on hand to refer patients to. Information can be available in leaflet form, on the internet, in videos, or help-lines. Information needs to include • The type of problems people can encounter when first taking hormone replacement. Until the body adjusts to the thyroid medication and they are at optimal dose, euthyroid, patients could experience hair loss, constipation, depression, skin and nail abnormalities, muscle weakness, joint pain, tinnitus, weight gain, drier skin, poorer memory, slower thinking, greater tiredness, more muscle cramps, cold/heat sensitivity,	

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			deeper and hoarser voice, puffier eyes whilst achieving their optimum dose over a period of a few months. This should help explain to families that the problems encountered are real and have a clinical basis • The timing of dosing should be explained (at least an hour before eating or 2 hrs after to allow the medication to be absorbed into the system) • Some people have found taking T4 before going to bed provides improvement especially when trying to schedule taking vitamin and minerals away from thyroid hormone replacement • Patients need to understand that it is a slow process getting back to full health, refer to line 120 & 172 • Initial testing whilst adjusting dose should be carried out 12 - 24 hrs from last thyroid dose, to allow consistent comparison, taking Thyroid hormone after blood test. Refer to line 111 of this submission for testing required • Explanation of test results and how to obtain results. Primary care should ensure that patients who are managing thyroid dysfunction have access to paper copy or online records • Subsequent diagnosis of additional autoimmune diseases, e.g. arthritis should be recognised as possible effects of under dosing or need for T3 in Hashimotos autoimmune patients for example • If antibodies are also above range when tested, advice on the effect of gluten, dairy, soy and fluoride on the thyroid should be available, as elimination has proved beneficial, refer to line 138. • Information on the full range of treatment options should be available to patients I. Many relevant research papers support the benefit of patient information https://stopthethyroidmadness.com/medical-research/.	

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			II. "Hands, ears and eyes of the thyroid clinician are cost-effective tools to evaluate thyroid. Thus, despite the elegance of today's thyroid function tests their proper use and interpretation still require careful observation of the patient's symptoms and signs and assessment of the overall clinical situation of the patient." (8,9) http://www.journalrmc.com/volumes/1394805078.pdfobservation III. Hypothyroid Patients Encoding Combined MCT10 and DIO2 Gene Polymorphisms May Prefer L-T3 + L-T4 Combination Treatment – Data Using a Blind, Randomized, Clinical Study Carlé A.a · Faber J.c,d · Steffensen R.b · Laurberg P.a · Nygaard B.c,d HypothyroidismThyroid failureSingle nucleotide polymorphismsL-T3 treatmentRandomized clinical trial IV. Effects of low-carbohydrate diet therapy in overweight subject with autoimmune thyroiditis: possible synergism with ChREBP I.Authors Esposito T, Lobaccaro JM, Esposito MG, Monda V, Messina A, Paolisso G, Varriale B, Monda M, Messina G Received 15 February 2016 Accepted for publication 11 May 2016 Published 14 September 2016 Volume 2016:10 Pages 2939—2946 DOI https://doi.org/10.2147/DDDT.S106440 V. http://drflannery.com/study-confirms-autoimmune-paleo-aip-diet-works/ VI. http://www.eurothyroid.com/files/download/Wiersinga-EDITORIAL-ETJ-2015-4-438909.pdf Guidance in Subclinical Hyperthyroidism and Subclinical Hypothyroidism: Are We Making Progress? Wilmar M. Wiersinga Department of Endocrinology and Metabolism, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands	
Improve Thyroid Treatment	8	212-214	*"6.1 What information should people with thyroid disease, their family and carers receive?"*	Thank you for your comment. The guideline will seek to address appropriate information to provide people with. Pregnancy has not

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Campaign Group			Regarding the impact of RAI induced hyperparathyroidism, the outcomes in pregnancy can be extremely serious, even fatal, and the apparent lack of any established policies or guidelines regarding screening for this post RAI is very concerning. ITT consider that the development& promotion of in patient information pre & post RAI & for pregnancy requires inclusion in the scope. II. Post RAI development of hyperparathyroidism in women https://www.ncbi.nlm.nih.gov/m/pubmed/17693276/ "In this collective experience, the average latency time to the development of HPT after RAI treatment was 13.5 +/- 9.1 years and was found to be inversely correlated with age at RAI exposure." III. https://www.ncbi.nlm.nih.gov/m/pubmed/2588108/?i=7&from=/6689566/related "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. IV. Consequences of maternal hyperparathyroidism http://onlinelibrary.wiley.com/doi/10.1111/j.1365-2265.2008.03495.x/abstract "Conclusions HPT during pregnancy is under recognized and is associated with a 3·5-fold increase in miscarriage rates. Pregnancy loss often occurs in the second trimester and is associated with multiple miscarriages when not addressed. Pregnancy loss is more common as calcium levels exceed 11·4 mg/dl (2·85 mmol/l), but can be seen at all elevated calcium levels. Emphasis is placed on earlier recognition and surgical	been included because there will be a new green top guideline on thyroid disease in pregnancy produced by the Royal College of Obstetricians and Gynaecologists.

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			cure before becoming pregnant, however, once pregnant, surgery should be offered early in the second trimester for those with calcium levels above 11·4 mg/dl." V. http://www.parathyroid.com/pregnancy.htm "Hyperparathyroidism (parathyroid disease with high calcium) occurring during pregnancy is a very serious problem. Hyperparathyroidism during pregnancy puts both the mother and child's life at risk, and the chance for life-long calcium problems for the child exists. Hyperparathyroidism during pregnancy is treated with mom's surgery during the late first or early second trimester.	
Improve Thyroid Treatment Campaign Group	8	207	*"5.1 What is the clinical and cost effectiveness of treating subclinical hypothyroidism?"* ITT believes significant savings can be achieved by treating currently "subclinical" patients. A subclinical diagnosis (or lack of diagnosis) can leave patients in ill health for many years. ITT and thyroid support groups evidence that patients have a reduced quality of life that include giving up work, reducing work hours, being made redundant because of absence due to hypothyroid symptoms, or companies incurring occupational health review costs, additional costs are currently incurred to Department of Work and Pensions due to underemployment of "subclinical patients" resulting in their claiming benefits, underemployment of their families who are acting as carers, both resulting in less revenue for HMRC and less productivity. Further costs can also be incurred in supporting young and elderly dependants of these patients and their families. There is also considerable evidence that patients are also costly on primary and secondary health care because of investigations into the symptoms of hypothyroidism. Costs of supporting undertreated patients include; patients being sent to inappropriate support clinics e.g. fibromyalgia, ME / CFS, gastroenterology, cardiology,	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of diagnostic options. An NHS and personal and social services perspective will be adopted when assessing the cost effectiveness of all areas in the guideline.

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			neurology, psychiatry, rheumatology and gynaecology. The cost is then compounded by inappropriate prescriptions to suppress signs and symptoms, painkillers and treatments, which can inadvertently exacerbate the hypothyroid state. ITT believe subclinical is simply a grade of hypothyroidism it makes economic sense to monitor based on tests and patient symptoms, family profile (hereditary) and contributing risk factors, and discussion of treatment with patients. Alongside monitoring and treatment; assessing antibodies to ensure any new regimes and health care approaches, are reducing the autoimmune action; advising patients regarding autoimmune protocols; ensuring all vitamins and minerals are optimal; identifying dietary triggers are examples, which can result in significant reduction of the costs of sustained intervention and improved long-term clinical outcome.	
Improve Thyroid Treatment Campaign Group	8	209	*5.2 What is the clinical and cost effectiveness of treating subclinical thyrotoxicosis?* It is thought that some thyrotoxicosis is self-limiting. It may be caused by viral infections or other illness. Monitoring reoccurring subclinical thyrotoxicosis is important to identify early signs of Graves' ophthalmology. There is also research that shows that subclinical thyrotoxicosis carries a greater risk of atrial fibrillation. (Fatourechi:2001) Therefore close monitoring of this condition is necessary. Antithyroid medication should be considered to balance the thyroid function. I. Adverse effects of subclinical hyperthyroidism. Vahab Fatourechi [2001] http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(01)06036-6/fulltext ITT considers subclinical thyrotoxicosis to be simply a grade of thyrotoxicosis and should be treated with the same considerations	Thank you for your comment. The guideline will seek to address appropriate treatment of subclinical thyrotoxicosis.

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			as overt thyrotoxicosis. Subclinical thyrotoxicosis causes the same symptoms as overt. ITT considers that it is false economy to ignore subclinical thyroid disease of any sort. Early diagnosis and treatment should lead to earlier and possibly more likely remission of symptoms. To this end ITT believes treatment with anti-thyroid drugs (ATD) should be given full consideration balanced with thyroid hormone replacement to control the patients' debilitating symptoms and the long-term risks.	
Improve Thyroid Treatment Campaign Group	8	211	*"5.3 How should subclinical thyroid dysfunction be monitored?"* It is estimated that 8% of women and 4% of men have subclinical hypothyroidism using the current testing ranges. Evidence supports the impacted patient cohort is higher if the reference ranges are lowered to comparative levels used in America and Europe. ITT believes subclinical thyroid dysfunction should be approached simply as a scale of hypothyroidism. Patients will experience many of the symptoms of hypothyroidism. This means that many of the issues associated with poor thyroid function are still present among those with subclinical hypothyroidism. Those patients who experience subclinical hypothyroidism may have symptoms that reduce their quality of life. Clinical papers and reports indicate an association between subclinical hypothyroidism and poor outcomes of pregnancy, as well as atherosclerosis, dyslipidemias, atherogenesis, and increased mortality in the long term. The most prominent danger of subclinical hypothyroidism is that it can go on for many years without diagnosis and treatment. ITT believes these consequences are sufficiently compelling to warrant screening and treatment with hormone replacement when found, to halt progression to overt hypothyroidism, and improve symptoms, pregnancy outcomes, lipid abnormalities, and cardiovascular function. ITT considers patient signs and symptoms; gender and age should be considered equally as important as clinical tests in the treatment. Patients are experts in their own symptoms and signs and can provide a useful source of information to assist with monitoring and treatment. ITT believes that	Thank you for your comment. The guideline will seek to address appropriate monitoring of subclinical thyroid dysfunction.

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			early diagnosis of subclinical thyroid disorders is essential to ensure progression to overt hypothyroidism is not left untreated, to prevent the symptoms set out at line 29 - 30. The American Association of Clinical Endocrinologists state that patients with TSH levels between 3 and 5 should be watched closely and monitored because it may signal a deteriorating thyroid condition. A study by Pacchiarotti A, et al (1986) indicates that FT4 should be measured in addition to TSH for the diagnosis of impending thyroid failure, and showed that in many cases patients with so-called subclinical hypothyroidism are actually already mildly hypothyroid. ITT recommends that the monitoring commence at a lower level, 2.0mIU/l and where a lower T4 level is present, to ensure adequate monitoring. At present, ITT understands that there is no clinical guidance for primary care about sharing the potential for thyroid disorder with patients. Patient experience stories evidence poor quality of life outcomes with many leaving work or reducing work hours, suffering miscarriages, or being under investigation for a range of symptoms in primary and secondary care. ITT advocates communication and sharing of information with patients to allow informed patients to be more engaged in lifestyle changes, treatment options and manage their own health. ITT asks that the scope include communication to patients of a subclinical status. I. Subclinical hypothyroidism is associated with increased risk of adverse pregnancy complications including preterm delivery and placental abruption with an increased risk of neurocognitive deficits in the developing foetus. https://doi.org/10.1210/jc.2009-2009 II. Studies suggest a relationship between higher levels of maternal TSH and pregnancy loss. https://www.ncbi.nlm.nih.gov/pubmed/20534758 The largest study investigating the association of maternal hypothyroidism and premature delivery was performed by Casey et al. https://www.ncbi.nlm.nih.gov/pubmed/17470594 Although this	

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			trial shows no benefit in obstetric outcomes, treatment did not start until 20 weeks, so too late for treatment benefit, although miscarriage rates are still lower in the treated group, but not statistically significant. If treatment were started earlier the benefit would have been shown to be far greater. ITT recommends that subclinical hypothyroidism be treated in pregnancy if the TSH concentration is greater than 2.5 mU/L. III. Andersen S, Petersen KM, Brunn NH, Laurberg P (2002). Narrow individual variations in serum T4 and T3 in normal subjects: a clue to the understanding of subclinical thyroid disease. Journal of Clinical Endocrinology and Metabolism. 2002;87:1068–72. IV. Pacchiarotti A, Martino E, Bartalena L, Aghini Lombardi F, Grasso L, Buratti L, Falcone M, Pinchera A (1986). Serum free thyroid hormones in subclinical hypothyroidism. Journal of Endocrinological Investigation. 1986 Aug;9(4):315-9.	
Improve Thyroid Treatment Campaign Group	8	220	*"Quality of Life"* ITT recommends that this should include not only the patient but consider ramifications of the patient's health on work and career, family and carer quality of life. ITT advocates the use of patient surveys and stories to provide input on the impact to quality of life.	Thank you for your comment. Quality of life is an important outcome across all NICE guidelines for assessing both clinical and cost effectiveness; however, it is worth noting these are the main outcomes and not an exhaustive list Additional outcomes that will be more specific to each evidence review will be considered on a case by case basis as the protocols are established.
Improve Thyroid Treatment Campaign Group	8	223	*"Adverse effects of treatment"* ITT patient stories and review of clinical papers indicate adverse effects of treatment included below. • Long term consequences of over medication of levothyroxine can, if not corrected, have implications including osteoporosis and cancer • Adverse effects can occur when a patient generic brand is	Thank you for this information. The committee will agree specific outcomes for each question when the review protocol is drafted.

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			changed. Patient stories evidence that they do better on some brands of generic than others. This is because of the fillers, which autoimmune patients can react to. This was demonstrated recently by French patients who objected to the change in formulation of one brand, Merek, of levothyroxine. The results of that change in filler included hair loss, cramps, weight gain, extreme fatigue, headaches, diarrhoea, dizziness, memory loss, and heart palpitations. In the UK brands of levothyroxine have similarly been removed and the incident of yellow card reports is increasing • Adverse effects of long term under prescribing of T4 or not prescribing T3 as a combination with T4 in order to keep patients' TSH at the higher end of the reference range thereby keeping them subclinical with the associated consequences set out line 2 29-30 • Recent emphasis in several studies has also shown that low T3 levels are implicated in cardiac disease, chronic kidney disease, and liver disease. ITT patient stories evidence that many thyroid patients with low T3 are usually suffering from 'gastric acid' and prescribed PPI's (proton pump inhibitors) such as Omeprazole and Lanzaprazole or Ranitidine, which is an H2-Receptor-Blocker, • The impact of RAI induced hyperparathyroidism, the outcomes in pregnancy can be extremely serious, even fatal, and the apparent lack of any established policies or guidelines regarding screening for this post RAI is very concerning (references as line 212 – 214) I. Umberto Cornelli. Levothyroxine and lung cancer in females: the importance of oxidative stress. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3765368/ II. Adverse Event Reporting in Patients Treated with Levothyroxine: Results of the Pharmacovigilance Task Force Survey of the American Thyroid Association, American Association of Clinical Endocrinologists, and The Endocrine	

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			Society. James Hennessey, Alan Malabanan, Bryan Haugen, and Elliot Levy (*2010*) Adverse Event Reporting in Patients Treated with Levothyroxine: Results of the Pharmacovigilance Task Force Survey of the American Thyroid Association, American Association of Clinical Endocrinologists, and The Endocrine Society. Endocrine Practice: May 2010, Vol. 16, No. 3, pp. 357-370. https://doi.org/10.4158/EP0362.OR III. Duffy, E.P.: Stability of levothyroxine sodium products, 2006. http://www.fda.gov/ohrms/dockets/ac/06 /slides/2006-4228S1-01-04-Eric%20Duffy%20 slides .pdf IV. Lowe, J.C.: Thyroid hormone replacement therapies: ineffective and harmful for many hypothyroid patients. Thyroid Science, 1(1):C1-21, 2006. http://www .thyroidscience.com/Criticism/lowe.dec.2006/t4%20vs%20t4t3%20studies.htm V. Singh,S et al: Impact of subclinical thyroid disorders on coronary heart disease, cardiovascular and all-cause mortality. https://www.ncbi.nlm.nih.gov/pubmed/17434631 VI. Duggal A, et al: Cardiovascular risk with subclinical hyperthyroidism and hypothyroidism: pathophysiology and management. https://www.ncbi.nlm.nih.gov/pubmed/17786084 VII. https://www.gov.uk/drug-safety-update/teva-levothyroxine-100-microgram-tablets-suspension-of-marketing-authorisation VIII. https://info.mhra.gov.uk/drug-analysis-profiles/dap.html?drug=./UK_EXTERNAL/NONCOMBINED/UK_NON_000435224532.zip&agency=MHRA	
Midlands Thyroid Support Group	General	General	No mention is made in the scope of the likelihood of developing other diseases when autoimmune illnesses are linked. Costs of non-treatment are likely to increase the overall patient life costs to the NHS. This should be considered for patient guidance, education of consultants and access to treatment.	Thank you for your comment. The Guideline Committee will consider including the development other diseases as an outcome for applicable reviews. Relevant costs will be considered for each of the review questions.
Midlands Thyroid	General	General	Thyroid hormones are needed in every cell in the body - by having an Endocrine Speciality Department in hospitals that deal with the	Thank you for your comment. The effects of thyroid dysfunction throughout the body will

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Support Group			thyroid only is missing the point. Low T3 affects mood, fertility and miscarriages, can be a cause of chronic heart failure, chronic kidney disease and many more. A lot of symptoms are missed and dismissed because of adherence to mainly TSH testing, which is a pituitary hormone, without exploring what the real thyroid hormones T4, an inert prohormone and T3 the biologically active hormone levels are. It has never been mentioned that magnesium, selenium and zinc levels are important in making sure that thyroid hormones have enough 'partners' to ensure euthyroidism. **NB Links to studies relating to comments made in points 15 – 19 inclusive ('General') have not been included here but can be provided if required at this stage of the development process.**	be considered in the evidence reviews determining clinical effectiveness.
Midlands Thyroid Support Group	General	General	The Chief Medical Officer Dame Sally Davies has said that she would like everyone to have a genetic analysis so that in future disease management will improve and medications can be tailor made. This is urgently required in the cause of thyroid disease management. Totally missing from current management of thyroid issues is the acknowledgement of genetic polymorphisms. DIO2 polymorphism is now, or should be, widely acknowledged amongst Endocrinologists as having a profound effect on the conversion of T4 to T3. Those patients found to be homozygous for DIO2 should definitely be considered as suitable to trial a course of T3, or even NDT (natural desiccated thyroxine). Polymorphisms are also being discovered in thyroid transport enzymes.	Thank you for your comment. The role of genetic subgroups and the impact on treatment options will be considered as part of the evidence reviews on appropriate management of hypothyroidism.
Midlands Thyroid Support Group	General	General	Testing TSH levels alone and only looking at whether it is in range or not, and declaring that the patient should be 'normal' is an unacceptable way to treat hypothyroidism.	Thank you for your comment. The guideline will seek to cover aspects of thyroid disease investigation and monitoring.
Midlands Thyroid Support Group	General	General	Lifestyle change advice to be given at every thyroid diagnosis must include making sure that patients are gluten free. Fluoride, a known thyroid interrupter should also be avoided. Routine testing should include Ft3, Ft4, T3, T4, Reverse T3 TPO ab and Tg ab. Previously used tests (before the advent of TSH testing) were heel flexing,	Thank you for your comment. The guideline will consider the appropriate information to provide to people with thyroid disease.

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			palpating the neck and these should be used in conjunction with other tests. Drs looking at the TSH test may be waiting for the numbers to start rising and not consider that low thyroid TSH numbers (under 0.4) should also be considered for screening against possible hypopituitary problems.	
Midlands Thyroid Support Group	General	General	Women should be considered as a subgroup for equality purposes as 9 out of 10 thyroid patients are women; as should coeliac patients as more than 10% also have a thyroid co-morbidity which is above the normal background incidence in the general population of 2-3%. In 2009 the British Thyroid Association noted that 3% of the population have thyroid issues but in 2015 that had changed to 2%. The difference of 1%, though small equates to over 650,000 extra thyroid patients if the 3% holds true.	Thank you for your comment. The committee will consider the role of co-existing conditions and the impact on the evidence base on a review by review basis.
Midlands Thyroid Support Group	General	General	The good sense in the paper shown below shines out and should be taken into consideration by NICE. "Reducing the Scope of Guidelines and Policy Statements in Hypothyroidism" Eric K Pritchard JOM Vol28, No 2	Thank you for this information.
Midlands Thyroid Support Group	1	23/24	An enlargement of the thyroid gland is a clear sign of abnormality. The premise that "…normal thyroid function need no treatment", begs the question of - What is "Normal thyroid function? There is controversy regarding the results of the usual thyroid function blood tests (TFT's) and the levels required to diagnose why there is an enlargement of the gland, e.g. Thyroid Stimulating Hormone [TSH] Thyroxine [T4] and Triiodothyronine [T3]. A combined approach assessing clinical signs, symptoms, physical examination and TFT's should be used to diagnose whether the "normal thyroid function" requires treatment and monitoring as partially mentioned on Page 5, Line number 117.	Thank you for this information. It will be considered when the committee decide on the review protocols.
Midlands Thyroid Support Group	1	26	Hashimoto's thyroiditis is a complex autoimmune disease, the exact cause of which is not completely understood and still under research investigation, but is also known to have a genetic pre-disposition, in addition to other known factors such as environmental, viral infections, Epstein Barr Syndrome and other unknown factors.	Thank you for this information.

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			Having a close relative with known Hashimotos disease or other autoimmune disease increases the risk of developing the condition.	
Midlands Thyroid Support Group	2	29/30	"Long-term consequences of hypothyroidism include etc…", and increased risks of other auto-immune diseases such as vitiligo, rheumatoid arthritis, Addison's disease, type 1 diabetes, multiple sclerosis, pernicious anaemia, osteoporosis, coeliac disease.	Thank you for your comment. This is a brief introduction and not meant to be comprehensive. The clinical and cost effectiveness analyses will seek to include all relevant consequences of thyroid dysfunction.
Midlands Thyroid Support Group	2	46	Patients picked up "incidentally", whether symptomatic or not should have regular screening to monitor progression of their blood test results and/or symptoms.	Thank you for this information. The guideline will seek to address appropriate monitoring of thyroid dysfunction.
Midlands Thyroid Support Group	3	61	Not only are replacement strategies currently lacking, the only treatment offered is limited to a single medication, (T4) which does not suit all patients or those who have conversion issues such as the D102 gene fault. The T4 treatment offered may actually cause such patients to become more unwell.	Thank you for your comment. The guideline will seek to address the most clinically and cost effective management of hypothyroidism.
Midlands Thyroid Support Group	4	95/96	The Draft scope unfairly excludes stakeholder groups from commenting on thyroid disease in pregnant women due to a guidance draft currently being developed by the Royal College of Obstetricians & Gynaecologists (RCOG's). The experience of issues including miscarriage and fertility problems are well known and researched, and as NICE state that patient experience is equal to medical advice this should not be excluded. As a minimum, the impact on fertility and the high risk of miscarriage associated with thyroid disease must be included in this guidance. It should then be linked to the guidance being developed by the RCOG's, stating where additional information may be sought.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green top guideline on thyroid disease in pregnancy produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
Midlands Thyroid Support Group	4	104	'It may not be possible to make recommendations': At the NICE Question Time and Public Board Meeting held at Heartlands Hospital, Birmingham on 20th September 2017, NICE Chairman, Professor David Haslam, acknowledged that even without recommendations in the guidance, "no recommendation does not	Thank you for this information.

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			mean withdrawal of treatment and care". Primary care consultants should not use lack of guidance as evidence to withdraw support from patients.	
Midlands Thyroid Support Group	5	118/119	"Management of primary hypothyroidism" does not include other treatments such as gut function, liver/renal health, vitamin deficiency or methylation. These are distinctly different to the exceptions cited in line 138 as they are managed as clinical issues. "Treatment options" do not include Natural Desiccated Thyroid (NDT). This should be included as a scope option. NDT, once the mainstay of thyroid treatment from 1890's-1970's has been standardised in its thyroid hormone content and should once again be used, especially where heterozygous polymorphisms of the DIO2 gene are discovered. Currently NDT is not considered suitable as a treatment for hypothyroidism because it has hormone content in a ratio closer to 4:1 (that is T4:T3) whereas some research shows it to be 3:1.	Thank you for your comment. Dietary interventions were not prioritised as topics for inclusion during scope development. Thyroid extract is being considered as an intervention.
Midlands Thyroid Support Group	6	159 - 166	If guidance is cost driven then this should be made clear and should not preclude a consultant prescribing privately or importing to ensure access to the correct medication for the patient.	Thank you for your comment. The guideline would consider the clinical and cost effectiveness of treatments including anti-thyroid drugs, T4, T3, surgical and non-surgical procedures. Cost is one factor but not the only one. NICE guidelines only make recommendations with reference to NHS supply chains and costs and do not consider other sources for medications.
Midlands Thyroid Support Group	6	159	Economic aspects should ensure that procurement issues that artificially distort the benefit and value equation of additional treatment options such as Liothyronine (T3), NDT, Armour and other thyroid treatments are considered. Because T3 in the UK is excessively expensive, it is viewed as not good value, if pricing were corrected to EU and other countries market prices it would be viable. The price of T3 in the UK has ballooned from £14.92 per 100 tablets in 1997 to £258.20 per 28 tablets (3.5 boxes of 28 tablets = 98	Thank you for your comment. The guideline will seek to assess the clinical and cost effectiveness of treatment options for hypothyroidism.

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			tablets) costing £903.70 in 2017.	
Midlands Thyroid Support Group	7	186/187	The clinical and cost effectiveness of treating only with LT4 monotherapy is only relevant when the patient fully responds to it. If that is not the case, then patients should be trialled with LT3 alone or LT3 and LT4 combined or NDT and other thyroid extracts to assess which treatment is most suitable for them. The cost effectiveness of this can be monitored against the extra burden on the NHS in multiple GP visits, hospital referrals, inability to work therefore having to rely on benefits which can be the result of not prescribing the correct treatments.	Thank you for your comment. The guideline will seek to address the most appropriate management of primary hypothyroidism and the role of these options will be considered in this area.
Midlands Thyroid Support Group	8	207	Given ranges are significantly higher than other advanced countries in treatment and diagnosis, what are the longer-term impacts of not managing thyroid disease due to the term "sub-clinical"? Longer-term impact of non-treatment could exacerbate and increase complications in later life. Are UK testing ranges correct? (Clearly not, but even with current guidance there is huge misunderstanding in interpretation of results amongst clinical practitioners).	Thank you for your comment. The guideline will seek to address appropriate testing and treatment of subclinical hypothyroidism.
Midlands Thyroid Support Group	8	220, 221, 222, 223	Many patients quality of life is massively affected by classic signs and symptoms not being taken into account during GP and Consultant appointments. This reflects on their already low mood and knowing there is something drastically wrong, but not being listened to. Untreated or undertreated hypothyroidism, with other comorbidities can lead to shorter life and occasionally can lead to myxoedema coma and death. There is a desperate need for GP training in thyroid conditions as thyroid problems can and do affect the whole body and they should also be able to advise patients on the importance of dietary changes. Adverse effects of treatment should be monitored closely by the patient, GP and Consultant so that any surgery required, changes of medication and/or diet can be put in place to reduce the adverse effects.	Thank you for this information. The guideline will consider the role of adverse effects across the evidence reviews and seek to provide recommendations on appropriate monitoring. Training of clinicians is not usually covered by NICE guidelines. However, the recommendations made in the guideline will hopefully alert GPs of issues of importance to patients.

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NHS England	General	General	The proposed scope is acceptable, however guidance on post-partum testing for new diagnosis would be helpful.	Thank you for your comment. We anticipate that post-partum testing will be covered a new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists therefore this was not prioritised for inclusion here.
Royal College of General Practitioners	general	general	We think that clear criteria for management and referral , is really important The management of sublinical hypothyroidism is again an area where clarity would be helpful Defining a Criteria for referring patient from primary to secondary care setting were not mentioned.	Thank you for your comment. The committee will consider the appropriate setting for any intervention they recommend and, where evidence and consensus permits, will make recommendations.
Royal College of General Practitioners	general	general	Who should investigate diagnose and monitor thyroid disease?	Thank you for your comment. The committee will consider the appropriate setting for any intervention they recommend and, where evidence and consensus permits, will make recommendations.
Royal College of General Practitioners	general	general	Hypothyroidism is currently normally managed in primary care and there is little reason to change this if education and support enables this.	Thank you for this information.
Royal College of General Practitioners	general	general	A GP will normally be the person who initially investigates thyroid over activity. What then? My practice is normally to initial medical treatment- Advice B Blockade if safe and Carbimazole with warnings as secondary care does not consider this 'urgent' Should there be a timescale in assessment in secondary care. Can secondary care then come up witha a care plan and either agree telephone review or primary care management with telephone report. Brief trip to secondary care are rarely time efficient for the patient.	Thank you for your comment. The guideline will seek to make recommendations on what interventions should be offered to people and how they should be delivered. Where the evidence and committee consensus permits this may include defining the skills required of healthcare professionals involved in providing those interventions.
Royal College of Pathologists	General	General	There is no mention at all about laboratory factors causing differences in interpretation of thyroid hormones. It is well recognised that there are major differences between thyroid hormone measurements made using different manufacturer's kits	Thank you for this information. The committee will consider the importance of laboratory factors when making any recommendations on testing.

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			and therefore there will be different decision making values depending on which laboratory performs the tests. Secondly, there is no relation between the reference ranges given and the analytical method which means that using upper or lower reference limits (or multiples thereof) cannot be safely used as indicators. I would assume that NICE will make recommendation regarding diagnosis and treatment in relation to laboratory results. These laboratory factors need to be included in order to ensure equality across the nation.	
Royal College of Pathologists	6	171	Most pathology laboratories are inundated with requests for TFTs. My laboratory performs the equivalent of 1 test for 5 of the population every year. This workload is similar to other colleagues. This means that there is effectively a random screening process underway. It would be extremely useful if NICE could make recommendations related to the issues of screening versus case finding.	Thank you for your comment. Screening interventions fall outside the remit of this guideline.
Royal College of Surgeons of Edinburgh	General	General	RCSEd believe that there needs to be recognition of the new techniques in managing thyroid disease (both hormonal and benign Nodular disease), specifically, the role of High intensity Focussed Ultrasound and Radiofrequency ablation. If these techniques are to be considered it should be within a framework ongoing evaluation and reporting of outcomes. RCSEd remain keen to be involved in this subject matter given the importance that surgery plays in this area.	Thank you for your comment. These will be considered as part of the question on non-surgical management of non-malignant thyroid enlargement.
Society for Endocrinology	General	General	There is no mention at all about laboratory factors causing differences in interpretation of thyroid hormones. It is well recognised that there are major differences between thyroid hormone measurements made using different manufacturer's kits and therefore there will be different decision making values depending on which laboratory performs the tests.	Thank you for this information. The committee will consider the importance of laboratory factors when making any recommendations on testing.

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			Secondly, there is no relation between the reference ranges given and the analytical method which means that using upper or lower reference limits (or multiples thereof) cannot be safely used as indicators. NICE should make recommendation regarding diagnosis and treatment in relation to laboratory results. These laboratory factors need to be included in order to ensure equality across the nation.	
Society for Endocrinology	1	14-15	This definition should include thyroid eye disease. We would support additional wording to include this as it is a critically important condition.	Thank you for your comment. The purpose of this brief introduction is to cover what will be in the guideline and is not meant to be comprehensive or list all of the sequelae of thyroid dysfunction.
Society for Endocrinology	1	18	It is important the link between thyroid and iodine is made clearly. It is worth a sentence linking the importance of iodine to thyroid in terms of goitre and thyroid dysfunction.	Thank you for your comment. This brief introduction is not meant to be comprehensive. However the role of iodine in thyroid disease will be considered in the guideline.
Society for Endocrinology	2	43	Isolated hypothyroxinemia has not been included here – may be worth including given the growing adverse associations with this.	Thank you for this information. This is a brief introduction and not meant to be comprehensive.
Society for Endocrinology	3	61	There is substantial dissatisfaction on T4 therapy (around 15%) and the evidence base for T3 therapy is sub-optimal. Given current issues with T3 costs and areas of research, T3 needs to be explicitly indicated as a key research area.	Thank you for your comment and suggestion. The guideline will seek to address the most clinically and cost effective management of hypothyroidism.
Society for Endocrinology	4	96	Given the importance of thyroid in pregnancy the recent trials and the vigorous contested debate of universal thyroid screening in pregnancy, this should be included. Also guidance on pre-conception good control of thyroid function and education on possible increased dosing of levothyroxine would be useful to include. An alternative solution would be to link the RCOG guideline to the NICE guidance.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green top guideline on thyroid disease in pregnancy produced by the Royal College of

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				Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
Society for Endocrinology	5	119	Guidance on armour thyroid would be beneficial, given a minority of patients may be on this and primary care physicians as well as endocrinologists would benefit from guidance here	Thank you for your comment. This will be covered by the guideline: this has been clarified in the scope.
Society for Endocrinology	5	129	Thyroid eye disease should be covered, it has such an impact on QOL and there is new data from recent trials. It has been a long neglected condition and this is an excellent opportunity to improve education. NICE guidance is relied heavily on by GPs and they are often the first to see TED. Good guidance here may reduce misdiagnosis.	Thank you for your comment. The scope specifically excludes the management of thyroid eye disease (TED) as it was not prioritised for inclusion and would not be possible to cover in appropriate depth; however, TED is likely to be a topic that features in the section on "information for people with the thyroid disease" to reflect the importance of recognition.
Society for Endocrinology	6	171	Most pathology laboratories are inundated with requests for TFTs. One laboratory stated that they the equivalent of 1 test for 5 of the population every year. This workload is similar to other colleagues. This means that there is effectively a random screening process underway. It would be extremely useful if NICE could make recommendations related to the issues of screening versus case finding.	Thank you for your comment. Screening interventions fall outside the remit of this guideline.
Swansea University	General	General	Definitions and references would strengthen the document.	Thank you for your comment. The guidelines will include full referencing and definitions.
Swansea University	General	General	Omissions: population screening, screening in mental health, monitoring for agranulocytosis in association with carbimazole.	Thank you for your comment. The guidelines will seek to address appropriate monitoring for people being treated for thyrotoxicosis. Screening interventions fall outside the remit of NICE guidelines.
Swansea University	1	25	Does this refer to clinical or laboratory hypothyroidism? The contribution of iodine deficiency might be mentioned.	Thank you for your comment. This refers to clinical hypothyroidism. This is a brief introduction and not meant to be comprehensive. However the role of iodine in thyroid disease will be considered in the

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				guideline.
Swansea University	2	30	CNS effects of hypothyroidism warrant inclusion.	Thank you for your comment. This is a brief introduction and not meant to be comprehensive. The clinical and cost effectiveness analyses will seek to include all relevant consequences of thyroid dysfunction.
Swansea University	2	35	Is this T3 or T4 thyrotoxicosis?	Thank you for your comment. Both are included in the guideline.
Swansea University	2	45	Is this free or total hormone concentration?	Thank you for your comment. This section of the scope refers to free hormone concentration.
Swansea University	4	95	Will the pregnancy guideline cover pre-conception and post partum care?	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green top guideline on thyroid disease in pregnancy produced by the Royal College of Obstetricians and Gynaecologists (RCOG). The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline. We understand that the topics you identify will be covered by the RCOG work.
Swansea University	7	189	To optimise well-being in people with thyroid disorder, it is important monitor physical and mental health, not just laboratory tests. For example, an ECG will detect any cardiac arrhythmia, and laboratory values do not always reflect well-being.	Thank you for your comment. The guideline will seek to address appropriate monitoring of people with thyroid disease.
Swansea University	8	220	Quality of life is too imprecise to capture the impact of thyroid disease.	Thank you for your comment. Quality of life is an important outcome across all NICE guidelines for assessing both clinical and cost effectiveness; however, it is worth noting these are the main outcomes and not

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				an exhaustive list. Additional outcomes that will be more specific to each evidence review will be considered on a case by case basis as the protocols are established.
Swansea University	8	223	Adverse effects of treatment should be listed in full. Adverse effects of under-treatment should be included.	Thank you for your comment. These are the main outcomes and not an exhaustive list: additional outcomes that are specific to each evidence review will be considered on a case by case basis as the protocols are established.
The Royal College of Ophthalmologists	7	184	Monitoring should include clear guidance on the development of thyroid eye disease. Early referral is essential, but commonly missed. This is not to consider the treatment of eye disease but to emphasise the early symptoms and signs – and to recognise the risk factors	Thank you for your comment. The guideline will seek to address appropriate monitoring of people with thyroid disease.
The Royal College of Ophthalmologists	7	189	As above	Thank you for your comment.
The Royal College of Ophthalmologists	7	199	Risks of radio-iodine treatment for the development of thyroid eye disease should be considered	Thank you for your comment. When considering the clinical and cost effectiveness of radio-iodine treatment, the committee will consider all relevant and important outcomes: this will likely include thyroid eye disease but will be discussed at the time of review protocol setting.
The Thyroid Trust, also known as Thyroid Friends Network			**Regarding Committee Membership** - Should there be a psychiatrist or psychologist as a full or co-opted member? Thyroid disorders have an impact on mental functioning at all stages of life and also have a complex relationship with mood disorders such as depression.	Thank you for your comment. A psychiatrist/psychologist has now been added as a co-opted member the guideline will seek to recruit.
The Thyroid Trust, also known as			**Regarding the name of the guidelines** - One group member, who has had a very hard journey with hypothyroidism caused by PBDEs, comments: *'Existing guidance is specific to primary hypothyroidism*	Thank you for your comment. We asked a question from stakeholders at consultation regarding whether the title of the guideline

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Thyroid Friends Network			*but it is common for doctors to assume this guidance applies to all causes of impaired thyroid hormone activity. Hypothyroid signs and symptoms which respond to thyroid hormone treatment include primary and secondary hypothyroidism, resistance to thyroid hormone (RTH), dysregulated hypothalamic pituitary thyroid hormone axis, effects of endocrine disrupting chemicals (EDCs) and perhaps other causes. The draft scope limits the guidelines to disease of the thyroid gland. I feel strongly that the guideline should be retitled 'NICE Guidelines on Thyroid Gland Disease'. Whilst the current title is strictly correct I fear that the majority of doctors and patients will not appreciate that the new guidelines only address diagnosis and treatment of disorders of the gland, this limitation needs to be made absolutely clear.'*	should change. Unfortunately, because few stakeholders supported this, it is not possible to change to the title. The points you make about appropriate management of thyroid disease based on the cause will be considered throughout the recommendation making process.
The Thyroid Trust, also known as Thyroid Friends Network		43 and 44	"normal' and 'abnormal' are misleading terms and should be replaced with 'inside/outside the reference interval' or some other wording which recognises that there is no such thing as normal and blood tests are only part of the picture for diagnosis. The term 'reference interval' is preferential to the more commonly used 'reference range' as it importantly draws attention to the fact that this is a statistical interval and not a diagnostic or therapeutic range to be rigidly adhered to.	Thank you for your comment. This has been amended as suggested.
The Thyroid Trust, also known as Thyroid Friends Network		43 to 52	The meaning of 'Subclinical' thyroid disfunction is not clear, as the document goes on to say 'some people may have symptoms of hypothyroidism or hyperthyroidism'. This is confusing as if symptoms are present would it be subclinical? The term 'subclinical hypothyroidism' is challenging, we believe it is recognised to be a misnomer. Perhaps 'mild thyroid failure' would be better. The term 'subclinical hypothyroidism' is not a good one to use where no clinical assessment has taken place and in many cases there are clear clinical signs and symptoms of hypothyroidism which are associated with long term risks of cardiovascular harm.	Thank you for your comment. The term subclinical thyroid dysfunction refers to the specific situation outlined in the paragraph you are commenting on and the guideline will seek to address whether this is a situation in which treatment is clinically and cost effective.
The Thyroid Trust, also known as Thyroid		60	It worries us that this only refers to "standardisation" of treatment for hypothyroidism being lacking. We think it should also state that optimal treatment and patient centred care protocol are lacking and that there needs to be recognition that patients are individuals and	Thank you for your comment. As with all NICE guidelines, the recommendations will be intended to be interpreted in the context of each individual patient; however, the

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Friends Network			not everyone will respond to a standard treatment. And this sentence should mirror the sentence following it which talks about guidance on optimal treatment and follow-up strategies for thyrotoxicosis.	intent of the recommendations will be to indicate which treatments are clinically- and cost-effective for all people to reduce unfair variability in service provision.
The Thyroid Trust, also known as Thyroid Friends Network		67	It is not clear to us what this means and we feel there needs to be something here about the significance of blood test results and symptoms. We fear that straight away it is confusing, perhaps just inserting the word 'also' might help i.e. This guideline will ALSO aim to. This then clarifies that the guideline will cover hypo, hyper, and non-malignant nodules.	Thank you for your comment. This has been amended as you suggest.
The Thyroid Trust, also known as Thyroid Friends Network		95	We feel that pregnant women should be included as the issue of thyroid disease in pregnancy is too important to be left out. Although we recognise that separate guidance will be forthcoming from the RCOG, GPs may very well not see this separate guidance, they will expect NICE guidance to be comprehensive. Also, and we don't know yet what the RCOG guidance may include. At any rate we feel it should be supplementary to the NICE document, not an alternative, because GPs are perhaps unlikely to have time to look in two places . We feel it is absolutely vital that the NICE guidelines do not overlook the needs of pregnant women and their unborn children. The risks are too great.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
The Thyroid Trust, also known as Thyroid Friends Network		111	Indications for thyroid function tests. Patients may present with a range of symptoms which may not give a clear indication for thyroid function tests, so should routine blood testing in primary care be considered? There might be an advantage in establishing thyroid blood levels in early adult life, which would give the 'normal' baseline for each individual against which later changes could be compared. Screening (rather than looking for indications) could be cost effective if it resulted in early diagnoses, as late diagnoses may result in slow or poor recovery and involve referrals to other specialities with cost implications, and also result in the social costs of chronic ill health.	Thank you for your comment. Diagnosis of thyroid disease is covered in section 1 of the scope, investigating thyroid dysfunction or enlargement. Conditions that qualify for national screening are instead examined by the National Screening Committee.
The Thyroid Trust, also known as Thyroid		128 onwards	We believe that the scope must also include information on differential diagnosis for conditions with similar symptoms that should be tested for, should treatment for a thyroid condition not restore wellbeing (eg Vit D deficiency, Gluten intolerance, B12	Thank you for your comment. Due to the considerable breadth of the scope, it will not be possible to focus on differential diagnoses extensively; although, pending

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Friends Network			deficiency, etc)	the results of the relevant evidence reviews and the committee's consensus, this may feature in the information provision recommendations.
The Thyroid Trust, also known as Thyroid Friends Network		130	Why not cover Management of thyroid eye disease - at least to flag up symptoms and guidance for specialist referral?	Thank you for your comment. The scope specifically excludes the management of thyroid eye disease (TED) as it was not prioritised for inclusion and would not be possible to cover in appropriate depth; however, TED is likely to be a topic that features in the section on "information for people with the thyroid disease" to reflect the importance of recognition.
The Thyroid Trust, also known as Thyroid Friends Network		135	We believe that information on iodine and selenium should be included as the public domain is full of misinformation, particularly with regards to kelp	Thank you for your comment. The guideline will seek to address appropriate information to provide people with. Iodine and selenium supplementation has been included in the scope and will be covered in the guideline.
The Thyroid Trust, also known as Thyroid Friends Network		138	We believe that some information on diet and lifestyle should be included - both standard lifestyle advice for anyone with a chronic health issue and the information that a gluten free diet may help some patients (many patients testify to this) but will not help everyone. We think this is important as GPs may not think of it otherwise and it may change some patients' lives dramatically for the better. https://www.ncbi.nlm.nih.gov/pubmed/?term=gluten+and+hashimoto%27s	Thank you for your comment. While the guideline will not look at specific dietary or lifestyle interventions, it will seek to address appropriate information to provide people with.
The Thyroid Trust, also known as Thyroid Friends Network		156	We clicked the link here and think that there needs to be a patient decision making tree for thyroid treatment optimisation to be created for NICE Guideline NG5	Thank you for your comment. The committee will consider the most appropriate ways to guide patient decision making for thyroid disease as the guideline is formulated.
Thyroid	Gener	General	As a priority, TPA is pressing for recognition of the fact that	Thank you for this information.

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Patient Advocacy	al		hypothyroidism does not solely occur because of adverse events in the thyroid gland. Past failure in recognising this, has resulted in misdirected guidelines.	
Thyroid Patient Advocacy	1	14 and 15	The definition of thyroid disease is unclear. Thyroid dysfunction can and often does happen without thyroid enlargement. The minimum change would be for the sentence to read: "..... thyroid enlargement **and/or** thyroid hormonal dysfunction." The preferred alternative definition, based upon the European Thyroid Association's definition of hypothyroidism is : **"Thyroid disease is condition characterised by the clinical and biological manifestations of thyroid hormone deficiency or excess in the target tissues of thyroid hormone"** (these tissues could be listed later, along with a Symptom Score List which could be used as a tool to aid diagnosis)	Thank you for your comment. This has been amended as suggested.
Thyroid Patient Advocacy	1	25 and 26	*The statement is misleading because a patient may be hypothyroid whilst showing normal or raised levels of thyroid hormones, especially if there is a T4>T3 conversion impairment.* *We would like to see acknowledgment of the different types of Hypothyroidism. If a person has symptoms but no antibodies then there are other likely reasons - there are 5 causes of hypothyroidism:* 1. Failure of the Hypothalamus to release TRH (Central Hypothyroidism) 2. Failure of the Pituary Gland to make Thyroid Stimulating Hormone (Central hypothyroidism) 3. Deficiency of thyroid hormone made by the thyroid – usually due to Auto Immune Disorders : Hashimoto's	Thank you for your comment. This brief introduction is not meant to be comprehensive. The guideline will consider the role of investigations in establishing the cause of hypothyroidism.

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			Thyroiditis which can present with a goitre and antibodies to thyroid antigens whilst Ord's disease presents with atrophy of the thyroid gland and antibodies.(Primary hypothyroidism) 4. Impaired conversion of Thyroxine to Triodothyronine (T4 to T3) 5. Peripheral T3 utilisation failure	
Thyroid Patient Advocacy	2	29	*Long term consequences of hypothyroidism include cardiovascular disease and an increase in cardiovascular risk factors, including hypercholesterolaemia.* The above statement could be changed to read: Long term consequences of, under or un-treated symptoms of hypothyroidism, include cardiovascular disease and an increase in cardiovascular risk factors, such as hypercholesterolaemia. (*Adequately treated hypothyroidism remits these problems)* However, the term Hypothyroidism is often misused and attributes symptoms of hypothyroidism solely to disorders of the Thyroid Gland. This clinical situation would be better described as: **Symptoms of hypothyroidism attributed to defective thyroid hormone function.** *So the statement would read:* Long term consequences of under or untreated symptoms of hypothyroidism, attributed to defective thyroid hormone function, include cardiovascular disease and an increase in cardiovascular risk factors such as hypercholesterolaemia	Thank you for your comment. This is a brief introduction and not meant to be comprehensive. The clinical and cost effectiveness analyses will seek to include all relevant consequences of thyroid dysfunction.
Thyroid Patient Advocacy	2	33	*".....disorder of excess circulating thyroid hormones caused by increased production and secretion (hyperthyroidism) or by release of stored thyroid hormones (thyroiditis)*	Thank you for this information.

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			Damage to the thyroid gland may cause the release of thyroid hormones, causing symptoms of apparent hyperthyroidism. However this release may be transient and intermittent as the gland breaks down. (Thyroiditis)	
Thyroid Patient Advocacy	5	135	*Management of thyroid disease with Iodine and Selenium supplementation.* This area should be given some consideration. The uk soil was officially declared to be Iodine deficient in 2010. Worldwide, iodine deficiency is the leading cause of hypothyroidism. It therefore follows that if a person has a goitre and no auto- antibodies, it may be worthwhile supplementing with iodine and selenium for a trial period. Selenium supplementation is essential for cellular conversion of Thyroxine to Triodothyronine. It is well documented and the uk soil was found to be deficient in 2003. If a patient has good levels of Thyroxine, and still complains of symptoms, then it cannot be assumed that the Thyroxine is being converted.	Thank you for your comment. The scope has been amended and the appropriate role of supplementation of iodine and selenium will be considered.
Thyroid Patient Advocacy	5	137	*Drug-induced thyroid dysfunction* *Consideration should be given as* prescribed drugs can interfere with thyroid hormone production or conversion. This is not well known by patients and some doctors,, so at least listing the main culprits would be prudent. These being: Beta Blockers, Valium, SSRIs, Steroids, medications for Diabetes and for Parkinson's disease.	Thank you for your comment. This was not raised as a high priority area for guidance; however, the importance of people and their healthcare professionals being aware of the impact of medication on thyroid function may feature in the information for people with thyroid disease, should the underlying evidence reviews and committee suggest this is appropriate.
Thyroid Patient Advocacy	5	138	*Management of Thyroid Disease with dietary and lifestyle interventions.* An article written by Dr O Okosieme in the 'Pulse Today ' magazine of August 28th 2015, details how a patient approached him with a request for Liothyronine because her Levothyroxine was not resolving her symptoms. A healthy diet, exercise and taking her levothyroxine with water, on an empty stomach , resolved the lady's problems without the need for further intervention. Why would we	Thank you for your comment. The scope excludes consideration of the management of thyroid diseases with dietary and lifestyle interventions; however, the scope does not seek to exclude any consideration of the role of diet and lifestyle in thyroid disease as a whole and it is anticipated that this may feature under in the question on information for people with thyroid disease, although this

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			not include this kind of advice? In addition to lifestyle choice, it is often found that low stomach acid which appears frequently with hypothyroidism, causes problems with absorption vitamins and minerals, resulting in low levels of B12, Folate , and Iron	will depend on the evidence identified and committee discussions.
Thyroid Petition Scotland	2	55	Not only are there no standardised diagnostic or referral criteria but the guidelines that were in existence from 2006 for the use of Thyroid Function Tests have now been archived. I consider it absolutely critical to the quality of any Thyroid Disease guidelines that new guidelines based on the highest quality evidence are produced for this area explicitly. Having good quality guidance on which tests to conduct will result in cost savings as there will be more timely diagnosis and treatment as well as fewer misdiagnosis.	Thank you for your comment. The guideline will seek to address the most clinically and cost effective diagnostic tests for thyroid disease.
Thyroid Petition Scotland	4	110	Will this area cover which tests to investigate thyroid function?	Thank you for your comment. That is the intention of the scope.
Thyroid Petition Scotland	5	115	I think the issue of 'consent' needs to be addressed. Currently patients are given basic information about the risks of surgery but it is not particularly stressed that the common outcomes of hypothyroidism and hypoparathyroidism can be as difficult to manage as it is. I believe exploring how consent is given would be a very worthwhile task here.	Thank you for your comment. The guideline will seek to address what specific information should be given to people with thyroid disease.
Thyroid Petition Scotland	5	134	There was broad consensus at the stakeholder meeting that thyroid disease in pregnancy ought to be covered. A thyroid function test at the same time as an anti-natal diabetic screen in pregnancy would be one suggestion. Even if the RCOG publish guidelines in this area, it makes sense to have them within the standard NICE guidance for simplicity.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
Thyroid Petition	7	172	As above, the evidence for which tests to conduct must be re-visited as the archived guidelines on the use of Thyroid Function Tests	Thank you for this information.

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Scotland			were based on generally poor quality evidence and are now archived.	
Thyroid Petition Scotland	7	185	This is where attention needs to be paid to other forms of hypothyroidism and not conflate secondary or tertiary hypothyroidism with Primary.	Thank you for this information.
Thyroid Petition Scotland	8	212	Information needs to be detailed and pre-surgery consent should outline the available data on statistics for resulting hypoparathyroidism and hypothyroidism. Information should be provided on all available treatments for hypothyroidism, including the unlicensed natural desiccated thyroid which was formerly used by the NHS and is still occasionally prescribed. Patients frequently buy Natural Desiccated Thyroid and it would be helpful if GPs were aware of how to manage these patients.	Thank you for your comment. The guideline will seek to address appropriate information to provide people with. The use of thyroid extract will be considered in the management of hypothyroidism.
Thyroid Petition Scotland	8	220	There needs to be guidance on how to treat the quoted 5-10% of hypothyroid patients who still cite low QOL and symptoms despite 'normal' thyroid levels on treatment.	Thank you for your comment. The management of hypothyroidism and the various treatment options will be considered. Recommendations on the appropriate treatment when first line treatment fails will be made if there is sufficient supporting evidence.
Thyroid UK	2	45	In my experience, T3 is never tested in primary care, even if asked, and so how do doctors know that patients have normal T3 levels? If T3 was always included as part of the thyroid function test, it might show that, actually, patients with a high TSH and normal FT4 may actually have a low FT3 meaning that they have overt hypothyroidism (secondary) and not subclinical hypothyroidism. This should be looked at more closely for these guidelines. The same applies for patients diagnosed with subclinical hyperthyroidism.	Thank you for this information. The guideline will seek to address appropriate investigation of thyroid dysfunction.
Thyroid UK	2	55	Since the Guidelines for Thyroid Function Tests 2006 are outdated and archived, Thyroid UK would like to see some guidance on what tests should be done to test for thyroid disease. Testing for TSH; FT3; FT4 and thyroid antibodies would save time for both the GP and the patient and in the long run, save NHS funds.	Thank you for your comment. The guideline will seek to address the most clinically and cost effective diagnostic tests for thyroid disease.
Thyroid UK	3	67	Some patients who have overt or subclinical hypothyroidism do not	Thank you for this information.

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			have thyroid enlargement, even with positive thyroid antibodies. In some cases, the thyroid gland is atrophied but in the UK, scanning of the thyroid is not part of the diagnostic process unless a tumour is suspected.	
Thyroid UK	4	91	Thyroid UK believes that patients who have had a total thyroidectomy or patients whose thyroid has atrophied need special consideration in respect of treatment with liothyronine.	Thank you for your comment. This section of the scope identifies subgroups in whom the evidence will need separate analysis in all situations. There may well be groups, as you have suggested, where specific consideration is needed in certain reviews. The committee will consider subgroups relevant to each review at the protocol setting stage.
Thyroid UK	4	109	Natural desiccated thyroid, as an unlicensed product in the UK, is prescribed by a lot of doctors and they need help with understanding the differences between this medicine and levothyroxine if they are to monitor their patients well. As far as I am aware, there is no information/training in regard to NDT (a drug that was used by the NHS before levothyroxine was manufactured) and therefore doctors are relying on their patients for this information which many patients receive from us. Even if NHS doctors do not prescribe it, they need to understand it so that they can monitor patients – unless the doctor refuses to monitor the patient, which Thyroid UK believes would be unethical but which has happened to some patients.	Thank you for this information.
Thyroid UK	4	111	Including FT3. There are no thyroid function test guidance	Thank you for this information.
Thyroid UK	5	115	In my experience, patients who have had treatment for hyperthyroidism are not informed a) that they are likely to become hypothyroid either immediately or over the next few years and b) that once they are hypothyroid, treatment can be problematic. Patients are informed that hypothyroidism is easy to treat with one little white pill but in 10-15% of patients this is not the case and hyperthyroid patients should be informed of this when treatment is discussed.	Thank you for your comment. The guideline will seek to address what specific information should be given to people with thyroid disease.
Thyroid UK	5	118	There should be a section in the guidance in respect of patients' own set point for thyroid hormone levels of FT4 and FT3. We hear all the	Thank you for your comment. The guideline will seek to cover appropriate monitoring of

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			time from patients that doctors have reduced their levothyroxine because their TSH is too low within the range and the patient has a return of their symptoms necessitating another visit to their GP to ask (sometimes fight) for an increase in their levothyroxine. If the patient was well and showing no signs whatsoever of thyrotoxicosis this exercise is time and money wasted. Also, some patients' doctors only increase their levothyroxine until they reach the middle of the range and their symptoms do not fully resolve. Patients will soon realise if they are on too much thyroxine by symptoms of overactivity and as long as they are aware of this and want to try an increase in dosage to relieve their symptoms, this should be easy to monitor.	hypothyroidism and its treatment.
Thyroid UK	5	119	NDT needs to be included in this or you will be missing a large section of the thyroid community, mostly women. Hypothyroid patients should be informed that for 10-15% of patients levothyroxine does not resolve all of their symptoms. They should be informed of ALL types of treatment including T3 and NDT. At the moment they are not being informed or given a choice.	Thank you for your comment. NDT will be covered by the guideline: this has been clarified in the scope.
Thyroid UK	5	134	As I understand it, at the scoping meeting, pregnancy and thyroid was discussed fully and the consensus was that it should be included in this guidance. I believe that a summary should be included with links to full guidance from other organisations. So many hypothyroid women are not aware that levothyroxine should be increased as soon as they find out they are pregnant and, in my experience, there are still doctors who refuse to increase levothyroxine in a pregnant woman just because she is already in the normal range.	Thank you for your comment. Given the breadth of the current guideline scope and the number of important issues to cover under the heading of pregnancy, the decision has been made to avoid duplication of guidance with the upcoming new green-top guideline produced by the Royal College of Obstetricians and Gynaecologists. The most appropriate way of signposting to this guidance will be considered during development of the NICE guideline.
Thyroid UK	5	135	As a charity we speak to many patients who have subclinical hypothyroidism. We suggest testing their iodine, selenium, iron and ferritin levels which are often shown to be deficient and once corrected, their symptoms are improved.	Thank you for your comment. The scope has been amended and the appropriate role of supplementation of iodine and selenium will be considered.

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			These vitamins and minerals are necessary for good thyroid function and, unfortunately, nutrition and thyroid are not mentioned by the GP and, in fact, we feel that many GPs are not aware of how important they are or that there is a general deficiency in patients with symptoms of hypothyroidism. We strongly feel that nutrition and particularly the above vitamins and minerals should be included in the guidance. In the long term, this would save time and money on behalf of both the patient and the doctor.	
Thyroid UK	5	138	We feel that patients should be informed about nutrition and thyroid if they present with symptoms of hypothyroidism. It is common for doctors to check vitamin B12 but not other vitamins and minerals that can impact on thyroid health. This should be included in this guidance.	Thank you for your comment. The scope excludes consideration of the management of thyroid diseases with dietary and lifestyle interventions; however, the scope does not seek to exclude any consideration of the role of diet and lifestyle in thyroid disease as a whole and it is anticipated that this may feature under the question on information for people with thyroid disease, although this will depend on the evidence identified and committee discussions.
Thyroid UK	6	159	The cost of T3 has risen over the past few years since it became a generic drug. NHS England are analysing the results of a consultation at the moment and will make a decision whether or not to withdraw this drug on cost grounds. They admit that it is an effective drug but that the cost to the NHS is a burden. However, T3 is available in Europe for pennies in some cases and in many cases for a few pounds rather than the £9.22 per tablet that the NHS is paying at the moment. We would like to see something in the guidance to the effect that doctors can prescribe T3 for the patients that need it and that pharmacists can access T3 from outside of the UK to save the NHS funds.	Thanks you for your comment. The guideline will seek to assess the clinical and cost effectiveness of treatment options for hypothyroidism including T3.
Thyroid UK	6	172	Thyroid UK believes that it would be more time and cost effective to	Thank you for your comment. The clinical

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			test for all the thyroid tests as well as some vitamin and mineral tests to quickly diagnose exactly what the problem is. Many doctors will not order an FT3 test and patients have been told due to the fact that the FT3 test is more expensive than an FT4 test. However, as far as I am aware, an FT3 test costs the same as an FT4 test.	and cost effectiveness of thyroid function tests will be considered in this guideline.
Thyroid UK	7	185	Thyroid UK believes that not including guidance for secondary hypothyroidism would be a mistake. If a patient has problems with conversion of T3, this, in many cases, is not due to primary hypothyroidism but due to secondary hypothyroidism. T3 is converted outside of the thyroid and therefore there is no problem with the gland itself (primary hypothyroidism). This is something that many patients are very angry about – clinicians are using the primary hypothyroidism guidance for all cases and this is not correct. In my experience, GPs need more training in respect of the interpretation of thyroid function tests instead of just noting that they are within or without the range.	Thank you for your comment. Primary hypothyroidism was considered to be the most appropriate area to prioritise for assessment of evidence. Where the committee agrees, and the evidence indicates, they will consider making a statement on the appropriateness of the recommendations being appropriate to other causes of hypothyroidism as well.
Thyroid UK	7	196	I hear from hyperthyroid patients that they are doing really well on Carbimazole but that the clinician is pushing for them to have radio-iodine treatment or surgery. Quite rightly, the patient is concerned about moving onto a treatment with unknown outcomes for them. If the patient has a preference for staying on a treatment that is only known for immediate side effects and they have no side effects, they should have their preference taken into account.	Thank you for this information. The guideline will seek to identify situations or reasons for which any one modality of treatment may be generally more appropriate for groups of people.
Thyroid UK	8	207	As mentioned before, all thyroid function tests should be done along with vitamin and mineral testing to search for the reason behind the subclinical hypothyroidism. In my experience, Hashimoto's disease is a primary cause but even though the patient has high antibodies, the doctor will not treat the patient until the TSH has at least gone above the range and in some cases, above 10. We are the only country that I know of that treats Hashimoto's disease in this way. If the patient has signs and symptoms of hypothyroidism and thyroid antibodies, then a trial of levothyroxine would be cost effective, saving many visits to the surgery and saving the cost of many non-thyroid related testing.	Thank you for your comment. The guideline will seek to address appropriate testing and treatment of subclinical hypothyroidism.

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Thyroid UK	8	218	There is nothing in this scope that covers the 10-15% of patients who do not do well on levothyroxine or those that require lactose free levothyroxine and who are being denied it.	Thank you for your comment. The management of hypothyroidism and the various treatment options will be considered, recommendations on the appropriate treatment when first line treatment fails will be made if there is sufficient supporting evidence.