Philippine Clinical Practice Guideline for the Diagnosis and Management of Hyperthyroidism

Disclaimers

This clinical practice guideline (CPG) is intended to be used by general practitioners and specialists. The Department of Health (DOH) encourages adherence to this guideline, however, this document does not restrict the clinicians in using their clinical judgement and considering patient's values, needs, and preferences while handling individual cases. Sound and just clinical decision-making must always be exercised by clinicians and all relevant stakeholders that are involved in patient care as the individual patient's history, current physical status, and responses to treatment may vary.

Payors, policymakers, hospital administrators and employers can also utilize this CPG. However, nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action.

Developers of this CPG are aware of its limitations. Evidence summaries are based on the best available scientific evidence at the time of its formulation which is stated in each Evidence Summary. As such, certain aspects of the interventions or diagnostic tests may not be completely addressed by the included studies.

This CPG is not intended to cover the entirety of the diagnosis and management of hyperthyroidism. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exists.

For any question or clarifications pertaining to this CPG, you may contact us through email at aldrichivanlois28@gmail.com

Contents

Participating Societies, Organizations, Agencies, and/or Institutions

List of Abbreviations

AE	Adverse events
ATD	Antithyroid drug
CAS	Clinical activity score
CBZ	Carbimazole
CMI	Chemiluminescent microparticle immunoassay
CVD	Cardiovascular disease
EUGOGO	European Group on Graves' orbitopathy
fT3	Free triiodothyronine
fT4	Free thyroxine
GD	Graves' disease
GO	Graves’ ophthalmopathy/orbitopathy
MMZ/MMI	Methimazole
PhilTiDeS	Philippine Thyroid Diseases Study
PTU	Propylthiouracil
QALY	Quality-adjusted life-years
QOL	Quality of life
PhilHealth	Philippine Health Insurance Corporation
RAI	Radioactive iodine
SRMA	Systematic review and meta-analysis
T3	Triiodothyronine
T4	Thyroxine
TFT	Thyroid function tests
TRAb	Thyrotropin receptor antibody
TSH	Thyroid stimulating hormone
TSH-R	Thyroid stimulating hormone receptor
TBII	TSH-R binding inhibitory immunoglobulin
TSI	TSH-R stimulating immunoglobulin
TT	Total thyroidectomy

List of Tables

Executive Summary

Thyrotoxicosis is a clinical state wherein excessive thyroid hormones circulate in the body due to hyperthyroidism (endogenous overproduction and secretion of T3 and T4 from the thyroid gland) or non-hyperthyroid causes (e.g., passive release of thyroid hormones from damaged thyroid follicles, excess exogenous thyroid hormones). The most common etiology of thyrotoxicosis due to hyperthyroidism is Graves' disease, followed by multinodular toxic goiter, and toxic adenoma (solitary toxic nodule). On the other hand, non-hyperthyroid causes of thyrotoxicosis may be due to subacute thyroiditis, excessive ingestion of synthetic thyroid hormones, or the side-effects of some drugs such as amiodarone.[66,141]

Manifestations of thyrotoxicosis include palpitations, tremors, weight loss, heat intolerance, and anxiety; in rare cases, patients may even exhibit life-threatening thyroid storm. [66,141]

Based on the 2012 Philippine Thyroid Diseases Study (PhilTiDeS 1), the national prevalence rates of subclinical hyperthyroidism and true hyperthyroidism were estimated at 5.33% and 0.61%, respectively.[83]

This is the first local clinical practice guideline on the diagnosis and management of hyperthyroidism. This guideline was done in collaboration with the Department of Health and East Avenue Medical Center.

This CPG covers key clinical issues related to the diagnosis and management of hyperthyroidism among non-pregnant adults, with some guidance pertaining to issues unique to children and pregnant individuals. The 15 questions with the corresponding recommendations in this guideline are listed in Table 1.

Table 1. Summary of clinical questions with recommendations

Clinical Questions	Recommendations	Certainty of evidence	Strength of recommendation
1. Should we do routine paired testing (fT4/T4 plus TSH) versus TSH testing alone as initial evaluation of thyroid function among patients with suspected thyrotoxicosis?	Recommendation 1A. Among patients with suspected thyrotoxicosis*, we recommend the routine use of TSH for initial evaluation. **In patients with florid signs/symptoms of thyrotoxicosis, treatment** may be initiated while pending laboratory results.* ***Treatment – Supportive treatment (beta-blockers, etc.) for adrenergic symptoms with or without thionamides*	Very low	Strong
	Recommendation 1B. Among patients with suspected thyrotoxicosis, we suggest against routine paired fT4/T4-TSH testing as initial evaluation due to no evidence.	Very low	Weak
2. Should we routinely do T3 testing on top of TSH and fT4/T4 testing in the workup of individuals suspected to have thyrotoxicosis?	Recommendation 2. Among patients suspected of having thyrotoxicosis, we suggest against routine T3 testing on top of TSH and fT4/T4 testing.	Very low	Weak
3. Should we use history and PE findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves' disease from non-Graves' disease (i.e., other etiologies) among patients with biochemically confirmed thyrotoxicosis?	Recommendation 3. Among non-pregnant patients with biochemically confirmed thyrotoxicosis, we suggest against history and physical examination findings alone to differentiate between Graves' disease from non-Graves' disease due to harms of unnecessary treatment.	Low	Weak
4. Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?	Recommendation 4A. Among adult patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease.	Low	Weak
	Recommendation 4B. Among pediatric patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease.	Low	Weak

5. Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves' disease from versus thyrotoxic phase of subacute thyroiditis?	Recommendation 5A. Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we recommend using 99m technetium pertechnetate thyroid uptake in differentiating Graves' disease from thyrotoxic phase of subacute thyroiditis.	Moderate	Strong
	Recommendation 5B. Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest against the routine use of radioactive iodine uptake (I-131) (RAIU) in differentiating Graves' disease from the thyrotoxic phase of subacute thyroiditis due to insufficient evidence	Very low	Weak
6. Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves' disease from thyrotoxic phase of subacute thyroiditis?	Recommendation 6. Among pediatric patients with biochemically confirmed thyrotoxicosis, we suggest against the routine use of 99m technetium pertechnetate thyroid uptake in differentiating Graves' disease from the thyrotoxic phase of subacute thyroiditis.	Very low	Weak
7. Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?	Recommendation 7. Among patients with biochemically confirmed thyrotoxicosis and thyroid nodules, we suggest against the routine performance of a thyroid scan to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)	Very low	Weak
8. Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?	Recommendation 8. Among hyperthyroid individuals with no palpable nodules, we suggest against routine screening for nodules using thyroid ultrasound due to low incidence of concomitant malignancy.	Low	Weak
9. Should beta-blockers be used as an adjunct for	Recommendation 9A. Among non-pregnant adults with thyrotoxicosis,	Very low	Strong

individuals with thyrotoxicosis?	we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors. **Unless contraindicated. Contraindications to beta-blockers includes moderate to severe asthma, slow heart rate, low blood, pressure, hypoglycemia, Raynaud's phenomenon*		
	Recommendation 9B. Among children with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors. **Unless contraindicated. Contraindications to beta-blockers includes moderate to severe asthma, slow heart rate, low blood, pressure, hypoglycemia, Raynaud's phenomenon*	Very low	Strong
10. Should we give methimazole/ carbimazole as first-line therapy instead of propylthiouracil among individuals with hyperthyroidism?	Recommendation 10A. Among non-pregnant adults with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as an initial treatment. In case methimazole is not available, we recommend the use of carbimazole.	Moderate	Strong
	Recommendation 10B. Among children and non-pregnant adolescents with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as initial treatment. In case methimazole is not available, we recommend the use of carbimazole.	Low	Strong
	Recommendation 10C. Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of propylthiouracil during the first trimester, due to the higher risk of congenital malformation with methimazole/ carbimazole.	Low	Strong
	Recommendation 10D. Among adult pregnant patients with	Low	Strong

	Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of methimazole during the second and third trimester due to the lower risk of maternal liver impairment with methimazole.		
	Recommendation 10E. Among women with Graves' hyperthyroidism requiring antithyroid therapy who are planning pregnancy, we suggest switching of methimazole/carbimazole to propylthiouracil due to the higher risk of congenital malformation with methimazole/carbimazole.	Very low	Weak
11. Should we give long-duration instead of short-duration ATD treatment among individuals with Graves' hyperthyroidism?	Recommendation 11A. Among non-pregnant adults with Graves' hyperthyroidism on ATD as first-line therapy, we suggest maintaining* antithyroid drug for at least 18 months. **as long as it is well tolerated by the patient*	Low	Weak
	Recommendation 11B. Among children with Graves' disease, we suggest maintaining antithyroid drug for at least 24 months* **as long as it is well tolerated by the patient*	Very low	Weak
12. Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?	Recommendation 12A. Among non-pregnant adults with Graves' disease, we recommend antithyroid drug as first-line treatment.	Low	Strong
	Recommendation 12B. Among children with Graves' disease, we recommend antithyroid drug as first-line treatment.	Very low	Strong
13. Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?	Recommendation 13A. Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest doing total thyroidectomy instead of RAI if a "high volume"* thyroid surgeon is available. **performs more than 25 thyroidectomies per year*	Low	Weak

	Recommendation 13B. Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest giving RAI if a "high-volume"* thyroid surgeon is not available. **performs more than 25 thyroidectomies per year*	Low	Weak
	Recommendation 13C. Among pediatric patients with hyperthyroidism who are refractory to medical management, we suggest thyroidectomy as the treatment of choice for definitive therapy in children if with access to a "high volume"** thyroid surgeon. ***performs more than 30 thyroidectomies per year*	Low	Weak
14. Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?	Recommendation 14. Among patients with mild* and active* Graves' orbitopathy, we suggest selenium supplementation for six months to improve clinical outcomes (i.e., clinical activity score, overall eye evaluation improvement, and improvement in quality of life).	Low	Weak
15. Should we routinely treat non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism?	Recommendation 15A. Among adult patients with persistent biochemically confirmed subclinical hyperthyroidism ≥ 65 years and serum TSH levels <0.1 mlU/L, we suggest routine treatment* with ATDs.	Very low	Weak
	Recommendation 15B. Among adult patients with subclinical hyperthyroidism ≥ 65 years and serum TSH levels greater than or equal to 0.1 mlU/L, we suggest against routine treatment* with ATDs due to insufficient evidence.	Very low	Weak
	Recommendation 15C. Among adult non-pregnant patients with subclinical hyperthyroidism who are <65 years, we suggest against routine treatment* due to insufficient evidence.	Very low	Weak

	**Treatment should be individualized and may be considered for certain conditions such as TSH levels (< 0.1 mlU/L), signs and symptoms of the patients, and presence of comorbidities. (eg cardiovascular disease, osteoporosis)*		
	Recommendation 15D. Among children with subclinical hyperthyroidism, we suggest against routine treatment* due to insufficient evidence. **i.e., ATD, RAI, surgery, etc*	Very low	Weak

Introduction

Background

Thyrotoxicosis is a clinical state wherein excessive thyroid hormones circulate in the body due to hyperthyroidism (endogenous overproduction and secretion of T3 and T4 from the thyroid gland) or non-hyperthyroid causes (eg passive release of thyroid hormones from damaged thyroid follicles, excess exogenous thyroid hormones). The most common etiology of thyrotoxicosis due to hyperthyroidism is Graves' disease, followed by multinodular toxic goiter, and toxic adenoma (solitary toxic nodule). On the other hand, non-hyperthyroid causes of thyrotoxicosis may be due to subacute thyroiditis, excessive ingestion of synthetic thyroid hormones (thyrotoxicosis factitia), or the side-effects of some drugs (amiodarone) (Table 2).[66,141,]

Table 2. Etiologies of Thyrotoxicosis[200]

Hyperthyroid causes	Non-hyperthyroid causes
I. **Excessive TSH-Receptor Stimulation** Graves disease Pregnancy-associated transient hyperthyroidism Trophoblastic disease TSH-producing pituitary adenoma	III. **Destruction of Thyroid Follicles with Release of Hormone** Subacute de Quervain thyroiditis Painless thyroiditis/postpartum thyroiditis Acute thyroiditis Drug-induced thyroiditis (eg amiodarone)
II. **Autonomous Thyroid Hormone Secretion** Multinodular toxic goiter Solitary toxic thyroid adenoma	IV. **Extrathyroidal Sources of Thyroid Hormone** Iatrogenic overreplacement with thyroid hormone Excessive self-administered thyroid medication (thyrotoxicosis factitia) Food and supplements containing excessive thyroid hormone Functional thyroid cancer metastases Struma ovarii

Manifestations of thyrotoxicosis include palpitations, tremors, weight loss, heat intolerance, and anxiety; in rare cases, patients may even exhibit life-threatening thyroid storm.[66,141]

Based on the 2012 Philippine Thyroid Diseases Study (PhilTiDeS 1), the national prevalence rates of subclinical hyperthyroidism and true hyperthyroidism were estimated at 5.33% and 0.61%, respectively.[83]

Objectives

The goal of this CPG is to define best practices in diagnosis and treatment of hyperthyroidism through a comprehensive and systematic assessment of the benefit, harm, and cost of select diagnostic and treatment interventions. Specifically, this CPG aims to determine the (1) effectiveness, safety, and cost of diagnostic tests and treatment interventions used in hyperthyroidism with the aim of reducing disease-specific morbidity and mortality; (2) certainty of the evidence for each of the selected diagnostic test and treatment intervention; and, (3) to develop evidence-based recommendations through a consensus process outlined in the DOH 2018 Manual for CPG Development.

Target Population

Views and preferences of the target population were sought/considered through different ways, including but not limited to the following:

1. Inclusion of a patient advocate/representative in the CPG development process, and as a member of the consensus panel

2. Explicit inclusion in the methodology for literature review of values and preferences of target population
3. Personal and/or directed consultation with a sample of target population (i.e., patients) on their views and preferences

The feedback and insights gathered were considered in the CPG development, drafting of the recommendations statement (including the strength of recommendations), and the applicability/implementability of the recommendations.

Target Users of this CPG

This CPG is primarily intended to be used by general practitioners and specialists. It focused on the existing and/or recent evidence on diagnosis and treatment of hyperthyroidism mainly among non-pregnant adults, with some guidance pertaining to issues unique to children and pregnant individuals. This clinical practice guideline (CPG) is intended to be used by primary care physicians or in the primary care setting. Although adherence to this guideline is encouraged by the Department of Health (DOH), it should not restrict the primary care physicians/clinicians in using their clinical judgment and considering patients' values, needs, and preferences while handling individual cases. Clinicians and relevant stakeholders must always exercise sound clinical decision-making as the individual patient's history, current physical status, and responses to treatment may vary.

Payors and policymakers, including hospital administrators and employers, can also utilize this CPG. Still, nonconformance to this document should not be the sole basis for granting or denying financial assistance or insurance claims. Recommendations from this CPG should not be treated as strict rules to base legal action

CPG Development Methodology

This CPG employed the de novo mode of CPG development. Following the recommended CPG process in the DOH Manual on Practice Guideline Development, the GRADE approach was used. The GRADE Adolopment (as applicable) and Evidence-to-decision (EtD) framework were utilized in finalizing the recommendations.

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Evidence Synthesis

Search Methods and Strategies

A systematic search of local and international electronic databases (i.e. MEDLINE, CENTRAL, Google Scholar, HERDIN, clinicaltrials.gov, and UpToDate) was done from database inception until September 30, 2022 by the Evidence Review Experts (ERE). For therapeutic interventions, at least two reviewers looked for direct evidence from randomized controlled trials (RCT), systematic reviews (SR), and/or meta-analyses. In their absence, quasi-randomized and observational studies were assessed for possible inclusion. For diagnostic interventions, RCTs and/or diagnostic test accuracy (DTA) reviews reporting clinical outcomes of benefit or harm of these diagnostic strategies or interventions and resulting treatment were sought. If no direct evidence was found, observational studies that reported sensitivity, specificity, and other diagnostic accuracy estimates were sought.

Inclusion and Exclusion Criteria

For each research question, the scope (inclusion and exclusion criteria) of the literature search was dictated by the population, intervention, comparator, outcomes, and methodology. Refer to the Annex document for the inclusion and exclusion criteria of each question.

Study Quality Assessment

The methodological quality of each study was appraised using the Cochrane Risk of Bias Tool (i.e., ROB1 tool) or QUADAS-2, whichever was applicable. Studies with similar PICO were pooled and the effect estimates were determined using RevMan 5.0.

Data Synthesis

A systematic synthesis of the evidence was done using RevMan 5.0 wherein appraisal of included studies in the review for each research question and the synthesis of their effect estimates for critical and important outcomes were analyzed. The synthesized data are then compiled into an evidence summary. The balance of benefits and risks became the basis for the draft recommendations. The evidence summaries guided the consensus panel meetings in the decision-making process of the multi-sectoral consensus panel.

Formulating Recommendations

Certainty of Evidence and Strength of Recommendations

The certainty of the evidence (CoE) for each outcome of interest was assessed using GRADEPro, which considers the risk of bias and the presence or absence of any indirectness, imprecision, inconsistency, and other considerations (i.e., publication bias). The overall certainty of the evidence was based on the lowest certainty rating of the top seven (7) critical and important outcomes. The rating of importance of outcomes into critical, important, or relevant was decided on by the multi-sectoral consensus panel.

Rating of Outcomes

The Consensus Panel members reviewed the evidence and the draft recommendation by the Technical Working Group. Through an online survey, they determined the relative importance of all outcomes for each research question in clinical decision-making. Each outcome was scored on a scale of 1 to 9. Outcomes rated 7 to 9 were considered as critical outcomes; 4-6 were considered as important but not critical outcomes; and, those outcomes that were rated 1 to 3 were considered of limited importance. The CP members determined the top seven (7) critical and/or important outcomes for each of the research questions.

Consensus Process

Virtual CP en banc meetings were conducted in 5 sessions (i.e., 3 to 4 questions per session). Prior to the actual meetings, evidence summaries were compiled as one evidence base and were sent to the CP members. An orientation regarding the CPG process and interpretation of the evidence was given by a guideline methodologist. Outcomes considered critical and important for decision-making by healthcare providers and consumers were identified by the CP through an online survey. During individual review of the evidence base, the CP members were asked to fill out an Evidence-to Decision (EtD) questionnaire. A technical facilitator moderated all CP meetings. Key findings for each guideline question were presented by an evidence reviewer. Using a nominal group technique, CP members were given the opportunity to address any issue or clarification related to the evidence and explain the rationale behind their votes.

CP members voted on the direction (for or against) and strength (strong or weak) of the final recommendation based on the certainty of the evidence, balance between benefits and harms, values, preferences, and burden on patients, cost and resource implications, equity, acceptability, feasibility, and appropriateness. Consensus was achieved when 75% of the CP members agreed on a proposed recommendation or decision. If no consensus was reached after three rounds of voting, a modified Delphi process was done as coordinated by the steering committee. A standardized language was used to indicate the direction, and strength of each recommendation (e.g., suggest for weak, recommend for strong recommendations).

Guideline Dissemination

The CPG was submitted to the National Practice Guideline Clearinghouse of the DOH for review, assessment, and approval. The DOH, EAMC, and the involved organizations shall also promote the use and uptake of these recommendations nationally through publications, lectures, and other forms of notifications of all possible stakeholders.

The Disease Prevention and Control Bureau of DOH will transmit copies of this CPG to the Philippine Health Insurance Corporation, health maintenance organizations, and pharmaceutical industry partners. This CPG will also be presented during conferences and annual conventions of medical societies. Copies of this CPG with the endorsement of relevant medical institutions will be sent to medical schools and libraries to integrate the recommendations in their training curricula, with the support of the faculty members and heads of hospital-based departments, including but not limited to surgery, radiology, pathology, and internal medicine. The Task Force of this CPG shall also develop a simplified version of this CPG and make it available in a format ready for reproduction and dissemination to patients in clinics and hospitals including online versions.

The evidence base and the final manuscript will be made available both in print and electronic media through the DOH, the EAMC, and the organizations involved in its creation.

Guideline Monitoring and Evaluation

The Task Force will distribute a questionnaire annually, aiming to determine the best practices of relevant stakeholders in terms of diagnosis and management of hyperthyroidism. Monitoring the use of this clinical practice guideline may also be a subject of research by interested parties.

For monitoring and auditing, the CPG group will use the final strength of recommendation to determine key performance indicators. Those recommendations voted with "Strong Recommendation" will be used as indicators. These indicators will be identified once the strength of recommendations is finalized for each of the guideline review questions.

Specific operational definitions of how the criteria should be measured will be based on the recommended standards as defined in the DOH Manual for CPG Development. These will also be defined after consultations with the EGMD of the DOH as there is limited local literature on how these are defined.

External Review

External reviewers representing end-users and/or stakeholders, or technical experts were identified and asked to perform a technical review of the draft manuscript. The manuscript of this Clinical Practice Guideline was reviewed by a clinical epidemiologist and methodology expert, a non-content clinician, and a content expert clinician. A customized template was used and a subset of items were asked per review question as follows:

1. General Response (to the guideline as a whole)
2. Comments/feedback on this specific recommendation
3. What is the level of completeness in terms of:
    a. search of evidence?
    b. Synthesis and analysis of evidence base?
4. Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.
5. What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.
6. Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)
7. Any comments on the "implementability" of this recommendation?

Comments or feedback gathered from the external review process were used as reference for revisions (as needed).

Guideline Updating

The recommendations herein shall hold until such time that new evidence on diagnostic tests, medicines, and surgical interventions for hyperthyroidism emerges or other contingencies compel the updating of this CPG (i.e., usually after three to five years).

The task force will follow the same methodology used for the development of the current CPG. The Hyperthyroidism Task Force intends to review this CPG no later than 2026.

The updating of the CPG wil follow the recommended CPG process in the DOH Manual on Practice Guideline Development and the GRADE approach will be used. The GRADE Adolopment (as applicable) and Evidence-to-decision (EtD) framework will be utilized in finalizing the recommendations.

Preparation

The Task Force Steering Committee will set the CPG objectives, scope, target audience, and clinical questions. The Task Force Steering Committee will convene 1. the technical working group involved in creating the evidence base and 2. the consensus panel involved in finalizing the recommendations for each clinical question included. Questions will be prioritized using the criteria set by DOH.

COI Management

All task force members will submit their declaration of conflict of interest (COI) and curriculum vitae. A COI committee will review and evaluate the potential conflicts of interest and give their recommendation on how to manage them. In general, those with financial COI will not be allowed to vote for questions related to the COI. Those with non-financial COIs (such as authorship related to the CPG topic) will be allowed to participate but COIs will be declared during the panel meeting and the final manuscript.

Evidence Synthesis

The clinical questions will be developed using the PICO (population, intervention, comparator and outcome) format.

For each question, we will perform a systematic medical literature search of the MEDLINE (via PubMed), The Cochrane Library, and (OTHER DATABASES). Systematic reviews that will meet our inclusion criteria to answer our clinical questions will be used directly to identify relevant articles and summary of findings. If no related reviews will be found, we will conduct de novo systematic reviews. We will critically appraise the methodological quality of the included studies using the standard tools such the Cochrane Risk of Bias tool (ROB 1.0) for randomized controlled trials (RCTs), Painless EBM appraisal criteria, the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) for diagnostic accuracy studies, and the Newcastle–Ottawa Scale (NOS) for observational studies. We will use the GRADE approach to rate the certainty of evidence and the strength of recommendations.

Evidence to Decision Consensus Approach

The multisectoral consensus panel (CP) will be tasked to review the evidence summaries and develop recommendations during the en banc meeting. Prior to the meeting, the CP will prioritize critical and important outcomes.

The CP will be provided with the evidence base for all the clinical questions and a draft recommendation solely based on the trade-offs between benefit and harm and the certainty of evidence. Each CP member will then be asked to complete an EtD questionnaire . The purpose of this questionnaire survey is for each CP member to explicitly incorporate other important factors such as cost-effectiveness, patient values and preferences, applicability, feasibility, appropriateness, equity, and resources in their decision-making.

The direction and strength of each recommendation will be determined by a formal consensus method. Recommendations will be considered to have reached a consensus when 75% or more of the voters

agreed on the proposed recommendation. If consensus will not reached initially, two further rounds of voting will be allowed. A modified Delphi methodology is planned in case no consensus will be reached during the en banc meetings. On the rare occasion that no consensus would not be reached, no recommendation would be indicated in the final CPG manuscript.

Editorial Independence

Funding Source

The development of this CPG was funded by the Department of Health through the East Avenue Medical Center but were not involved in the decision-making process of the guideline development and only provided feedback when sought by the task force.

Management of Conflicts of Interest

An independent oversight COI committee composed of three (3) members reviewed and adjudicated the accomplished COI forms of each member of the task force to find if there are any significant COI. The Oversight Committee (OC) thoroughly reviewed the declaration of conflict of interest (DCOI) of each of the Task Force members, particularly the Consensus Panelists (CP) who will make recommendations on how to manage the COI.

For task force members with potential significant COIs, the members of OC conducted additional investigations with due diligence to ensure the integrity of the CPG process and the final recommendations.

All task force members submitted a DCOI and their curriculum vitae (CV) prior to the initiation of the guideline development process. The disclosure included a 4-year period of personal potential intellectual and/or financial conflicts of interest (COI).

Management of the COI of the Consensus Panel, Technical Coordinators, and Task Force Steering Committees was deliberated and decided by the OC, using the pre-agreed criteria. Those with significant potential COI were not allowed to join or vote depending on the COI.

Recommendations and Evidence Summaries

Clinical Question No. 1 Should we do routine paired testing (fT4/T4 plus TSH) versus TSH testing alone for initial evaluation of thyroid function among patients with suspected thyrotoxicosis?

Recommendation No. 1A
Among patients with suspected thyrotoxicosis*, we recommend the routine use of TSH for initial evaluation *(Very low certainty of evidence; Strong recommendation)* **In patients with florid signs/symptoms of thyrotoxicosis, treatment** may be initiated pending laboratory results.* ***Treatment – Supportive treatment (beta-blockers, etc.) for adrenergic symptoms with or without thionamides*

Recommendation No. 1B
Among patients with suspected thyrotoxicosis, we suggest against routine paired fT4/T4-TSH testing as initial evaluation/work up due to no evidence *(No evidence; Weak recommendation)*

Introduction

Thyroid function tests are common blood tests composed of TSH (also called thyrotropin), fT4/T4 and fT3/T3, each of which entails expense in the evaluation of thyroid dysfunction. Pituitary TSH stimulates the thyroid gland to grow, manufacture and secrete thyroid hormones. T4 and T3 are highly protein bound in blood with less than 1% being in the free unbound forms, fT4 and fT3. Only the free hormones are biologically active and exert negative feedback on pituitary TSH secretion to prevent further stimulation of thyroid hormone production.[201] For these reasons, free hormone determinations are preferred over total hormone assays but either one will suffice depending on the availability of tests. The hypothalamic-pituitary-thyroid axis feedback mechanism is very sensitive, hence, small changes in thyroid hormones lead to wide swings in TSH levels in the opposite direction, making TSH the single best screening test. In the earliest stages of primary thyrotoxicosis, TSH is suppressed and is the first to become abnormal.[201] TSH alone may suffice in screening for thyroid dysfunction that are of low suspicion. Full interpretation of thyroid function tests, however, requires paired tests of TSH and fT4/T4 and, occasionally fT3/T3.

Summary of Efficacy and Safety

Sensitivity and Specificity

Indirect evidence from a diagnostic study showed the sensitivity and specificity of fT4, T4, and TSH in determining thyroid dysfunction in general.[101] Thyroid hormone tests and reference tests were done among normal volunteers, patients with nonthyroidal illness, healthy pregnant women, and untreated hyperthyroid patients. [101] Thyroid function tests included total T4 or free T4 from Amersham Corp, Arlington, III. The sensitive TSH IRMA was done with two kits (i.e., Abbott Laboratories, North Chicago, III; Serono Diagnostics Inc, North Chicago [IRMA]). The reference test was the physician's clinical judgment based on history and physical examination, the subject's general health, thyroid status, and use of drugs. However, the procedures to establish the classification were unclear. The manufacturers' suggested normal ranges for T4 and free T4 were 58-161 nmol/L and 10-28 pmol/L, respectively. For sensitive TSH assays, normal ranges were 0.45-6.2 mU/L (test 1) and 0.2-5 mU/L (test 2).[101]

TSH values by IRMA in test one had a slightly higher sensitivity than in test two (95% vs. 89%). Test two had marginally higher specificity (95% vs. 92%) than test one. In terms of discriminating the euthyroid among those who tested negative, TSH test two had a slightly higher value (Sp 95%) compared with fT4 (94%) and T4 (90%). The sensitivity of the T4 tests (T4: 76%; fT4: 82%) is lower than that of sensitive TSH tests.[101]

Association with Clinical Parameters

Indirect evidence from one systematic review on the association of clinical parameters (e.g., atrial fibrillation, other cardiac parameters, cancer, frailty, dementia, pregnancy outcomes, and death) was also included.[102] The meta-analysis classified each result in a study as showing a significant result or a non-significant result. A significant result indicates an association between the thyroid hormone or TSH levels and the medical condition at a 5% significance level. The systematic review treated the result as a binary response: significant for success and failure for non-significant. They performed statistical test for those types of tests that were found significant. Further, they performed simple logistic regression analysis for each identified stratum (smallest and largest number of subjects; simple or complex model).

There were 58 studies included in this meta-analysis of cross-sectional and prospective cohort studies with diverse populations (ages ranging from 18 to 82.7 years), both sexes, and various assays. Thirty-six studies examined associations with only free T4 and TSH levels.[103-138] The study populations comprised strictly euthyroid subjects, subjects either euthyroid or with subclinical thyroid dysfunction, and subjects euthyroid or with subclinical/overt thyroid dysfunction. The number of results of associations in each study ranged from 3 to 180. Analysis of these data confirmed associations with fT4. Free T4 levels had a significant association with a clinical parameter in 50% of the comments of the studies, whereas TSH had a significant association in only 23% (fT4 vs. TSH, p <0.0001). It is important to note the varied populations (i.e., strictly euthyroid, subclinical thyroid dysfunction, and overt thyroid dysfunction) used for analyzing these associations.[102]

Results showed that atrial fibrillation, osteoporosis, and cancer were associated with higher thyroid function using TSH and/or thyroid hormone levels across and beyond the reference range. Features of metabolic syndrome were associated with lower thyroid function levels. Compared to mid-range thyroid function, both high and low thyroid functions were associated with clinical and pathological features of cognitive decline, frailty, total/cardiovascular mortality, cardiac physiology, cardiac disease, and pregnancy outcomes.[102] This study was downgraded to very low certainty evidence due to the study design, serious risk of bias, and indirectness.

Correlation with Primary Hyperthyroidism

An observational study reviewed the utility of paired test of fT4 and TSH in the assessment of functional thyroid status of the population with or without treatment.[139] 34,159 paired tests done by chemiluminescent microparticle immunoassay (CMIA) in two years were studied. Combined reference values of fT4 and TSH were used to classify the study population into 9 classes which included primary hyperthyroidism. The paired-test analysis included both pediatric [neonates (< 1 month, 1.48%), infants (1-12 months, 3.71%), children and adolescents (>1 year to 18 years, 14.07%)] and adult population (80.73%).

Each class has distinct reference ranges of fT4 and TSH and their correlation pattern. Only moderate correlation (r =0.386; Sig. 0.000) was found between the paired testing and primary hyperthyroidism (high fT4, low TSH). The frequency of cases in primary hyperthyroidism class was 1.65% (564/ 34,159 paired tests). The reference ranges used for determining these cases wer 35.59 to 38.45 (for fT4, pmol/ml) and 0.12 to 0.13 (for TSH, µIU/L). This study was downgraded to very low certainty evidence due to the study design, serious risk of bias, and indirectness.

Safety Outcome

The research findings did not indicate any unfavorable occurrences resulting from the examinations.

Additional Considerations for Decision-making

Cost

We did not find any recent study that tackled the cost-effectiveness of using thyroid hormone level (T4) and/or TSH level other than the 1989 study.

Patient's Values and Preference, Equity, Acceptability and Feasibility

There is currently no local study that looked into patients' values, preferences, and equity. Combined fT4 and TSH levels seemed acceptable as these were used in classifying thyroid dysfunctions in the prevalence study conducted by endocrinologists in the country.

Consensus Issues

The choice between paired and sequential testing for patients suspected of having thyrotoxicosis is a common dilemma among clinicians. TSH testing alone stands out as a highly sensitive and specific test for thyrotoxicosis. Although, thyrotoxicosis may be treated outright, TSH testing is highly recommended to ensure that patients will be given the right care.

On occasion, thyrotoxicosis may be treated while awaiting the results of the diagnostic test, especially among patients with florid signs (e.g., tremors and tachycardia). The diagnostic accuracy of TSH can be significantly enhanced when combined with fT4 or T4 testing, particularly in cases where there is a high suspicion of thyrotoxicosis. Moreover, among the pediatric population, repeated blood sampling often causes anxiety and distress not only to the child but also to the parents. Healthcare providers are challenged to balance the economic implications of diagnostic testing with the well-being of their patients. Hence, in this population, conducting an initial assessment of both TSH and ft4/T4 should be considered to minimize the need for repetitive blood sampling and potential delays in diagnosis due to patient non-compliance.

Despite the undeniable advantages of paired testing, it's important to acknowledge that it comes at a higher cost compared to TSH testing alone. Consequently, the choice between paired and sequential testing for thyrotoxicosis necessitates a comprehensive assessment that takes into account various factors, including the degree of suspicion, convenience, and the patient's age. It is crucial to ensure that the selected diagnostic approach aligns with the patient's clinical needs while also considering broader healthcare disparities and resource constraints, particularly in marginalized areas. In addition, it is important for the government to make these tests available to all areas in the country to ensure correct diagnosis.

Clinical Question No. 2 Should we routinely do T3 testing on top of TSH and fT4/T4 testing in the workup of individuals suspected to have thyrotoxicosis?

Recommendation No. 2
Among patients suspected of having thyrotoxicosis, we suggest against doing routine T3 testing on top of TSH and fT4/T4 testing *(Very low certainty of evidence; Weak recommendation)*

Introduction

It is unclear whether ordering combined TSH+T4+T3 tests will be more beneficial compared to sequential testing (i.e., ordering T3 only after knowing TSH+T4 results) among patients with suspected thyrotoxicosis. Although some T3 (20%) are secreted by the thyroid gland, majority of circulating T3 are from peripheral deiodination of T4. Therefore, T3 levels generally follows that of T4 with one important exception.

The most common etiology of thyrotoxicosis with hyperthyroidism (ie increased thyroid gland production and secretion of thyroid hormones) is Graves' disease, followed by solitary toxic adenoma, multinodular toxic goiter, and trophoblastic tumors.[66] In hyperthyroidism, there is a predominance of T3 overproduction over T4. A high T3/T4 ratio of more than 20 ng/µg or a high fT3/fT4 ratio of >4.4 (10^{-2} pg/ng) favors hyperthyroid causes of thyrotoxicosis.[202,203] In 5% of patients Graves' disease, only T3 is elevated and T4 remains normal, this is called T3 toxicosis. On the other hand, thyrotoxicosis without hyperthyroidism may be due to subacute thyroiditis, excessive ingestion of synthetic thyroid hormone, or the side-effects of some drugs (amiodarone), where T4 elevation predominates and is associated with lower T3/T4 and fT3/fT4 ratios.

Given the widespread use and variability in the ordering of these tests, this review aimed to determine the clinical utility and cost-effectiveness of routine testing using all three tests (TSH, T4, T3) in this patient population.

Summary of Efficacy and Safety

No evidence was found assessing the efficacy or adverse effects associated with combined TSH+T4/fT4+T3 tests compared to TSH+T4/fT4 only.

Certainty of Evidence

The certainty of evidence regarding these reported diagnostic accuracy estimates is very low and implies that more well-designed observational studies are needed. Reasons for downgrading include serious inconsistency (high heterogeneity), serious indirectness (triple testing not directly compared with paired TSH+T4), and serious risk of bias in the included studies (use of a case-control design, varying cut-off values for index tests).

The certainty of evidence supporting the potential benefit of adding fT3 with TSH+fT4 is very low due to serious indirectness (unclear effect for populations other than hospitalized aged patients), serious risk of bias (observational study design limitations).

Recommendations from Other Groups

Existing guidelines from other groups have not explicitly recommended routine testing using all three thyroid function tests for adults or children with suspected thyrotoxicosis (see Table 3).[10, 44, 79, 147] Of these

guidelines, only UK-NICE has conducted a formal evidence review but found no evidence comparing any thyroid function testing strategy.[147]

The UK NICE guideline recommended a cascading approach instead of simultaneous TSH, T4, T3 testing, with fT4 and fT3 being taken only if TSH suggests hyperthyroidism to avoid unnecessary laboratory costs. Serum fT3 may be useful for identifying mild hyperthyroidism,[8] T3-toxicosis,[43] non-thyroidal illness,[44] as well as for adjusting levothyroxine dosage if TSH and fT4 are elevated. Repeating thyroid function tests was recommended when symptoms worsen or new symptoms develop, but no sooner than 6 weeks from the last testing period.

For children, the 2022 European Thyroid Association mentioned the need to do all three tests, citing that an elevated fT3 is more sensitive for detecting overt hyperthyroidism than fT4.[44] The UK NICE guidelines also justified that fT4 and TSH may be ordered simultaneously in children as the etiology of thyroid disease in this population tends to include more secondary causes and because of the difficulty in obtaining multiple blood samples. fT3 should be measured if TSH is low.[44]

Additional Considerations for Decision-making

Cost

We did not find any local or international economic evaluation studies relevant to this guideline question. Table 3 provides some estimates of the costs of TFTs in the Philippines. Local prices vary depending on the institution or type of assay. Some institutions offer combined T3/fT3, T4/fT4, and TSH as part of a package or thyroid function panel.[148-150]

Table 3. Estimated unit costs of TFTs

Procedures/Medications	Unit Cost (PHP)[151]
Individual tests	
TSH-ECLIA	420 – 715
TSH-IRMA	1,902
fT4-ECLIA	715 – 1,742
T4	500
T3	500
fT3	485
Combined tests	
fT4 + TSH-ECLIA (enhanced chemiluminescence immunoassay)	710 – 1,430
fT4 + TSH-IRMA (immunoradiometric assay)	3,642 – 6,250
fT3 + fT4 + TSH	2,200 – 9,000+

A retrospective records review in Ethiopia involving 382 patients (n=8,313 thyroid function tests) seen in a 1-year period found that combination tests are commonly done (75.7%) and results in extra financial burden for patients.[16] The estimated out-of-pocket cost of unnecessary testing (i.e., diagnosis could have been made by performing TSH only) was highest with TSH+T3+T4 at USD 1,803 (PHP ~98,652), followed by TSH+fT3+fT4 at USD 490 (Php ~26,810). Most (59-63%) of these triple tests turned out normal. If only an initial TSH was ordered, about USD 425,000 (Php ~23.2 million) could have been saved from the cost of the reagents required to perform TFTs.

Patient's Values and Preference, Equity, Acceptability and Feasibility

No relevant local evidence was found. In other countries, inappropriate ordering of free thyroid hormone tests is reportedly common.[152-155] To curb this practice, several behavioral strategies have been proposed. A 2016 systematic review found that various behavioral interventions may be effective in reducing the volume of unnecessary thyroid function tests and improving the pattern of test ordering, including educational events, guidelines and protocols, audit and feedback, and decision-making tools.[156] Studies on this subject were assessed to have poor methodological quality, which introduces uncertainty as to whether implementing these strategies will really be effective.

Consensus Issues

T3 testing, while available, is not commonly included as a routine component of clinical practice when evaluating suspected cases of thyrotoxicosis. This decision is primarily driven by a careful consideration of cost-effectiveness and the limited diagnostic advantages it offers in conjunction with the standard tests, such as TSH and T4 or free T4 (fT4).

Incorporating T3 testing alongside TSH and T4 or fT4 does indeed come with an associated financial burden for the patient. This is an important consideration in modern healthcare where cost-efficiency is paramount. It's essential to weigh the potential benefits against the additional expense.

Most thyrotoxicosis cases can be effectively identified and managed through the evaluation of TSH and T4 or fT4 alone. The marginal increase in diagnostic accuracy achieved by including T3 does not typically justify the added costs and complexity associated with the test. T3 is needed only if a suppressed TSH cannot be explained by normal fT4/T4 to differentiate T3 toxicosis (low TSH, normal fT4/T4 and high fT3/T3) from subclinical hyperthyroidism (low TSH, normal fT4/T4 and normal fT3/T3).

Clinical Question No. 3 Should we use history and physical examination findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves' disease from non-Graves' disease (i.e., other etiologies) among non-pregnant patients with biochemically confirmed thyrotoxicosis?

Recommendation No. 3
Among non-pregnant patients with biochemically confirmed thyrotoxicosis, we suggest against history and physical examination findings alone to differentiate between Graves' disease versus non-Graves' disease due to harms of unnecessary treatment *(Low certainty of evidence; Weak recommendation)*

Introduction

Palpitations, tachycardia, tremors, weight loss and heat intolerance are non-specific signs and symptoms found in both Graves' disease (GD) and non-Graves' causes of thyrotoxicosis. Ophthalmopathy, pretibial myxedema and acropachy (clubbing of fingers) are considered specific to Graves' disease but they are more often not present.

Graves' ophthalmopathy is present in up to 50% of cases.[194] Graves' ophthalmopathy and hyperthyroidism mostly present simultaneously, occasionally Graves' ophthalmopathy precedes or follows the onset of hyperthyroidism by many years.[207] Pretibial myxedema, a nodular or diffuse thickening of the pretibial skin, is diagnosed on physical examination in only 13% of patients with severe Graves' ophthalmopathy. Only about 20% of patients with pretibial myxedema have thyroid acropachy.[207]

Prompt diagnosis and treatment in geographically isolated areas may be particularly concerning due to limited access to TSH receptor antibody testing or thyroid scintigraphy to definitively diagnose GD. However, overtreatment with anti-thyroid drugs (ATDs) may also unnecessarily put patients at risk for serious adverse effects such as liver injury and agranulocytosis. Therefore, we evaluated whether the use of history and physical examination alone is sufficient to differentiate GD versus non-GD.

Summary of Efficacy and Safety

Efficacy

Clinician diagnosis of GD had a sensitivity of 87.65% (78.74 to 93.15%) and a specificity of 65.82% (54.85 to 75.33%). Using history and physical examination alone, 34,194 out of 100,000 people assessed will have a "positive" GD clinical diagnosis, 23 of these will have Graves' disease (true positive). However, 34,171 of these people will not have Graves' disease, even though their test result was positive (false positive). Table 21 below summarizes the diagnostic accuracy of clinical diagnosis of GD compared to TSH receptor antibody.

Table 4. Diagnostic accuracy of clinical diagnosis of GD compared to TSH receptor antibody

Outcome	Point estimate	95% Confidence Interval	Certainty of Evidence
Sensitivity	88%	79% to 93%	low
Specificity	66%	55% to 75%	low
Positive likelihood ratio	2.57	1.87 to 3.52	low
Negative likelihood ratio	0.19	0.10 to 0.34	low
Positive predictive value	72.45%	62.88 to 80.32%	low

Negative predictive value	83.87%	72.79 to 91.00%	low

Harms of overtreatment

If 342 out of 1,000 patients were falsely diagnosed with GD and were treated with ATD, it is estimated that 26 patients will develop agranulocytosis. The computed rates of adverse events of overtreatment with ATDs based on a systematic review and meta-analysis of the side effects of ATDs are seen in Table 22.[198]

Table 5. Probability of adverse events with treating false positive patients with ATDs

	Incidence of AE from ATD	Rate of AE from overtreatment with ATDs (per 1,000)
skin reaction	15.4%	53
elevated transaminase	15%	52
agranulocytosis	7.4%	26
impaired liver function	0.7%	3
elevated bilirubin	0.2%	1

Certainty of evidence

The study was assessed to have serious risk of bias due to the lack of blinding in the performance of the reference test. Since it was a retrospective study, the conduct of the clinical diagnosis and flow of patients were unclear. The evidence was also rated as having low certainty due to serious risk of bias and issues on indirectness. The clinical diagnosis of GD was not explicitly mentioned to be based on the presence of exophthalmos, pretibial myxedema, and acropachy. Likewise, the ability to differentiate between GD and non-GD may differ from a specialist and a primary care physician, which may further limit the sensitivity and specificity of a clinical diagnosis.

Recommendations from Other Groups

Only the Brazilian Society of Endocrinology and Metabolism had a consensus statement[199] on this question. They stated that "the diagnosis of Graves' hyperthyroidism can be established with relative confidence in patients with moderate to severe symptoms of thyrotoxicosis, recent ophthalmopathy, and diffuse goiter. In these cases, no additional tests are needed to investigate its etiology." There was no mention of the certainty of evidence or the strength of the recommendation.

Additional Considerations for Decision-making

Cost

We did not find any local cost-effectiveness study comparing the use of a clinical diagnosis versus TSH receptor antibody testing to differentiate GD from non-GD. The cost of arriving at the diagnosis is listed below.

Parameter	Diagnostic Test (or treatment)
Cost of a clinical diagnosis	Endocrinologist= Php 500-1,000/consultation Internist = Php 400-800 General Practitioner = Php 300-600
Cost of TSH receptor antibody	Php 5,000-9,000
Cost of Thyroid scintigraphy	Php 2,500-5,000

Consensus Issues

In the management of any medical condition, the process of history-taking and physical examination (PE) holds a pivotal role. These fundamental clinical practices allow healthcare providers to gather crucial information and assess the patient's condition. However, it is important to acknowledge that the interpretation of symptoms and physical examination findings can be inherently subjective, and this subjectivity can affect both the sensitivity and specificity of relying solely on history and PE for diagnosis.

Moreover, distinguishing between specific subtypes of a condition, such as Graves' disease versus non-Graves' disease in the case of thyrotoxicosis, can vary among physicians. This variability in clinical judgement can also limit the accuracy of a clinical diagnosis.

While certain clinical findings may raise suspicions of Graves' disease, prompting the need for further diagnostic procedures, it is worth noting that in some cases, a definitive diagnosis can indeed be achieved through history-taking and physical examination alone. In such instances, patients can potentially benefit from cost savings by avoiding additional tests, especially in resource-limited settings.

However, it is paramount to underscore the critical importance of accurate diagnosis in the context of patient care. Committing to an incorrect diagnosis can have far-reaching consequences, potentially causing psychological distress to the patient and leading to misdiagnosis or overdiagnosis. These scenarios can result in adverse effects, under or overtreatment, and ultimately compromise the patient's well-being. Confirmatory testing becomes essential to avoid these pitfalls.

In summary, while a comprehensive clinical history and physical examination remain foundational in medical practice, they may not suffice for all cases, especially in conditions like hyperthyroidism. To ensure health equity and optimal patient outcomes, a holistic approach to diagnosis is essential. Accurate diagnoses not only help in providing appropriate treatment but also prevent unnecessary healthcare expenses, including hospitalizations, which can further promote efficient and equitable healthcare delivery.

Clinical Question No. 4 Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?

Recommendation No. 4A
Among adult patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease *(Low certainty of evidence; Weak recommendation)*

Recommendation No. 4B
Among pediatric patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease *(Low certainty of evidence; Weak recommendation)*

Introduction

While the most common cause of overt thyrotoxicosis worldwide is still Graves' disease, there are several other etiologies, such as toxic multinodular goiter, acute and subacute thyroiditis, drug-induced thyroid dysfunction, and factitious ingestion of excess thyroid hormones.[26] Accurate determination of the etiology of thyrotoxicosis is important for proper management. Differentiating Graves' disease from other forms of thyrotoxicosis is particularly important as the natural history and management options differ.[66]

Graves' disease causes thyrotoxicosis through autoimmune stimulation of the thyroid gland by circulating immunoglobulins that lead to overproduction of thyroid hormones by binding to the thyroid-stimulating hormone receptors (TSH-Rs) of the thyroid gland. This process variably uncouples the thyroid from its usual regulatory feedback mechanism, the TSH from the anterior pituitary gland.[3] The same autoantibodies are proposed to also cause ophthalmopathy, pretibial myxedema and acropachy in susceptible patients. The presence of circulating autoimmune TSH-R antibodies (TRAb) have been utilized to confirm the diagnosis of Graves' disease among patients presenting with thyrotoxicosis.

Summary of Efficacy and Safety

Diagnostic and accuracy outcomes

The sensitivity and specificity of TRAb in diagnosing Graves' disease compared to the final clinical diagnosis among adults were 0.93 (95% CI 0.87, 0.96; N=3991; 8 studies, 14 assay types) and 0.92 (95% CI 0.85, 0.96; N=3991; 8 studies, 14 assay types).

In the pediatric age group, the sensitivity and specificity of TRAb in diagnosing Graves' disease compared to the final clinical diagnosis were 0.99 (95% CI: 0.52, 0.1; N=548; 2 studies, 2 assay types) and 0.94 (95% CI 0.90, 0.96; N=548; 2 studies, 2 assay types).

Safety

We did not find any study on safety outcomes with TRAb determination.

Certainty of evidence

Out of the 11 studies in the adult population, 2 studies had high overall risk for bias due to inclusion of the index test in the reference standard leading to incorporation bias.[86-88] The studies of John, Liu, Silva and Struja had unclear patient selection risk of bias. While the studies of John and Silva were unclear on whether the reference standard results were interpreted without knowledge of the results of the index tests. Overall certainty of evidence was downgraded due to risk of bias and indirectness owing to the difference between the study and locally available assays.

Both studies in the pediatric age group also had high risk of bias due to incorporation of the index test in the reference criterion. Overall certainty of evidence was downgraded due to risk of bias and indirectness because of lack of representative race in the study population and the assays used in the pediatric studies were both cell-based bioassays dissimilar to locally available assays. Certainty of evidence for the sensitivity outcome was further downgraded due to imprecision.

Recommendations from Other Groups

The American Thyroid Association[10] strongly recommends TRAb measurement "if the diagnosis is not apparent based on the clinical presentation and initial biochemical evaluation". The European Thyroid Association[24] strongly recommends TRAb as "a sensitive and specific tool for rapid and accurate diagnosis and differential diagnosis of Graves' hyperthyroidism." Both societies cited moderate to high quality of evidence.

Additional Considerations for Decision-making

Cost

We did not find any local study on the economic evaluation of TRAb use in Graves' disease. One study in the United States developed an evidence-based economic model to determine the average time to diagnosis and annual costs associated with various diagnostic algorithms for Graves' disease in a population of 100,000 managed care enrollees. They found that algorithms incorporating a TRAb assay that specifically determines thyroid stimulating immunoglobulins is projected to result to a 47% overall savings due to reductions in procedures and specialist office visits.[89]

TRAb test costs from Php 5,100 to 9,100 in the private setting and around 3,500 to 7,000 in the public setting.[90-94]

Procedure	Public Settings Unit Cost (PHP)	Private Settings Unit Cost (PHP)
TRAb assay	3,500 - 7,000	5,100 – 9,100

Patient's Values and Preference, Equity, Acceptability and Feasibility

We did not find any study on patient values and preferences, equity, nor acceptability of TRAb. For feasibility, TRAb test is available in some large tertiary centers and in large diagnostic laboratories. Determination of serum TRAb requires blood extraction and fasting is unnecessary.[95]

Alternatively, a thyroid scan may be utilized to confirm Graves' disease. This is locally available in some but not all large tertiary centers. Cost of procedure ranges from Php1,000 to 3,700 in the public setting and Php 2,000 to 5,000 in private settings.[96-98]

Consensus Issues

The utilization of TRAb testing has witnessed a notable increase, serving not only as a means to confirm Graves' disease but also as a valuable tool for prognosticating the likelihood of remission. By measuring TRAb levels, healthcare providers can effectively confirm the diagnosis of thyrotoxicosis and distinguish its underlying cause. Moreover, TRAb testing is also valuable for pregnant women in their first trimester, aiding in differentiating between hyperemesis gravidarum and hyperthyroidism. This information is vital for proper patient management and ensuring optimal care during pregnancy.

TRAb testing is considered a safe and well-tolerated procedure for most individuals. The primary side effect typically experienced is slight discomfort or bruising at the blood draw site, which is generally manageable for adults. However, it's important to be mindful that the experience may be more distressing for children, and efforts should be made to minimize any discomfort or anxiety they may encounter during the testing process. Healthcare providers can employ child-friendly techniques and gentle approaches to ensure the procedure is as comfortable as possible for pediatric patients. Overall, TRAb testing remains a valuable diagnostic tool with minimal associated risks when performed with proper care and consideration for patient comfort.

TRAb testing is not readily available nor accessible in our country though. Moreover, it is relatively expensive compared to other diagnostic tests. The cost of TRAb testing may present a financial challenge for some patients, hence this factor should be taken into consideration when ordering the test.

Despite the cost and availability considerations, TRAb testing remains a valuable tool for diagnosing and managing thyroid-related conditions, providing critical information for healthcare providers to make informed decisions regarding patient care. Efforts should be made to strike a balance between the benefits of TRAb testing and its associated costs, ensuring equitable access to this important diagnostic tool for all patients who may benefit from it.

Clinical Question No. 5 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves' disease from the thyrotoxic phase of subacute thyroiditis?

Recommendation No. 5A
Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we recommend using 99m technetium pertechnetate thyroid uptake in differentiating Graves' disease from the thyrotoxic phase of subacute thyroiditis *(Moderate certainty of evidence; Strong recommendation)*

Recommendation No. 5B
Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest against the routine use of radioactive iodine uptake (I-131) (RAIU) in differentiating Graves' disease from subacute thyroiditis due to insufficient evidence *(Very low certainty of evidence; Weak recommendation)*

Introduction

Nuclear medicine has been an integral part of diagnostics and therapeutics for thyroid disorders. Thyroid uptake and scans may be used in the differential diagnosis of thyrotoxicosis when the etiology cannot be determined based on clinical and biochemical evaluation.[66] Patients with Graves' disease and other hyperthyroid causes of thyrotoxicosis usually have elevated thyroid uptake levels, while those with subacute thyroiditis and other non-hyperthyroid causes will have near zero uptake.[67] Iodine I-123, I-131 and 99m-technetium pertechnetate, are the usual agents used in these tests. Both I-123 and I-131 emit gamma rays detected by thyroid uptake and scan but I-131 also emits the tissue destroying beta particles, hence its utility for RAI therapy in Graves' disease and well-differentiated thyroid cancers. I-123 is preferred due to its shorter half-life and less radiation exposure to the body. I-123 however is more expensive and not available in the Philippines. The non-iodine 99m-Technetium pertechnetate is an analog of iodine, so it gets trapped and transported to the thyroid gland similarly to iodine but is not organified. It is cheaper and contains less amount of radiation to the body making it preferable over I-131.

Summary of Efficacy and Safety

Efficacy

Using a cutoff value of >1.00% thyroid uptake , the sensitivity and specificity of ^{99m}Tc pertechnetate uptake in diagnosing Graves' disease were 0.94 (95% CI 0.85, 0.99; N=78; 1 study) and 1.00 (95% CI 0.86, 1.00) respectively among adults with thyrotoxicosis when compared to the final clinical diagnosis.[68] When using a higher cutoff value of 1.55% thyroid uptake, lower sensitivity (0.92; 95% CI 0.79, 0.98) and lower specificity (0.87; 95% CI 0.69, 0.96) estimates were obtained using ^{99m}Tc pertechnetate uptake, compared to the final clinical diagnosis.[69] The certainty of the evidence ranged from low to moderate and was downgraded due to the high risk of bias in the reference standard and imprecision of results. Pooled estimates cannot be reported due to the heterogeneity of the studies (i.e., different cutoff scores and reference standards).

Table 5. Diagnostic accuracy of ^{99m}Tc pertechnetate uptake in the differential diagnosis of Graves' disease versus subacute (painless) thyroiditis among adults with thyrotoxicosis

Outcomes	No. of Studies (Participants)	Effect Estimate [95% CI]	Certainty of Evidence
Cutoff value: >1.00% ^{99m}Tc uptake [a]			
Sensitivity	1 (78)	0.94 [0.85, 0.99]	Moderate
Specificity		1.00 [0.86, 1.00]	Moderate
Positive Likelihood Ratio		–	–
Negative Likelihood Ratio		0.06 [0.02, 0.17]	Moderate
Cutoff value: >1.55% ^{99m}Tc uptake [b]			
Sensitivity	1 (69)	0.92 [0.79, 0.98]	Low
Specificity		0.87 [0.69, 0.96]	Low
Positive Likelihood Ratio		6.92 [2.77, 17.32]	Low
Negative Likelihood Ratio		0.09 [0.03, 0.27]	Low

CI: confidence interval

[a] Reference standard: final clinical diagnosis by an experienced endocrinologist based on thyroid scintigraphy, laboratory findings, and clinical data in the follow-up

[b] Reference standard: final diagnosis based on thyroid uptake results and clinical findings

Safety

The included studies did not report any safety outcomes regarding the use of ^{99m}Tc pertechnetate or radioiodine uptake among adults with thyrotoxicosis. While generally seen as a safe procedure, complications of thyroid uptake include pain at the injection site, hypersensitivity to radiotracer, and exposure of the fetus or baby during pregnancy or lactating period.[67] Thyroid uptake is contraindicated among pregnant and lactating women.[70]

Certainty of evidence

The overall certainty of the evidence was low due to the high risk of bias in the reference standard and imprecision of results.

Recommendations from Other Groups

The American Thyroid Association (ATA) and the Indonesian Society of Endocrinology (ISE) recommend using RAIU when the etiology of thyrotoxicosis cannot be determined based on clinical and biochemical evaluation. For patients with thyroid nodules, ATA, ISE, and the European Thyroid Association suggest using thyroid scan or scintigraphy.

Additional Considerations for Decision-making

Cost

We did not find any local or international economic evaluation study on thyroid uptake.

Procedures	Public Settings Unit Cost (PHP)	Private Settings Unit Cost (PHP)
^{131}I thyroid scan	2,500.00	–
^{99m}Tc thyroid scan	1,000.00	–

Patient's Values and Preference, Equity, Acceptability and Feasibility

We did not find any local study on patient values and preferences, equity, acceptability, and feasibility of thyroid uptake. In terms of equity and acceptability, thyroid uptake and scan is recommended by international groups for the differential diagnosis of thyrotoxicosis when the etiology cannot be determined based on clinical and biochemical findings. For feasibility, the confirmatory tests and linked treatments for thyrotoxicosis are available in various tertiary hospitals and private laboratory clinics in the country.

Consensus Issues

Diagnostic imaging plays a crucial role in accurately diagnosing and distinguishing various thyroid conditions, significantly influencing treatment decisions and patient management. Among the diagnostic tests, thyroid uptake tests are generally considered safe, with minimal risk associated with thyroid accumulation. However, there are other tests that may be used before utilizing thyroid uptake tests such as conducting clinical assessment or evaluation of biochemical markers. Majority of the patients with thyrotoxicosis present with symptoms that can be easily diagnosed without doing thyroid uptake tests. Thyroid uptake tests, specifically 99m Technetium pertechnetate (Tc 99m), may be used in the event that it is difficult to clinically and biochemically delineate Graves' disease from subacute thyroiditis and if the etiology is not apparent.

The use of Tc 99m is particularly safe due to its short half-life of only six hours and low radiation emissions.

Thyroid uptake tests pose challenges in terms of accessibility, particularly in marginalized areas where availability is limited. Additionally, the cost of these tests depends on the institution providing the test, which can be a significant financial burden for many patients. Consequently, it becomes imperative to carefully assess the clinical picture, symptoms, potential benefits, and risks, as well as the overall condition of the patient before deciding to proceed with the test. This approach ensures that thyroid uptake tests are judiciously employed, maximizing their value in the diagnostic process while also considering the economic implications and the well-being of the individuals undergoing the examination. Efforts should be made to make these tests more affordable and accessible to promote equitable healthcare for all patients, regardless of their socioeconomic background.

Clinical Question No. 6 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves' disease from the thyrotoxic phase of subacute thyroiditis?

Recommendation No. 6
Among pediatric patients with biochemically confirmed thyrotoxicosis, we suggest against routine use of 99m technetium pertechnetate or radioactive iodine thyroid uptake in differentiating Graves' disease from the thyrotoxic phase of subacute thyroiditis *(Very low certainty of evidence; Weak recommendation)*

Introduction

Radioactive iodine uptake (RAIU) and 99mTechnetium thyroid uptake may be used in the differential diagnosis of thyrotoxicosis when the etiology cannot be determined based on clinical and biochemical evaluation.[66] However, radioactive iodine, specifically I-131, is contraindicated among children due to increased risk of thyroid cancer.[78] Therefore, 99mTechnetium is the preferred radioactive tracer for children.[79]

Summary of Efficacy and Safety

Efficacy

Using a cutoff value of >0.40% thyroid uptake, the sensitivity and specificity of ^{99m}Tc pertechnetate uptake in diagnosing Graves' disease, compared to the final clinical diagnosis, were 1.00 (95% confidence interval [CI]: 0.91 to 1.00; N=47; 1 study) and 1.00 (95% CI: 0.69 to 1.00; N=47; 1 study) respectively among children with hyperthyroidism.[80] The certainty of the evidence was downgraded to very low due to the high risk of bias in the reference standard, indirectness of study population, and imprecision of estimates.

Table 6. Diagnostic accuracy of ^{99m}Tc pertechnetate uptake in the differential diagnosis of Graves' disease versus non-Graves' disease (subacute or autoimmune thyroiditis) among children with thyrotoxicosis

Outcomes	No. of Studies (No. of Participants)	Effect Estimate [95% CI]	Certainty of Evidence
Cutoff value: >0.40% ^{99m}Tc uptake [a]			
Sensitivity	1 (47) [80]	1.00 [0.91, 1.00]	Very low
Specificity		1.00 [0.69, 1.00]	Very low
Positive Likelihood Ratio		–	–
Negative Likelihood Ratio		0	–

CI: confidence interval

[a] Reference standard: final clinical diagnosis based on subsequent laboratory tests and clinical progress

Safety

We did not find any study on the safety issues of 99mTechnetium and RAI uptake. There is a systematic review on the side effects of RAI (131I) as treatment. 131I therapy generally utilizes 131I doses that are much higher than the dose used for diagnostic scans. This systematic review of cohort studies provided information on the long-term and short-term side effects of RAI treatment on pediatric Graves' disease.[71] Short-term side effects included vomiting, radiation thyroiditis, local inflammation, palpitations, and myxedema. Long-term side effects included benign thyroid nodules, multinodular benign goiter, hyperparathyroidism, and papillary thyroid carcinoma. No cases of leukemia, impaired reproductive

capacity, and increased frequency of congenital abnormalities were reported in the patients who received RAI treatment for pediatric GD.[71]

The included studies did not report any safety outcomes regarding the use of ^{99m}Tc pertechnetate uptake among children with thyrotoxicosis. While generally seen as a safe procedure, complications of thyroid uptake include pain at the injection site, hypersensitivity and anaphylaxis to radiotracer.[67]

Certainty of evidence

The overall certainty of the evidence was very low due to the high risk of bias in the reference standard, indirectness of study population, and imprecision of estimates.

Recommendations from Other Groups

The National Institute for Health and Care Excellence (NICE) suggests using technetium scanning among children with confirmed thyrotoxicosis if the TRAb is negative. For patients with thyroid nodules, the American Thyroid Association, Indonesian Society of Endocrinology, and the European Thyroid Association suggest using thyroid scan or scintigraphy.

Additional Considerations for Decision-making

The American Thyroid Association (ATA) and the Indonesian Society of Endocrinology (ISE) recommend using RAIU when the etiology of thyrotoxicosis cannot be determined based on clinical and biochemical evaluation. For patients with thyroid nodules, ATA, ISE, and the European Thyroid Association suggest using thyroid scan or scintigraphy.

Consensus Issues

In the management of thyrotoxicosis in children, guiding treatment decisions primarily rely on non-invasive tests and clinical assessments. These encompass a thorough evaluation of the patient's symptoms, a comprehensive physical examination, and relevant laboratory tests. It should be noted that 95% of thyrotoxicosis in children is due to Graves' disease. The common differentiating factor is the presence of eye signs.

Thyroid uptake tests serve as valuable diagnostic tools when faced with challenges in differentiating between various disease entities. However, it is essential to acknowledge that radioactive iodine is not administered to children due to its associated risks. An acceptable alternative in such cases is Tc 99m, which possesses a short half-life and emits minimal radiation. This makes Tc 99m a safer and more suitable option for conducting thyroid uptake tests in pediatric patients, ensuring their well-being while obtaining accurate diagnostic information.

Performing thyroid uptake tests in pediatric patients can be challenging, though, due to the requirement of stillness during the procedure. Hence, selecting the appropriate diagnostic tool for diagnosing children warrants careful consideration, taking into account the balance between its benefits and potential drawbacks. Furthermore, it is important to acknowledge that thyroid uptake tests for children can be costly and may not be widely accessible, particularly in marginalized areas. This disparity in availability raises concerns about equitable healthcare access for all children, highlighting the need for improved accessibility and affordability of such diagnostic tests in underserved communities.

Clinical Question No. 7 Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?

Recommendation No. 7
Among patients with biochemically confirmed thyrotoxicosis and thyroid nodules, we suggest against the routine performance of a thyroid scan to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter) *(Very low evidence; Weak recommendation)*

Introduction

Graves' disease remains the most common cause of hyperthyroidism in iodine-sufficient areas (84.4%). However, in the presence of thyroid nodularity, other differentials to consider are a solitary toxic adenoma (6.9%), and multinodular toxic goiter (6.2%).[157] In a thyrotoxic patient with clinical manifestations such as a recent onset of orbitopathy and diffusely enlarged thyroid, especially when paired with a positive TSH receptor antibody (TRAb) level, the diagnosis of Graves' disease is highly likely and further investigation of the etiology of hyperthyroidism may not be necessary.[10] While cases of Graves' disease may be responsive to anti-thyroid drugs, autonomously functioning thyroid nodules are more appropriately treated with radioactive iodine therapy or surgery.[10,70] This highlights the importance of distinguishing Graves' disease from toxic adenoma or multinodular toxic goiter when clinical examination alone is inconclusive in a patient with thyrotoxicosis and thyroid nodules.

Thyroid scanning or scintigraphy is the only technique that allows the assessment of thyroid nodular function.[158] It utilizes radioisotopes like 99mTc and 123I or 131I as markers which are actively trapped by thyroid cells. This test is useful in evaluating potential tracer variability in the thyroid which may be consistent with diffuse or focal overactivity within the gland.[159] It is considered the gold standard in diagnosing functionality of thyroid nodules. The pattern of uptake in a patient with a solitary toxic adenoma would reveal focal uptake on the adenoma with suppressed uptake in the surrounding thyroid tissue. In multinodular toxic goiter, the image would show multiple areas of focal increased and suppressed uptake. In cases where Graves' disease and nodular goiter coincide, heterogeneous uptake may be observed.[157]

Summary of Efficacy and Safety

There were no direct or indirect studies looking into the diagnostic accuracy (with thyroid scan as the index test) and patient-important/clinically relevant outcomes among patients with thyrotoxicosis and thyroid nodules who did and did not undergo thyroid scanning prior to receiving therapy.

Thyroid scanning is considered as the reference standard to diagnose toxic thyroid nodules, and has been compared to other modalities (i.e., thyroid ultrasound and clinical diagnosis versus thyroid scintigraphy) to determine their diagnostic accuracy in differentiating causes of thyrotoxicosis among patients with thyroid nodules.[158-161]

Recommendations from Other Groups

The American Thyroid Association (ATA) and the Indonesian Society of Endocrinology (ISE) recommend using RAIU when the etiology of thyrotoxicosis cannot be determined based on clinical and biochemical evaluation. For patients with thyroid nodules, ATA, ISE, and the European Thyroid Association suggest using thyroid scan or scintigraphy.

Additional Considerations for Decision-making

Cost

A cost-analysis study was done by Cappelli et al in the UK to compare cost-effectiveness of thyroid ultrasound versus scintigraphy for diagnosing Graves' disease.[163] Ultrasound and scintigraphy investigations were not suggestive of Graves' disease in 20 and 11 out of these 426 patients, respectively (p = 0.763). Ultrasound cost € 31.25 while scintigraphy cost € 45.96. The total cost to obtain a diagnosis by ultrasound was € 14645.34 (€ 13312.5 for ultrasound + € 1332.84 for scintigraphy in the 29 patients in which ultrasound was not suggestive of Graves' disease), versus € 19922.71 to have a diagnosis by scintigraphy (€ 19578.96 for scan + € 343.75 for ultrasound in 11 patients in which scintigraphy was not suggestive for Graves' disease). These results showed no significant differences in terms of diagnosis of Graves' disease with ultrasound versus thyroid scan, with a slight increase in direct-cost with the latter.

Locally, thyroid scan costs from Php 1930 to Php 6136. Due to the absence of studies that reported patient-important outcomes with the use of thyroid scan, we were unable to evaluate cost-effectiveness of this procedure.

Patient's Values and Preference, Equity, Acceptability and Feasibility

There are no documented adverse effects related to the use of thyroid scan. The only absolute contraindication to performing a thyroid scan is pregnancy.[159] Lactating women who undergo thyroid scan will need to interrupt breastfeeding depending on the tracer used. If 99mTc is used, breastfeeding should be avoided for up to 24 hours depending on the dose. For 123I, recommendations for interruption vary up to 3 weeks. If 131I is used, breastfeeding should be stopped completely.[164]

In the local setting, facilities that offer thyroid scans may not be readily available in the rural areas. As of 2016, 58 nuclear medicine centers have been established in the country – 48 in Luzon (28 of which are in Metro Manila), 6 in the Visayas, and 4 in Mindanao.[165] This may pose as a challenge for clinicians and patients residing in these locations who present with a diagnostic dilemma in need of this procedure for appropriate diagnosis and treatment.

Consensus Issues

Thyroid scan or scintigraphy is a diagnostic tool that should not be routinely employed in clinically apparent thyrotoxic patients, particularly in cases of severe thyrotoxicosis. The primary reason for this caution lies in the fact that waiting for the results of a thyroid scan may lead to further deterioration in the patient's health. Physicians tasked with managing such cases should possess the expertise to discern which patients stand to gain from undergoing a thyroid scan, and they should avoid its routine use. However, if the test is affordable, readily accessible, and does not cause undue delays in initiating treatment, then a thyroid scan may be considered.

Scintigraphy, the technique used in thyroid scans, is generally safe and well-tolerated because it employs low-level radiation doses. Nevertheless, it is essential to exercise caution, particularly in specific populations such as pregnant women and individuals with hypersensitivity to radioisotopes.

The merits of a thyroid scan are considerable. It allows for precise diagnosis, tailored management, and informed treatment decisions, which can include options like ATD, RAI, or thyroidectomy for patients with thyrotoxicosis.

However, it's worth noting that thyroid scans can be expensive and may not be readily available, especially in rural or underserved areas. Therefore, the financial implications for the patient must be carefully weighed against the potential benefits before proceeding with the scan. Governments and healthcare authorities should make concerted efforts to make this diagnostic tool more accessible and affordable to patients, given its significant clinical utility.

Ultimately, the patient's preferences, risk tolerance, and individual circumstances should also be considered when deciding whether to pursue a thyroid scan. A collaborative and informed decision-making process involving both healthcare providers and patients is crucial to ensure the best possible outcome in the management of thyrotoxicosis.

Clinical Question No. 8 Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?

Recommendation No. 8
Among hyperthyroid individuals with no palpable nodules, we suggest against routine screening for nodules using thyroid ultrasound due to low incidence of concomitant malignancy *(Low certainty of evidence; Weak recommendation)*

Introduction

There is an increasing prevalence of thyroid nodules globally, with rates a little higher in developing countries [26% (95% CI 22 to 31%)] compared to that of developed countries [22% (95% CI 16 to 29%)].[181] A study comparing the prevalence and sonographic features of thyroid nodules in autoimmune thyroid disorders showed that close to 40% of patients with Graves' Disease (GD) also had nodules.[182] Although it was previously believed that malignancy is rare among patients with hyperthyroidism, several studies have reported increasing incidence of thyroid carcinoma among patients with GD.[183, 184] Another study reported a 1.8% prevalence of differentiated thyroid cancer among patients with GD.[185]

Thyroid ultrasound is a test utilized to detect or confirm the presence of thyroid nodules. A meta-analysis on the diagnostic accuracy of ultrasound in detecting thyroid nodules showed sensitivity and specificity of 0.88 [95% CI (0.83 to 0.91)] and 0.86 [95% CI (0.70 to 0.90)], respectively.[186] One study by Nys et al published in 2014 investigated the use of thyroid ultrasound to screen for thyroid cancer among 208 newly diagnosed individuals with GD who do not have palpable nodule/s. The prevalence of non-palpable nodules among these patients is 26%. However, all of the 57 nodules biopsied via fine needle aspiration turned out to be benign.[187]

Summary of Efficacy and Safety

Harm of doing thyroid ultrasound

Although ultrasound has been used to evaluate the presence or absence of thyroid nodules, especially among patients who were suspected to have malignancy, several studies have explored the possibility of this diagnostic test leading to overdiagnosis and overtreatment of thyroid malignancy with an indolent course.[188-190]

A systematic review and meta-analysis by Edwards et al in 2021 revealed that the prevalence of inappropriate thyroid ultrasound ranged from 11% to as high as 53%.[12] In this review, appropriateness of ultrasound was based on guideline recommendations, and the definition of inappropriate thyroid ultrasound as the procedure done in patients with nonspecific symptoms or functional thyroid disease without palpable nodule.[188] Overtreatment could lead to unnecessary surgeries and perioperative complications, exposure to radiation from treatment with radioactive iodine, and lifelong levothyroxine therapy on top of the economic burden it poses, not only to the patients but also to the healthcare system.[189] Common drivers of inappropriate thyroid ultrasound include lack of familiarity with the indications, lack of awareness of harms of overdiagnosis and overtreatment, non-universal definition of inappropriate ultrasound, fear of litigation or negative evaluation from the patient, and potential revenue in practice.[189]

Thematic analysis of 34 semi-structured interviews of surgeons, endocrinologists and patients showed that healthcare providers may have similar approaches or perspectives on the decision making when it comes

to the management of small, low risk cancer of the thyroid where most patients would prefer having nodules taken out despite understanding the slow-growing nature of thyroid cancers, and majority of the providers interviewed believe that no one could really "treat cancer by watching".[190] Responses of the surgeons and endocrinologists in the interview revolved around the theme that "overdiagnosis fuels overtreatment." Discovery of a nodule in imaging procedures lead to the cascade of events: biopsy then surgery.[190] These providers stated that it is actually overdiagnosis that is to be blamed more but it was emphasized that biopsy is the "critical point for intervention."

Certainty of Evidence

All three observational studies were assessed to have overall moderate risk of bias using the ROBINS-I assessment tool. The overall certainty of evidence was deemed to be low due to issues on indirectness, inconsistency, and imprecision despite the large magnitude of effect.

Recommendations from Other Groups

The European Thyroid Association recommends thyroid ultrasound in patients with palpable thyroid nodule/s.

Additional Considerations for Decision-making

Cost

The systematic search for evidence did not yield any articles that investigated the cost-effectiveness of ultrasound to detect nodules among hyperthyroid patients, however, published rates of this procedure in government and private institutions ranged from Php 800.00 Php 3054.00

Patient's Values and Preference, Equity, Acceptability and Feasibility

In the qualitative study by Jensen et al, patients who were noted to have thyroid nodules "pushed" for a biopsy to be done.[190] They felt there was a need to have certainty of the diagnosis and upon learning the biopsy results, most would actually prefer to have the thyroid taken out as it provided them "peace of mind."

Consensus Issues

The evaluation of thyroid nodules with ultrasound enters the picture if the physical examination raises suspicions. The decision to employ thyroid ultrasound ultimately depends on whether thyroid nodules are palpable or visibly present. In a low resource setting, systematic neck palpation should be done to screen for nodules. It's crucial to acknowledge that inappropriate or unnecessary procedures may lead to overdiagnosis and subsequently over-treatment. Therefore, it falls upon the physicians to exercise sound clinical judgement in determining whether a thyroid ultrasound is warranted for a given patient.

Routine thyroid ultrasound should not be performed unless there is a clear indication to do so, such as indications suggestive of carcinoma. Engaging in routine ultrasound examinations without strong clinical reasons can yield incidental findings, trigger unnecessary procedures, and increase healthcare expenses without providing significant clinical benefits.

In summary, the decision to conduct a thyroid ultrasound should be made judiciously, considering the clinical context and indications. Physicians should prioritize the patient's clinical well-being and cost-effectiveness in healthcare while avoiding unnecessary procedures. Thyroid ultrasound is a valuable tool when deployed for the right reasons, but it should not be performed routinely in the absence of compelling clinical factors.

Clinical Question No. 9 Should beta-blockers be used as an adjunct for individuals with thyrotoxicosis?

Recommendation No. 9A
Among non-pregnant adults with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for treatment of tachycardia, palpitations, and tremors *(Very low certainty of evidence; Strong recommendation)*

Recommendation No. 9B
Among children with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for treatment of tachycardia, palpitations, and tremors. *(Very low certainty of evidence; Strong recommendation)*

**Unless contraindicated. Contraindications to beta-blockers include moderate to severe asthma, slow heart rate, low blood pressure, hypoglycemia, Raynaud's phenomenon*

Introduction

Thyroid hormones can affect almost every organ system particularly the cardiovascular system which leads to some of the more obvious signs and symptoms. These include tachycardia and cardiac arrhythmias, including atrial fibrillation. The palpitation that is felt by patients is due to the increased systolic force and may be seen on inspection and palpation of the precordium. Although some symptoms of thyrotoxicosis may be similar to manifestations of sympathetic nervous system activation, the excess thyroid hormones exert a separate effect through an increase in sympathetic tone or increased cardiac sensitivity to catecholamines rather than an increase in the catecholamine levels.

Beta blockers are drugs that block catecholamines at the receptor site and are used to decrease some symptoms of thyrotoxicosis. They can rapidly improve complaints of tremulousness, palpitations, excessive sweating, and eyelid retraction.[204] Commonly used beta blockers that are given as adjuncts in the management of hyperthyroidism include atenolol, metoprolol and propranolol. They are useful during the time while waiting for the results of thyroid function tests and during the interval while waiting for the effects of antithyroid medications or RAI therapy.

The most widely used beta blocker in the treatment of hyperthyroidism is propranolol. It is a non-selective beta-blocker that can be given at a dose of 10-40 mg 3 to 4 times a day. At high doses, it may also block peripheral T4 to T3 conversion. It is contraindicated in patients with bronchial asthma and chronic obstructive pulmonary disease.

Atenolol can be given at a dose of 25-100 mg in 1-2 divided doses. Metoprolol can be given at a dose of 25-50 mg in 2-3 divided doses. Both atenolol and metoprolol have relative beta-1 selectivity.

Summary of Efficacy and Safety

Efficacy

Decrease in severity of symptoms

The severity of neck swelling, easy fatigability, general malaise, weight loss, shortness of breath, irritability, apathy, and lack of concentration improved significantly in patients on propranolol, metoprolol, or atenolol plus methimazole. Furthermore, comparing those who received either propranolol, metoprolol, or atenolol, scores for the "shortness of breath" increased more significantly in the group treated with atenolol or metoprolol than in the group treated with propranolol.[30]

Decrease in heart rate

The heart rates of patients given either propranolol, metoprolol, or atenolol and methimazole measured at four weeks were significantly lower compared to those who received methimazole only. Furthermore, propranolol, metoprolol and atenolol were equally effective in improving the heart rate.[31]

Effect on thyroid hormones

No significant differences in the levels of fT4 or fT3 were observed in patients who received either propranolol, metoprolol, or atenolol and methimazole compared to those who received methimazole alone.[30]

Improvement of quality of life

No statistically significant differences were observed in the initial and final scores in any parameter on the SF-36 assessment of patients given either propranolol, metoprolol, or atenolol and methimazole and those given methimazole only. However, the parameter "physical functioning" was found to be significantly improved in the group who received propranolol, metoprolol, or atenolol and methimazole.[30]

We did not find any study on mortality and cardiovascular disease outcomes.

Safety

All four studies reported that beta-blockers are generally well-tolerated in the treatment of thyrotoxicosis.[30-33] Adverse reactions (i.e., dizziness, nausea and vomiting, severe heartburn, and flatulence) caused two patients to stop taking propranolol. Other side effects from propranolol were headache, tiredness, insomnia, drowsiness, dreams, dry mouth and tongue, and constipation.[31] Propranolol was well-tolerated and no one discontinued treatment with propranolol because of side effects. However, one case of cold extremities was noted after propranolol.[32] There were no significant changes in terms of laboratory parameters such as aspartate aminotransferase, alanine aminotransferase, and white blood cells in patients taking propranolol, metoprolol or atenolol. No other adverse reactions were noted.[30] Table 9 below summarizes the outcomes of this study.

Table 7. Summary of findings for adult population with thyrotoxicosis

Outcomes	Basis	Effect size (mean difference)	95% CI	Interpretation	Certainty of evidence
Decrease in severity of symptoms (clinical evaluation – questionnaire)	1 RCT				Low

Total Neck swelling Easy fatigability General malaise Body weight loss Shortness of breath Irritability Apathy Lack of concentration		-0.8 -0.1 -1.0 -0.6 -0.7 -0.9 -0.4 -0.4 -0.3	Cannot be computed	Favors treatment Favors treatment Favors treatment Favors treatment Favors treatment Favors treatment Favors treatment Favors treatment Favors treatment	
Decrease in heart rate (bpm) (clinical evaluation – electrocardiography)	1 RCT	-11.3	Cannot be computed	Favors treatment	Low
Effect on thyroid hormones Free T4 (ng/dL) Free T3 (pg/mL)	1 RCT	 0.1 1.1	 Cannot be computed	 No effect No effect	Low
Improvement in quality of life (SF-36 questionnaire) Physical functioning Role-physical Bodily pain General health Vitality Social functioning Role-emotional Mental health	1 RCT	 1.8 1.2 -1.7 1.2 3.1 -2.4 1.8 -2.1	Cannot be computed	 Favors treatment No effect No effect No effect No effect No effect No effect No effect	Low
Occurrence of adverse reactions*	4 clinical trials	Difference in frequency	Cannot be computed	No effect	Low

*At least one of the following: dizziness, nausea, vomiting, severe heartburn, flatulence, headache, tiredness, insomnia, drowsiness, dreams, dry mouth and tongue, constipation, cold extremities, shortness of breath, tiredness, itchy rash, and significant changes in aspartate aminotransferase, alanine aminotransferase, and white blood cells

Certainty of Evidence

Overall certainty of the evidence is low due to the risk of bias and imprecision. There was a serious risk of bias due to the small sample size. For the pediatric population, the certainty of the evidence was further downgraded to very low because of indirectness.

Recommendations from Other Groups

The recommendations in this CPG are similar to those given by different international groups, including the American Thyroid Association, Japan Thyroid Association, European Thyroid Association, etc. See Appendix for the complete list.

Additional Considerations for Decision-making

Cost

We did not find any cost-effectiveness studies on the use of beta-blockers as adjunct in the treatment of thyrotoxicosis.

Table 8. Price ranges for commonly used beta-blockers as adjunct in the treatment of thyrotoxicosis

Drug	Dose	Lowest (in Php)	Median (in Php)	Highest (in Php)
Propranolol	10 mg	1.99	4.92	7.70
Propranolol	40 mg	1.01	8.0	20.00
Metoprolol	50 mg	0.56	0.95	2.50
Metoprolol	100 mg	0.90	1.55	2.97
Atenolol	50 mg	1.40	1.96	4.00
Atenolol	100 mg	2.55	4.28	6.00

Source: Drug Price Reference Index 11th ed. 2023. https://dpri.doh.gov.ph/downloads/2023-DPRI-AS-OF-AUG31.pdf

Patient's Values and Preference, Equity, Acceptability and Feasbility

We did not find any study looking into patient values and preference, equity, acceptability and feasibility.

Consensus Issues

Beta-blockers have demonstrated their efficacy as a valuable addition to antithyroid medications for managing the symptoms of thyrotoxicosis in both adults and children. They are particularly effective in controlling tachycardia, a common symptom of hyperthyroidism. Among pregnant women with thyrotoxicosis, propranolol is the preferred beta-blocker, proven to be safe for use during pregnancy.

Moreover, beta-blockers have been shown to minimize the occurrence of other thyrotoxicosis-related symptoms such as atrial fibrillation and congestive heart failure. While generally considered safe, caution is advised when using beta-blockers in patients with pre-existing cardiac conditions, as they can potentially cause heart block. Bronchospasm is also a potential adverse effect.

The accessibility and affordability of beta-blockers further contribute to their widespread use, making them equitable treatment options for patients. Their effectiveness and availability in local pharmacies make them routine components of the treatment plan for patients with thyrotoxicosis, enabling healthcare providers to optimize symptom control and improve the overall well-being of affected individuals.

Clinical Question No. 10 Should we give methimazole (MMZ)/carbimazole (CBZ) as first-line therapy instead of PTU among individuals with Graves' hyperthyroidism?

Recommendation No. 10A
Among non-pregnant adults with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as initial treatment. In case methimazole is not available, we recommend the use of carbimazole. *(Moderate certainty of evidence; Strong recommendation)*

Recommendation No. 10B
Among children and non-pregnant adolescents with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as initial treatment. In case methimazole is not available, we recommend the use of carbimazole. *(Low certainty of evidence; Strong recommendation)*

Recommendation No. 10C
Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of propylthiouracil during the first trimester, due to the higher risk of congenital malformation with methimazole/carbimazole. *(Low certainty of evidence; Strong recommendation)*

Recommendation No. 10D
Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of methimazole during the second and third trimester due to the lower risk of maternal liver impairment with methimazole. *(Low certainty of evidence; Strong recommendation)*

Recommendation No. 10E
Among women with Graves' hyperthyroidism requiring antithyroid therapy who are planning pregnancy, we suggest switching of methimazole/carbimazole to propylthiouracil due to the higher risk of congenital malformation with methimazole/carbimazole. *(Very low certainty of evidence; Weak recommendation)*

Introduction

Management of hyperthyroidism includes antithyroid drugs (ATDs), radioactive iodine therapy (RAI) and thyroidectomy. All options are satisfactory, thereby leaving the choice to the patient and clinician after taking into consideration the underlying pathology, age, sex, patient preference and availability of expert thyroid surgical care. Usually, ATDs are the first-line treatment for patients with GD. Additionally, ATDs are favored because of the possibility of achieving a long-lasting remission without the need for lifelong thyroid hormone replacement.

The ATDs used to treat hyperthyroidism belong to the thionamide class of medications: propylthiouracil (PTU), methimazole (MMZ/MMI), and carbimazole (CMZ). Carbimazole is rapidly decarboxylated in the liver to produce MMZ in the blood. Equivalent doses are 40 mg CMZ, 30 mg MMZ, and 400 mg PTU.[205] MMIZ, CBZ, and PTU inhibit the production of new thyroid hormone by the thyroid gland. They act by inhibiting the enzyme thyroid peroxidase, resulting in decreased synthesis of thyroid hormone by inhibiting both organification (incorporation of iodine) and coupling (conjugation) steps.[6]

MMZ has a longer half-life (about 6 hours) and can be given as a single daily dose. The starting dose of methimazole is based on the degree of hyperthyroidism (5 to 10 mg if serum T_4 is <1.5 times upper limit of normal, 10 to 20 mg if serum $T_{4\ is}$ 1.5 to 2 times upper limit of normal, 20 to 40 mg if serum T_4 >2 times upper limit of normal).[206]. Dosing above 20 mg per day may be given in divided doses. The dose should be eventually tapered and kept at the lowest possible dose to achieve euthyroidism (typical maintenance of 5 to 10 mg/day).

PTU has a shorter half-life (about 1.5 hours) and has to be administered two to three times daily. Usual starting dose is 50-150 mg three times a day, depending on the severity of hyperthyroidism[B]. When thyroid function tests are normalized and the patient becomes less symptomatic, the dose can be reduced to 50 mg two to three times a day.

During the initial phase of treatment, both serum T_4 and T_3 are typically measured because serum T_3 may remain high despite normalization of T_4. Also, it usually takes months for TSH to become normal. Once both serum T_4 and T_3 are normal, only T_4 and TSH are tested during the stable maintenance period. [10]

Serum T_4 and T_3 are re-assessed at 4 to 6 weeks' intervals until stable doses of thionamides. Once serum T4 and T_3 are normal, the dose of methimazole can be decreased by 30 to 50%. Subsequent thyroid function tests which may include TSH and T_4 should be performed 4 to 6 weeks after every dose adjustment. Thereafter, repeat tests can be done every 3 to 6 months.[10]

Common adverse events associated with ATDs include skin rash, urticaria, arthralgia, polyarthritis, and transient mild leukopenia. They can occur in 1-5% of patients taking these medications[A]. Minor cutaneous reactions may be managed with antihistamines without stopping the medications. They can also resolve spontaneously or after switching to another antithyroid drug.

Rare adverse events, seen in 0.2-1%, include gastrointestinal issues like abnormal taste and smell, and agranulocytosis (<500 neutrophils/mm^3). Very rare adverse events (<0.1%) include aplastic anemia (PTU, CBZ), thrombocytopenia (PTU, CBZ), vasculitis (PTU), hepatitis (PTU), hypoglycemia (PTU), cholestatic jaundice (CBZ, MMZ).[205]

Complete blood count and liver function tests are not routinely monitored unless the patient exhibits signs of adverse reactions such as fever and pharyngitis (agranulocytosis) as well as jaundice, dark urine, acholic stool and/or pruritic rashes (hepatotoxicity)[B]. When patients are started on ATDs, they should be instructed to discontinue the medication and notify the physician immediately when these symptoms develop[A]. Once a patient experiences a severe adverse reaction to any of the ATDs, they should not be switched to another ATD. Other therapies (RAI therapy or surgery) must be offered to the patient.

Thyroid experts recommend MMZ over PTU due to less risk for side effects in non-pregnant patients particularly in children. On the other hand, they recommend PTU over MMZ due to less risk for congenital/fetal side effects during the first trimester of pregnancy.[7,8,9,10,11]

Summary of Efficacy and Safety

Efficacy

A higher proportion of patients treated with MMZ had biochemical euthyroidism at 12 weeks compared to those treated with PTU in all 3 studies.[12-14] Pooled estimates showed that patients treated with MMZ are about 6 times more likely to have biochemical euthyroidism at 12 weeks compared to those treated with PTU, (OR 5.61; 95% CI 3.24, 9.71).

Safety

Impairment of liver function was found as a significant safety outcome. Patients treated with MMZ or CBZ are about 3 times less likely to have impaired liver function compared to those receiving PTU (OR 0.30; 95% CI 0.22, 0.39). There is insufficient evidence to conclude a difference in risk of granulocytopenia between those receiving MMZ/CBZ and those receiving PTU (OR 0.72; 95% CI 0.43, 1.21).

Among pregnant patients in the first trimester, the risk of congenital malformations is 1.3 times more likely in those receiving MMZ/CBZ compared to those receiving PTU (OR 1.26; 95% CI 1.06, 1.49).[15]

For children, there is insufficient direct evidence to conclude a difference in risk of composite adverse events between those receiving MMZ/CBZ and those receiving PTU (OR 0.63; 95% CI 0.30, 1.29).[15] Indirect evidence based from studies among adults show that MMZ/CBZ is generally favored because of lower risk of liver function impairment.

Tables 3-5 summarizes the findings of this study.

Table 9. Summary of findings for non-pregnant adult patients with Graves' hyperthyroidism

Critical Outcomes	No. and Type Of Studies (Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Biochemical euthyroidism at 12 weeks	3 RCTs (n=261)	OR 5.61	3.24, 9.71	Favors methimazole	High
Impaired liver function	14 RCTs (n=1,863)	OR 0.30	0.22, 0.39	Favors methimazole	High
Granulocytopenia	8 RCTs (n=904)	OR 0.72	0.43, 1.21	Inconclusive	High

Table 10. Summary of findings for children with Graves' hyperthyroidism

Critical Outcomes	No. and Type Of Studies (Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Composite adverse events	2 Cohorts (n=154)	OR 0.63	0.30, 1.29	Inconclusive	Low

Table 11. Summary of findings for pregnant patients with Graves' hyperthyroidism

Critical Outcomes	No. and Type Of Studies (Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence

Congenital malformation among newborns of pregnant patients with first trimester exposure	4 Cohort (n=15,709) 1 Case-control (n=127)	OR 1.26	1.06, 1.49	Favors propylthiouracil	Low

Certainty of Evidence

Overall certainty of evidence for the efficacy and safety outcomes among the adult population is high. However, for children and pregnant women, the overall certainty of evidence is low due to the design of the included studies, i.e., observational studies. Due to imprecision, it was downgraded by one level because the presumed benefits and risks were indirectly inferred from RCTs involving adult nonpregnant subjects.

Recommendations from Other Groups

The recommendations in this CPG did not differ from those given by different international groups, including the Malaysia Endocrine and Metabolic Society, European Thyroid Association, American Thyroid Association, etc. See Appendix for the complete list.

Ongoing Studies and Research Gaps

We did not find any ongoing study on MMZ/CBZ as an initial treatment option for hyperthyroidism as of January 2023.

Additional Considerations for Decision-making

Cost

We did not find any cost-effectiveness study comparing MMZ/CBZ with PTU as initial treatment options for hyperthyroidism. Survey of local pharmacies (as of 04 January 2023) regarding the unit costs of these ATDs was done and summarized below.

Table 12. Price ranges for anti-thyroid medications

Drug	Dose	Lowest (in Php)	Median (in Php)	Highest (In Php)
PTU	50 mg	12.49	14.25	21.00
Methimazole	5 mg	1.89	4.73	9.50

Source: Drug Price Reference Index 11th ed. 2023. https://dpri.doh.gov.ph/downloads/2023-DPRI-AS-OF-AUG31.pdf

Table 13. Price ranges for anti-thyroid medications in commercial pharmacies

Drug	Dose	Price range (in Php)
PTU	50 mg	9.90 - 11.75
Methimazole	5 mg	6.75 - 9.50
Methimazole	20 mg	26.75 - 29.25
Carbimazole	5 mg	9.50 - 10.50
Carbimazole	20 mg	30.00

Sources: https://www.rosepharmacy.com; https://southstardrug.com.ph; https://www.watsons.com.ph

Patient's Values and Preference, Equity, Acceptability and Feasibility

We did not find any study comparing MMZ/CBZ or PTU in terms of patient values and preferences, including stigma, social impact, or other perspectives.

Consensus Issues

In current clinical practice, MMZ is the preferred initial treatment for patients requiring antithyroid therapy. Its use, along with CBZ, is favored over PTU due to several advantages. MMZ and CBZ have higher remission rates, better tolerability, and are more convenient for patients in terms of administration. Furthermore, they have a higher likelihood of achieving euthyroidism. CBZ, however, is less potent than MMZ. In situations where MMZ is unavailable, CBZ can be considered as a suitable alternative, particularly for younger patients. Despite recommendations from multiple clinical guidelines, some non-endocrinologists still initiate treatment with PTU.

It is crucial to exercise extra caution when using PTU, especially among pediatric patients, as it is highly associated with liver failure. The US Food and Drug Administration has issued a red warning due to seven reported deaths in the United States caused by the use of PTU. International pediatric societies strongly advise against its use in children due to the significant risk of liver dysfunction.

For pregnant patients requiring antithyroid therapy, the Consensus Panel recommends PTU during the first trimester, despite low certainty of evidence, to reduce the risk of congenital malformations associated with MMZ/CBZ use. However, switching to MMZ is encouraged during the second and third trimesters to minimize the risk of maternal liver impairment. For women with Graves' hyperthyroidism planning to get pregnant, consultation with a physician is crucial, as switching to PTU is advisable to prevent potential harmful effects on the fetus caused by MMZ/CBZ.

The use of MMZ, CBZ, or PTU among pregnant adolescent women requiring antithyroid therapy should be approached with great care, considering the significant risks associated with each drug as mentioned earlier. Adolescent pregnancy is highly discouraged, especially in patients with Graves' hyperthyroidism, due to the treatment options available that pose substantial harm to both the mother and fetus.

Physicians should thoroughly explain to their patients the possible side effects of antithyroid drugs, including urticaria, allergic reactions, granulocytopenia, liver dysfunction, fever, and tonsillitis. Patients must be vigilant in monitoring for any symptoms themselves and seek immediate medical care if they experience any side effects. Timely attention to these side effects is crucial, as they may lead to severe consequences, such as sepsis from fever or tonsillitis, fulminant hepatic necrosis and death from liver dysfunction, and anaphylactic shock and death from allergic reactions.

Clinical Question No. 11 Should we give long-duration instead of short-duration ATD treatment among individuals with Graves' hyperthyroidism?

Recommendation No. 11A
Among non-pregnant adults with Graves' hyperthyroidism on ATD as first-line therapy, we suggest maintaining antithyroid drug for at least 18 months*. *(Low certainty of evidence; Weak recommendation)*

**as long as it is well tolerated by the patient*

Recommendation No. 11B
Among children with Graves' hyperthyroidism, we suggest maintaining antithyroid drug for at least 24 months* *(Very low certainty of evidence; Weak recommendation)*

**as long as it is well tolerated by the patient*

Introduction

Conventional or traditional use of antithyroid drugs (ATD) for Graves' hyperthyroidism lasts for 12 to 18 months followed by assessment for remission. A patient is considered to be in remission if he has had a normal serum TSH, T4, and T3 for 1 year after discontinuation of ATD therapy. The remission rate varies considerably between geographical areas. In earlier studies in the United States, about 20–30% of patients were reported to have a lasting remission after 12–18 months of medication, but more recent data are not available. The remission rate may be higher in Europe and Japan; a long-term European study indicated a 50–60% remission rate after 5–6 years of treatment, and a study in Japan reported a 68% remission rate after 2 years of treatment. About 30-70% of patients will relapse, necessitating a decision for definitive therapy.

A recent study by Chen suggests that ATD is equally effective as radioactive iodine (RAI) in reducing thyroid hormone levels quickly. Long-term ATD is highly effective at maintaining euthyroidism. The consequence of hypothyroidism from definitive therapy such as RAI therapy and thyroidectomy is unacceptable to a certain subgroup of patients. The Colorado Thyroid Disease Prevalence Study showed that among patients taking thyroid hormone replacement for any reason, a significant proportion had abnormal values: 0.7% had biochemical evidence of overt hypothyroidism, 17.6% had subclinical hypothyroidism, 0.9% had overt hypothyroidism, and 20.7% had subclinical hyperthyroidism.

The current evidence suggests that euthyroidism is more prevalent with long-term ATD. Relapse risk varies with ATD treatment duration. The risk of recurrence is highest with 12-18 months of ATD, lower after long-term ATD and RAI, and lowest after surgery. The major advantage of ATD is the preservation of endogenous thyroid hormone production. Evidence supports the conclusion that patients with Graves' disease have a lower quality of life (QoL) than the general population, and RAI treatment is associated with worse QoL than ATD. Likewise, RAI therapy has been strongly associated with thyroid eye disease worsening compared to gradual decreases during a prolonged course of ATD. Medical therapy with antithyroid medications is not free of adverse events (AE). Current recommendations to limit the use of ATD to 12-18 months reflected concerns for AE.[10,24,44]

In pediatric patients with Graves' hyperthyroidism, long-term remission rates are generally lower than in adult patients. Studies conducted in the pediatric population have shown that pubertal more than

prepubertal, those with small goiters, and higher BMI at presentation will most likely achieve remission if ATD is stopped after 24 months*.[208]

In current practice, some clinicians would opt to discontinue antithyroid medications abruptly after achieving biochemical euthyroidism without considering the favorable effect of long-term therapy on remission. The recommendations that were presented are based on the latest evidence from randomized controlled trials and observational studies.

Summary of Efficacy and Safety

Efficacy Outcomes

Adult patients

One RCT compared the conventional duration of antithyroid drug and patients with Graves' disease on long-term antithyroid drug.[47] The study included patients with untreated Graves' disease who were randomized to the "long-term group" (LT) and "conventional group" (ST) after 18 to 24 months. The long-term group received methimazole for additional 36 to 102 months (total 60-120 months) while the conventional group discontinued methimazole. Patients from the two groups were followed up for 48 months post-methimazole cessation. Methimazole was given for a median of 95 months in the LT group and 19 months in the ST group.

By 48 months post-methimazole discontinuation, relapse of hyperthyroidism had been detected in 65 of 123 (63%) in the ST group versus 18 of 121 (15%) in the LT group (p<0.001). By the end of the 48 months of follow-up, 101 of 121 (83%) of the LT group were in remission versus 56 of 123 (46%) in the ST group. Long-term ATD provided 71% risk reduction (RR 0.29; 95% CI 0.18, 0.45) compared with short-term ATD.

Table 14. Long-term ATD vs short-term ATD in non-pregnant adult patients

Outcomes	Basis (No. of studies, N)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Relapse	1 RCT (Azizi) N = 158 adult patients	RR 0.29	0.18,0.45	Favors LT	Low *downgraded due to risk of bias and imprecision
Remission		By the end of the 48 months of follow-up, 101 of 121 (83%) of the LT group were in remission versus 56 of 123 (46%) in the ST group (reciprocal of relapse rate)		Favors LT	Low *downgraded due to risk of bias and imprecision
Major AE		There was no direct comparison between LT and ST groups. 14 adverse cutaneous reactions and 2 liver enzyme elevations occurred during pre-randomization. No further adverse reaction was noted thereafter in the LT group.		Low risk of AE	Moderate *downgraded due to risk of bias
Minor AE				Low risk of AE	Moderate *downgraded due to risk of bias

**Median age: 41 (LT) versus 38 (ST)*

*** Prerandomization: Methimazole was given (20-30 mg/day initially) and titrated to maintain normal fT4 and TSH for 18 to 24 mos.*

****LT group: Additional course of 60-120 months based on patient preference, visit intervals or elevated risk of hypothyroidism with continued therapy - reflected by methimazole dose titration repeatedly failing to prevent increasing TSH levels.*

Pediatric patients

Another RCT by Azizi et. al in 2019 compared LT and ST antithyroid drugs in pediatric Graves' disease.[48] The study enrolled patients with untreated juvenile Graves' disease (median age 15 +/- 2.85 years). After a median of 22 months of methimazole treatment, 56 were randomly assigned to LT (n=24) or to ST who discontinued therapy (n=24). Patients in both groups were further followed-up 48 months after discontinuation of treatment. The median dose of methimazole at 22 months was 5.17 +/- 1.05 mg. In the LT group, it was decreased to 3.5 +/- 1.3 mg between 96 and 120 months.

After 48 months of methimazole withdrawal, the primary outcome which was relapse of hyperthyroidism was detected in 3/24 (12.5%) patients in the LT group (12.5%) versus 16/24 (67%) patients in the ST group (p<0.001). Long-term ATD provided 81% risk reduction (RR=0.19, CI 0.06, 0.56) compared with short-term ATD, albeit, at a wide confidence interval.

After 1 year, the remission rate for hyperthyroidism was 92% for the LT group versus 46% for the ST group. After 4 years, the remission rate for hyperthyroidism was 88% for the LT group versus 33% for the ST group.

Table 15. Long-term ATD vs short-term ATD in pediatric patients

Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Relapse	1 RCT (Azizi) N = 48 pediatric patients	RR 0.19	0.06,0.56	Favors LT	Low *downgraded due to risk of bias and imprecision
Remission		Remission rates were 92% for the LT versus 46% for the ST after 1 year and 88% for the LT versus 33% for the ST after 4 years.		Favors LT	Low *downgraded due to risk of bias and imprecision
Major AE		There was no direct comparison between LT and ST groups. There was no adverse event throughout the duration of therapy except for 3 cases of cutaneous reactions.		Low risk of AE	Moderate *downgraded due to risk of bias
Minor AE				Low risk of AE	Moderate *downgraded due to risk of bias

**Median age: 15 years*
***Prerandomization: Methimazole was given (0.25 to 0.5 mg/kg initially) and titrated to maintain normal fT4 (between 10-22 pmol/L) and TSH (<5.06 mU/lL) for 18 to 24 mos (median of 22 months)*
****LT group: Additional course of 96 to 120 months (mean 109 +/- 10 months)*

Safety Outcomes

In terms of safety, there is no direct comparison between LT and ST groups. Additionally, while the LT group is being given low-dose methimazole, the ST group has already discontinued the treatment after the initial 18-24 months. Fourteen patients experienced cutaneous reactions and 2 liver enzyme elevations during the first 18 months of treatment (pre-randomization). No further adverse reaction was noted thereafter.

Overall, no adverse events were noted throughout the duration of therapy except for 3 cases of cutaneous reactions. Likewise, there was no direct comparison between LT and ST groups in terms of safety.

Recommendations from Other Groups

The recommendations in this CPG are similar to those from the American Thyroid Association and the European Thyroid Association.

Additional Considerations for Decision-making

Cost

Low-dose methimazole is still less expensive (Php 1640.00 to Php 3,285 per annum) compared to RAI therapy (Php 10,000.00 per dose) or surgery. Biochemical monitoring will more or less be the same across all treatment options.

Patient's Values and Preference, Equity, Acceptability and Feasibility

In a study by vans Kinschot (2021), remission rate was the most important determinant of treatment choice for patients and clinicians. ATD was the most preferred treatment option. Patients had a negative preference toward RAI compared to alternatives, whereas clinicians preferred RAI over surgery. Clinicians should be aware that their personal attitude toward RAI differs from that of their patients. This study on patients' and clinicians' preferences can support shared decision making and thereby improve clinical treatment.[49]

Consensus Issues

The consideration of ATD treatment is a crucial factor in effectively managing patients with Graves' hyperthyroidism. Abrupt and premature discontinuation of ATD treatment can significantly increase the risk of relapse. Therefore, careful and timely decisions regarding the continuation or cessation of ATD therapy are paramount to ensure the long-term stability and well-being of patients with this condition.

Recent studies have shown that long-term ATD treatment leads to higher remission rates and reduces the likelihood of relapse in patients. On the other hand, short-term ATD treatment offers the advantage of fewer side effects and a shorter duration of therapy, but it carries a higher risk of relapse. It is essential to note that both short-term and long-term ATD treatments are generally safe, but patients need to be informed about potential side effects, such as allergies, fever, and agranulocytosis, associated with ATD use.

To ensure the best outcomes, physicians should emphasize the importance of proper ATD adherence and completing the entire prescribed duration of treatment. It is the physician's responsibility to have a thorough discussion with the patient, explaining the advantages and disadvantages of both short- and long-term ATD treatment options. By providing this information, patients can make informed decisions about their treatment approach, taking into account their individual preferences and medical circumstances. Open communication and patient education empower individuals to actively participate in their healthcare decisions and contribute to the success of their treatment journey.

The cost of treatment for hyperthyroidism varies based on the type of ATD used and the duration of the treatment. ATDs are readily available and easily accessible in local pharmacies. It is important for patients to be aware of the financial aspect of their treatment, and healthcare providers can assist by discussing the cost implications and exploring any potential options for financial assistance or insurance coverage to ensure that patients can access the necessary medications without undue burden.

Clinical Question No. 12 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

Recommendation No. 12A
Among non-pregnant adults with Graves' hyperthyroidism, we recommend antithyroid drug as first-line treatment *(Low certainty of evidence; Strong recommendation)*

Recommendation No. 4B
Among children with Graves' hyperthyroidism, we recommend antithyroid drug as first-line treatment *(Very low certainty of evidence; Strong recommendation)*

Introduction

Upon being diagnosed with GD, the patient has three treatment options: ATD, RAI therapy, or thyroidectomy. ATD reduces the synthesis of thyroid hormones, whereas the other two modalities reduce the amount of thyroid tissue.[35] Non-surgical treatments, ATD and RAI, are often preferred over thyroidectomy because of lesser morbidity and cost. ATD is usually considered the first-line treatment, especially in younger patients, whereas the RAI or surgery is often recommended for patients who develop significant adverse events due to the use of ATD or who had a recurrence of hyperthyroidism after a course of ATD.[10]

ATD and RAI therapy are both effective and relatively safe but the choice of treatment will have to be made after considering several factors such as age, sex, presence of other medical conditions, potential side effects, availability of facilities and expertise, cost, and other patient factors including personal preference. The choice often also depends on the prevailing practice of physicians in their particular country or area. In the United States, RAI is usually preferred over ATD but in recent years, there has been an increasing trend towards the use of ATD for maintenance therapy. On the other hand, ATD is usually the treatment of choice in Europe, Latin America, and Japan.[10]

Summary of Efficacy and Safety

Non-pregnant adults

Efficacy Outcomes: Euthyroidism and relapse of hyperthyroidism

A randomized controlled trial reported that in those patients [35] who were given RAI, none achieved euthyroidism unlike those who were given methimazole. However, relapse of hyperthyroidism was lower among participants who were treated with RAI compared to those who were given methimazole (RR 0.20; 95% CI 0.01 – 2.66, p value = 0.22).

Safety Outcomes: GO, hypothyroidism, drug-related reactions, quality of life

Studies have shown that the development and worsening of GO was more frequently observed participants treated with RAI compared participants treated with methimazole (38% vs 19% respectively; RR 1.94; 95% CI 1.40 – 2.70). A randomized controlled trial showed that[35] almost all participants developed hypothyroidism after RAI therapy, while none developed hypothyroidism in the methimazole-treated participants.

A meta-analysis showed that drug-related reactions were seen in 23/215 (11%) participants likely related to the use of methimazole. These adverse reactions ranged from mild such as pruritic rashes to more severe ones such as agranulocytosis and hepatic dysfunction.

Two randomized controlled trials assessed health-related quality of life. Although quantitative data for comparison between the 2 groups were not provided, results of one trial reported that there was no difference in the quality-of-life as measured using the 36-Item Short Form Health Survey between the 2 treatment groups.

Safety Outcomes: all-cause mortality and cardiovascular diseases

In one analysis, patients treated with RAI were found to have reduced risks of all-cause mortality (HR 0.931; 95% CI 0.882, 0.982) and CVD (HR 0.784; 95% CI 0.742, 0.828) as compared with ATD.[36] In another study, pooled results of ~~the~~ two cohorts showed that those given RAI had lower risk for CVD (HR 0.79; 95% CI 0.75, 0.84) and all-cause mortality (HR 0.93; 95% CI 0.88 – 0.98) as compared to those who were treated with ATD. [37]

Children

RAI therapy is associated with higher chances to achieve euthyroidism, (RR 1.70; 95% CI 1.29, 2.24), and higher risk to develop hypothyroidism (RR 6.46; 95% CI 1.16, 35.81) compared to ATD. More mild adverse and serious adverse events were seen with ATD therapy. No severe adverse events were seen with RAI therapy. No death (and hence, all cause-mortality) was seen in both trials included. The two trials reported few cases of relapse, precluding determination of risk. There were no significant differences in modifying GO between the two treatment strategies. No study analyzed health-related quality of life and economic outcomes.[38]

The use of RAI led to fewer patients developing euthyroidism, but conversely, there was a lower relapse rate of hyperthyroidism (Table 10). More patients who were given RAI developed hypothyroidism and experienced new-onset or worsening of GO. If each outcome were to be considered as an event due to treatment, RAI is shown to be favorable because, as stated, although more patients developed hypothyroidism, fewer patients will have a relapse of hyperthyroidism. On the other hand, ATD may be deemed favorable because fewer patients developed hypothyroidism while taking these medications. This should be balanced off, however, with the higher possibility of relapse of hyperthyroidism once anti-thyroid medications have been discontinued.

The goal of RAI is to reduce the amount of thyroid tissue, which, most of the time, will lead to hypothyroidism. Whether hypothyroidism is a desirable or undesirable effect of RAI depends on the view of the physician and the patient. For physicians, developing hypothyroidism after RAI is desirable as this will prevent recurrence of hyperthyroidism and consequently, the possibility of its long-term complications. However, for patients, hypothyroidism may be undesirable as this would entail lifelong hormone replacement with levothyroxine. The incidence of hypothyroidism after RAI is as high as 50% within the first year after treatment. Annually thereafter, hypothyroidism may develop at a rate of 3-5%, with some smaller studies reporting annual rates as high as 90%.[39, 40]

The goal of ATD is to reduce hormone production by the thyroid gland, which may lead to long-lasting euthyroidism after at least 18 months of treatment. Whether euthyroidism is a desirable effect of ATD depends on the view of the physician and the patient. For physicians, discontinuing ATD after euthyroidism is achieved may be undesirable since the recurrence of hyperthyroidism is possible. The maximum remission rate with ATD is reported to be 50-55%.[41] Relapse mainly occurs within 6-12 months of

discontinuation of ATD but may still happen years after. The relapse rate is as high as 52.7%, with 37% occurring within 2 years of ATD withdrawal.[42]

On the other hand, for patients, euthyroidism is desirable because it will avoid the necessity of lifelong hormone replacement therapy with levothyroxine.

Table 10 also shows the studies that have demonstrated that RAI was associated with a lower risk for CVD and all-cause mortality. However, when subgrouped depending on the outcome of RAI, the study of Okosieme et al. showed that the benefit is only seen in patients with resolution of hyperthyroidism or consequent development of hypothyroidism.[7] Patients with persistent hyperthyroidism after RAI, compared to ATD, have a higher risk for CVD but with the same risk for mortality.

Table 16. RAI vs ATD as treatment for GD in non-pregnant adults

Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Euthyroidism	1 RCT (n = 107)	RR 0.01	0.00, 0.21	Inconclusive	Moderate
Hypothyroidism	1 RCT (n = 104)	RR 130.4	8.24, 2062.62	Favors ATD	High
Relapse of Hyperthyroidism	2 RCTs (n = 417)	RR 0.20	0.01, 2.66	Inconclusive	Low
Development or worsening GO	2 RCTs (n = 417)	RR 1.94	1.40, 2.70	Favors ATD	High
Cardiovascular disease	2 observational studies (n = 10,077)	HR 0.79	0.75, 0.84	Favors RAI	Low
All-cause mortality	2 observational studies (n = 10,077)	HR 0.93	0.88, 0.98	Favors RAI	Low

Table 17. RAI vs ATD as treatment for GD in children

Outcomes	Basis	Effect Size	95% CI	Interpretation	Certainty of Evidence
Euthyroidism	2 RCTs (n = 167)	RR 1.7	1.29, 2.24	Favors ATD	Very Low
Hypothyroidism	2 RCTs (n = 167)	RR 6.46	1.16, 35.81	Favors ATD	Very Low
Relapse of Hyperthyroidism	2 RCTs (n = 167)	Total not selected/low events	--	Inconclusive	Very Low
Development or worsening of Graves' ophthalmopathy	2 RCTs (n = 167)	RR 1.30	0.56, 3.00	Favors ATD	Very Low

Certainty of Evidence

For non-pregnant adults, the certainty of evidence for the efficacy and safety of ATD maintenance and RAI therapy are low to high. The evidence reviewed had low risk for bias. However, overall, the certainty of

evidence was downgraded to low because of serious issues on inconsistency and imprecision in one of the outcomes of interest (relapse of hyperthyroidism).

For children, the two controlled clinical trials both have high risk of bias due to lack of blinding, randomization, allocation concealment, and a possible reporting bias. The studies also have other issues on other parameters. Overall, certainty of evidence is very low due to poor methodological quality and other deficiencies of included studies.

Recommendations from Other Groups

Non-pregnant adults

The Malaysian Endocrine Society (MMSE 2019), European Thyroid Association (ETA 2018), American Thyroid Association (ATA 2016) and Korean Thyroid Association (KTA 2013) did not specify any preference for the different treatment modalities. They recommend that adult patients with Graves' hyperthyroidism should be treated with any of the following modalities: ATDs, RAI therapy, or thyroidectomy, with the choice depending on several factors like comorbidities, pregnancy, contraindications to ATD, age, and presence of severe GO.

Children

The Japanese Society for Pediatric Endocrinology (JSPE 2016), ETA (2022), and ATA (2016) recommend ATD as the primary treatment option for children with Graves' hyperthyroidism.

All three organizations concur that I-131 should be avoided in children 5 years and younger.

Additional Considerations for Decision-making

Cost

Evidence for cost-analysis is based on two studies that utilized the Markov model to compare the cost and benefits or quality-adjusted life-years (QALYs). The model included efficacy, relapse rates, hypothyroidism, supplemental thyroxine, and major complications associated with ATD and RAI in a hypothetical 40-year-old female with symptomatic GD. One study gathered the cost of treatment in England and Australia combined and used Carbimazole.[20] The other was performed in Ethiopia and used PTU.[46]

In both studies, RAI has lesser QALYs and is less expensive than ATD. ATD therapy was about 3-4 times more costly than RAI in the short term. But in a base case analysis of a patient with relapsed GD, RAI still appeared more cost-effective.

Patient's Values and Preference, Equity, Acceptability and Feasibility

We did not find any study that looked into patient's values and preference, equity, acceptability and feasibility. However, the American Thyroid Association enumerated clinical situations wherein the use of either ATD or RAI is favored or contraindicated.

Table 18. Clinical situations that favor and contraindicate the use of ATD and RAI[10]

	ATD	RAI
Favors	Patients with high likelihood of remission (patients, especially women, with mild disease, small	Women planning a pregnancy in the future (in more than 6 months following RAI administration, provided thyroid hormone levels are normal)

	goiters, and negative or low-titer TRAb) Pregnancy Elderly or with comorbidities increasing surgical risk or with limited life expectancy Patients with previously operated or irradiated necks Patients with lack of access to a high-volume thyroid surgeon Patients with moderate to severe active GO	Individuals with comorbidities increasing surgical risk Patients with previously operated or externally irradiated necks Patients with lack of access to a high-volume thyroid surgeon Patients with contraindications to ATD use or failure to achieve euthyroidism during treatment with ATDs Patients with periodic thyrotoxic hypokalemic paralysis, right heart failure, pulmonary hypertension, or congestive heart failure
Contraindications	Previous known major adverse reactions to ATD.	Pregnancy and lactation Coexisting thyroid cancer or suspicion of thyroid cancer Individuals unable to comply with radiation safety guidelines and Women planning pregnancy within 4–6 months

Consensus Issues

Antithyroid drugs (ATDs) serve as the primary treatment for managing the thyrotoxic state, typically administered for a duration of two to three months before considering other options like radioactive iodine (RAI) or thyroidectomy. This initial ATD treatment helps prevent the occurrence of thyroid storm, a potentially life-threatening condition. However, in certain cases, such as active Graves' ophthalmopathy, resolving the condition before considering RAI becomes a priority.

Compared to RAI, the cost of ATD per se is generally more affordable. However, it is important to note that ATD usage requires regular monitoring of thyroid function, which may entail additional costs for the patient. Moreover, ATDs are widely available and easily accessible in local pharmacies, ensuring convenient access for those in need.

To optimize treatment decisions, healthcare providers should carefully weigh the benefits and potential costs associated with ATD therapy, considering the patient's individual condition and financial situation. By providing comprehensive information and support, patients can make informed choices that align with their health needs and financial capabilities. Regular monitoring throughout the treatment process is crucial to gauge the effectiveness of ATDs and ensure the patient's well-being.

RAI stands as an effective and definitive treatment for patients diagnosed with primary hyperthyroidism. However, it is crucial to exercise caution and not administer RAI immediately. Physicians must carefully determine the appropriate dosage, which typically ranges from around 10 to 15 mCi, to eliminate hyperthyroidism and to minimize the risk of its relapse. In the event of treatment failure, RAI can be re-administered after a six-month interval.

While RAI treatment may uncommonly lead to side effects lasting for 4-8 weeks, these effects, such as nausea, diminution of taste, dryness of eyes, neck and salivary gland tenderness and swelling, are generally mild, temporary, and manageable, especially with the aid of supportive treatment measures. Despite the

temporary discomfort, patients can tolerate the side effects well. The more serious adverse effect is the risk of exacerbation of hyperthyroidism or even thyroid storm after the administration of RAI. This, however, may be minimized or mitigated with proper patient preparation. It is important to highlight that RAI treatment will likely necessitate lifetime thyroid hormone replacement therapy with levothyroxine when the patient becomes hypothyroid, with the goal of maintaining thyroid hormone levels within the optimal range.

By ensuring precise dosing, offering necessary support during the recovery period, and providing appropriate follow-up care, physicians can optimize the benefits of RAI treatment while mitigating potential risks and ensuring long-term thyroid health for patients.

Treatment using RAI is known to incur higher long-term costs due to the necessity of daily thyroid hormone replacement therapy following the procedure. The overall cost of RAI varies based on the required dosage and the type of healthcare institution providing the treatment. Private hospitals typically charge between PhP15,000.00 to PhP20,000.00, while government hospitals offer RAI treatment at a lower cost, around PhP7,000.00 for doses not exceeding 15 mCi. Fortunately, RAI treatment is widely available across the country, especially in hospitals with nuclear medicine facilities. However, smaller cities and marginalized areas may still have limited access to this specialized treatment. Importantly, RAI is sourced from other countries, and only two suppliers are accredited by the Philippine Nuclear Research Institute, which could potentially affect the availability of RAI in the market.

To ensure proper patient care and access to RAI treatment, physicians should establish coordination with other healthcare facilities that offer RAI therapy, so as to facilitate seamless access to the required treatment. This collaboration between healthcare providers can contribute significantly to the comprehensive care and management of patients with hyperthyroidism undergoing RAI treatment.

Both RAI and ATD are recognized as effective and safe treatment options for patients with hyperthyroidism. The decision to utilize RAI or ATD hinges on various factors, including the underlying cause of hyperthyroidism, the patient's individual characteristics and preferences, the severity of symptoms, the presence of comorbidities, and the existence of ophthalmopathy. It is crucial for physicians to engage in comprehensive discussions with the patient, providing a thorough explanation of the treatment processes and the associated benefits, potential drawbacks, and costs of each treatment option.

Ultimately, the collaborative decision-making process between physicians and patients optimizes the management of hyperthyroidism, ensuring the most suitable and personalized care for each individual.

Clinical Question No. 13 Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?

Recommendation No. 13A
Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest doing total thyroidectomy instead of RAI if a "high volume"* thyroid surgeon is available *(Low certainty of evidence; Weak recommendation)* **performs more than 25 thyroidectomies per year*

Recommendation No. 13B
Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest giving RAI if a "high-volume"* thyroid surgeon is not available *(Low certainty of evidence; Weak recommendation)* **performs more than 25 thyroidectomies per year*

Recommendation No. 13C
Among pediatric patients with hyperthyroidism who are refractory to medical management, we suggest thyroidectomy as the treatment of choice for definitive therapy in children with access to a "high volume"* thyroid surgeon. *(Low certainty of evidence; Weak recommendation)* **performs more than 30 thyroidectomies per year*

Introduction

When diagnosis of hyperthyroidism is made, treatment options are discussed by the physician and the patient factoring in the risks, benefits, cost, feasibility, and preferences. Thionamides (ATD) , in particular methimazole, are usually the initial choice of therapy for hyperthyroidism. However, there are rare but serious adverse effects related to ATD therapy such as severe allergic reactions, agranulocytosis and hepatic dysfunction, which warrant their discontinuation. Furthermore, a study by Sundaresh et. al. noted that there is higher recurrence of hyperthyroidism with ATDs with overall failure rate of as high as 48.3%.[168] In cases wherein ATD is contraindicated or ineffective, definitive therapy is the next option for treatment. There are 2 options for definitive treatment that can be offered to patients with hyperthyroidism, namely radioactive iodine (RAI) or surgery (thyroidectomy).

RAI is given with the aim of rendering the patient hypothyroid through the destruction of thyroid cells. It is administered orally as sodium iodide (iodine-131) in a solution or a capsule, and the iodine is taken up by the thyroid that subsequently leads to its destruction or ablation.[166] The American Thyroid Association recommends RAI ~~to~~ be given at a dose of 10-15mci with the goal of rendering the patient hypothyroid.[167] Hypothyroidism is usually expected within 6-18 weeks, and when this occurs, thyroid hormone replacement with levothyroxine is initiated.[166] Complications of RAI include radiation thyroiditis and worsening of Graves' orbitopathy. Thyroiditis may develop in the first week of treatment in 1-5% of patients, and may progress to an exacerbation of thyrotoxicosis at 10-14 days post-treatment.[169] In a randomized prospective study based in Japan, the incidence of Graves' orbitopathy was at 9.8% after administration of RAI, which is less common as compared to other populations wherein the incidence is as

high as 20%.[170] Risk factors for exacerbation of GO include elevated thyroid stimulating antibodies (TRAb) and increased clinical activity score.

The theoretical lifetime risk for cancer of 0.8% as a consequence of RAI therapy was associated with RAI treatment at a dose of 15 mCi when given at 20 years or older.[166] However, in patients who are 5 years old and below, this theoretical risk increases to 4%, so RAI therapy is generally not recommended for children 5 years old and below.

RAI therapy can be recommended in patients who are elderly and those with comorbidities, increased surgical risk, liver disease, hypokalemic periodic paralysis, pulmonary hypertension or congestive heart failure, previous neck surgery or irradiation or in those with contraindications to ATD or thyroidectomy.[2,3] RAI is contraindicated in those who are pregnant or those who are planning for pregnancy within the next 6 months, those who are lactating and those in whom thyroid cancer is suspected.[166]

Thyroidectomy is an option especially for patients with a large goiter, those with compressive symptoms due to their goiter, those in whom thyroid malignancy is suspected, and those with Graves' ophthalmopathy or with concomitant hyperparathyroidism.[166,167] This modality results in rapid correction of hyperthyroidism.[166] Total thyroidectomy has near 0% risk of recurrence in contrast to subtotal thyroidectomy wherein recurrence rate might go up to 5% in the next 5 years.[167] Hence, total thyroidectomy is the recommended procedure of choice. Complications can vary, and is highly dependent on the skill of the surgeon.[171] In multiple studies, hypocalcemia and recurrent laryngeal nerve injuries are the most common complications post-operatively.[171,172] In local studies, hypocalcemia occurred in 12-20% of patients.[10] Incidence of recurrent laryngeal nerve injury occurs in 1.5-14% of patients.[173] Post-operative bleeding, the most life-threatening complication, occurs in <1% of surgeries performed by a highly skilled surgeon.[166,172] A study identified that surgeons with >25 thyroidectomies per year were considered as "high-volume" surgeons for whom improved patient outcomes were seen.[174] Patients who underwent surgery by low-volume surgeons had a 51% increase in the odds of having complications, and had 12% longer hospital stays.[174] In the pediatric age group, a high-volume surgeon is defined as having more than 30 thyroid surgeries per year.[175]

Both RAI and thyroidectomy are acceptable as therapeutic options for the definitive treatment of hyperthyroidism. Comparison of the benefits and risks are imperative in making the appropriate clinical decision in the management of Graves' disease.

Summary of Efficacy and Safety

Efficacy

An RCT has shown that adult patients who underwent RAI were 7.5x significantly more likely to have recurrence of hyperthyroidism than those who underwent thyroidectomy (RR 7.5; 95% CI 2.74, 20.55, p=0.0001).[174] A study among pediatric participants showed no significant difference in the relapse rate between the thyroidectomy and RAI group (RR 0.21; 95% CI 0.0120, 3.7278, p=0.28).[175]

A study on the quality of life of adult patients 6-10 years after definitive treatment showed that those who had RAI had significantly worse quality of life than those who were post-surgery in the parameters related to goiter, eye symptoms, hypothyroid and hyperthyroid symptoms, as well as emotional, psychological, social and mental symptoms, activities of daily living, and overall quality of life (all p<0.05) using the ThyPro questionnaire.[177] Patients post-RAI had a significantly worse quality of life in all domains as well when the SF-35 questionnaire was used).

Safety

The observational study with cardiovascular outcomes showed that during the post-treatment follow-up, hospitalizations due to cardiovascular disease (CVD) were more common in hyperthyroid patients than in controls (HR 1.15; 95% CI: 1.09, 1.21).[178] Compared to those who were treated with thyroidectomy, patients who underwent RAI and were unable to achieve euthyroidism or hypothyroidism had higher risk of hospitalization due to CVD (HR 1.17; 95% CI 1.05, 1.30), atrial fibrillation (HR 1.28; 95% CI 1.08, 1.54), and higher CV mortality (HR 2.56; 95% CI 2.08, 3.15). However, in those who were rendered hypothyroid post-RAI, there was no significant difference in CVD morbidity compared to those who underwent thyroidectomy.[178]

Another study showed that the type of treatment, either RAI or surgery, is not associated with risk of cancer (HR 1.03; 95% CI 0.86, 1.2) or cancer mortality (HR 1.04; 95% CI 0.91, 1.21).[179]

Table 19 summarizes the findings of this study.

Table 19. Comparison of RAI and thyroidectomy (adult)

Critical Outcomes	No. and Type of Studies (Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Relapse	1 RCT (n=179)	RR 7.5	2.74, 20.55	Favors surgery	Moderate
Quality of Life (6-10 years post-treatment)	1 Observational (n=1,186)		p <0.05	Favors surgery	Low
Cardiovascular outcomes: CV Mortality	1 Observational (n=6,148)	HR 2.65	2.08, 3.15	Favors surgery	Low
Malignancy	1 Observational (n=4334)	HR 1.55	0.86, 1.23	Inconclusive	Low

Certainty of Evidence

Out of all the studies looking at the different outcomes, only 1 study is an RCT and the rest are all observational cohort.[174-176, 178, 179] The risk of bias for the RCT was moderate because of the small sample size and the wide confidence interval. The rest of the studies have overall high risk of bias as they are observational; adjustments for the possible confounders were done during the statistical analysis.

The results of the study of Ryodi et. al. on CV morbidity and mortality post-treatment was adjusted for age, sex, prevalent CV, etiology of hyperthyroidism, and type of thyroidectomy. Regarding malignancy outcome, Ryodi et. al. also adjusted results based on prevalent national cancers. These studies utilized national registries, so attrition and reporting bias are minimized.

Due to the nature of the treatment modalities, implementation of RCTs are methodologically challenging, as some vignettes of individual cases are usually needed to decide if one treatment is more favorable than the other for each patient. Though RCTs are the ideal design for questions on therapy, observational studies were more feasible in comparing RAI with thyroidectomy due to these limitations.

Overall certainty of evidence was downgraded to low because of the serious risk of bias across the different critical outcomes. Because there were no studies with the same outcomes in the pediatric age group apart from efficacy, we utilized the data from the studies done in adults but downgraded the evidence to very low.

Recommendations from Other Groups

The ATA (2016) and ETA (2018) both state that the choice of definitive therapy for nonpregnant adults with Graves' hyperthyroidism depends on the clinical situations that favour the particular modality and patient preference.

For the pediatric age group, the ETA (2018) recommend thyroidectomy over RAI as definitive therapy, though RAI can be considered in post-pubertal children. RAI should be avoided in children 5 years and younger.

Table 20. Specific indications and contraindications of RAI and total thyroidectomy as recommended by other groups

	RAI	Total Thyroidectomy
2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other Causes of Thyrotoxicosis		
Conditions		
Comorbidities with increased surgical risk and/or limited life expectancy	√√	X
Inactive Graves' Ophthalmopathy (GO)	√	√
Active Graves' Ophthalmopathy (GO)	May give with steroids in mild cases	√
Liver Disease	√√	√
Major Adverse Reactions to ATDs	√√	√
Patients with previously operated or externally irradiated necks	√√	Cautious use
Lack of access to a high-volume thyroid surgeon	√√	Cautious use
Patients with high likelihood of remission (especially women, with mild disease, small goiters, and negative or low-titer TRAb)	√	√
Patients with periodic paralysis	√√	√√
Patients withpulmonary hypertension, or congestive heart failure	√√	Cautious use
Elderly with comorbidities	√	Cautious use
Thyroid malignancy confirmed or suspected	X	√√
One of more large thyroid nodule	Not first line therapy	√√

Coexisting primary hyperparathyroidism requiring surgery	Not First line therapy	√√
2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism		
Indications	Patients with side-effects to or recurrence after a course of ATD, cardiac arrhythmias, and thyrotoxic periodic paralysis	Goiter is large, there is coincident primary hyperparathyroidism or suspicion of malignant nodules, the patient wishes to avoid exposure to ATD or RAI
2022 European Thyroid Association Guideline for the Management of Pediatric Graves' disease		
	RAI	Total Thyroidectomy
General indications	Relapse after ATD treatment, serious or persistent side effects of ATDs, or poor compliance.	Relapse after ATD treatment, serious or persistent side effects of ATDs, or poor compliance.
Indications		Obstructive symptoms from a large goiter. When a euthyroid state is required quickly. Patients under 5 years.
Absolute contraindications	Patients under 5 years of age. Active GO.	Essentially none, however, patients must be euthyroid or have only mild thyroid dysfunction at the time of surgery
Relative contraindications	Patients between 5 and 10 years of age. Inactive GO. Large goiter – second dose may be required.	

Additional Considerations for Decision-making

Cost

There are no available economic evaluation studies that compared RAI with thyroidectomy in our setting. Cost-analysis done in the USA by In, et al concluded that total thyroidectomy was the most cost-effective strategy.[180] However because of the difference in the sources of healthcare funds in the USA and the Philippines, this might not be applicable in our setting as a federal health insurance (Medicare) shouldered the treatment for the patients included in the US study. The cost of thyroidectomy can range from PhP30,000-300,000 while the cost of radioactive iodine treatment ranges from PhP5,000-15,000 in our country.

Patient's Values and Preference, Equity, Acceptability and Feasibility

In the study of Torring, the patients were asked if they were satisfied with the treatment they received. More patients in the iodine-131-treated group were likely to recommend the same treatment to a friend than the patients in the other groups.[178] The relapse of the disease was considered a major disappointment in the young patients who received surgery, whereas those in the RAI group were least disappointed in

terms of relapse. There are no studies done in our setting exploring preference, equity, acceptability, and feasibility comparing surgery and RAI as treatment for hyperthyroidism.

Consensus Issues

Thyroidectomy and RAI are both definitive treatments for various thyroid conditions, and the choice between them requires a careful consideration of their respective advantages and disadvantages. Medical treatment is still the first line of therapy. However, RAI or thyroidectomy may be employed if medical treatment is unsuccessful. When opting for thyroidectomy, several crucial factors must be considered to make an informed decision.

Firstly, the size of the thyroid gland, the presence of nodules, and the overall risk of complications should be thoroughly evaluated. Additionally, the potential impact of thyroidectomy on vocal cord function is a vital concern, especially for patients whose professions or lifestyles heavily depend on vocal function. The patient's age and overall health condition also play pivotal roles in the decision-making process.

Thyroidectomy, when performed by an experienced surgeon, is generally considered a safe procedure. Moreover, thyroidectomy, specifically total thyroidectomy, typically results in a negligible recurrence rate of hyperthyroidism.

However, it is essential to note that thyroidectomy does come with its own set of considerations. It is a surgical procedure that carries inherent risks, and it can be costly. Additionally, patients who undergo thyroidectomy require lifelong monitoring and may need thyroid hormone replacement therapy to maintain normal thyroid function.

Among pediatric patients, it is important to maximize medical treatment in order to avoid rendering the patient hypothyroid permanently. Physicians who will perform these surgeries should be well equipped with knowledge, training, and experience so as to reduce complication rates and ensure patient safety.

Given the availability of multiple treatment options, it is imperative to provide patients with comprehensive information about the pros and cons of each treatment modality. This empowers patients to make well-informed decisions that align with their individual health needs, preferences, and circumstances. Informed decision-making not only contributes to better patient satisfaction but also ensures that the chosen treatment is optimized for the patient's overall well-being.

Clinical Question No. 14 Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?

Recommendation No. 14
Among patients with mild* and active* Graves' ophthalmopathy, we suggest selenium supplementation for six months to improve clinical outcomes (i.e., clinical activity score, overall eye evaluation improvement, and improvement in quality of life) *(Low certainty of evidence; Weak recommendation)*

Introduction

Graves' ophthalmopathy (GO), also known as thyroid-related eye disease, is an autoimmune, disabling eye condition affecting 25 to 50% of patients with Graves' disease (GD).[16] In the Philippines, a nationwide prevalence rate has not yet been determined, but in a government-owned tertiary hospital, the prevalence of GO among 121 patients with GD seen from February to September 2017 was 47.93%.[17] A cross-sectional analytical study of 163 adult patients with GD in another Philippine-owned tertiary hospital showed that most GO were mild (85%) and only 8% were moderate to severe. Male sex and elevated thyrotropin receptor antibody (TRAb) titers were associated with GO severity among Filipino nonsmokers.[18]

The natural history of GO is divided into three stages: (1) the initial phase of inflammatory changes in the orbit; (2) the plateau period where inflammation declines; and (3) the inactive phase, which may persist for 18-24 months.[16] Moderate to severe forms of GO may impair quality of life and may necessitate more intensive treatment, hence, referral to an ophthalmologist. The treatment options for GO are influenced by clinical activity and severity. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines recommended that GO be classified as active or inactive by clinical activity score (CAS) and as mild, moderate to severe, or sight-threatening by EUGOGO classification.[19]

Table 21. EUGOO Mild GO Criteria

European Group on Graves' Orbitopathy (EUGOGO) Mild GO criteria MILD GO: Patients whose features of GO have only a minor impact on daily life that have insufficient impact to justify immunomodulation or surgical treatment. They usually have one or more of the following:
Minor lid retraction <2mm
Mild soft-tissue involvement
Exophthalmos <3mm above the normal for race and gender
No diplopia
No corneal exposure
No optic nerve involvement

Table 22. Clinical Activity Score

Clinical Activity Score	
Initial Assessment	Follow-up Evaluation
Spontaneous retrobulbar pain	Increase in degree of proptosis
Eye pain upon upward or downward gaze	Decrease in ocular excursion in any direction
Redness of the eyelids	Decrease in visual acuity
Redness of the conjunctiva	

Swelling of the caruncle or plica (medial part of the eye near the medial canthus)	
Swelling of the eyelids	
Swelling of the conjunctiva	

*For further details regarding CAS and EUGOGO, refer to Bartalena L, Kahaly GJ, Baldeschi L, Dayan CM, Eckstein A, Marcocci C, et al. The 2021 European Group on Graves' orbitopathy (EUGOGO) clinical practice guidelines for the medical management of Graves' orbitopathy. European Journal of Endocrinology. 2021 Oct 1.
**Clinical activity score (CAS) ≥ 3 is considered "active"

Fundamental to the treatment and management of GO is smoking cessation and restoration and maintenance of euthyroidism.[16] Further, glucocorticoids may be considered for the prevention of GO exacerbation or progression among patients who require radioactive iodine therapy to achieve control of their hyperthyroidism. Since GO is also linked to increased oxidative stress, antioxidants like selenium may be of benefit. Investigations have shown a possible, although inconsistent, association between GO and selenium deficiency.[20,21]

Summary of Efficacy and Safety

Efficacy

Clinical Activity Scores

Studies have shown that there was a lower GO activity score with selenium supplementation at a dose of 200mcg a day compared to placebo, with a mean difference of -1.64 (95% CI -1.88, -1.40; I_2=24%) at 6 months and a mean difference of -1.20 (95% CI -1.93, -0.47) at 12 months.[22, 23]

Overall Eye Evaluation Improvement

The use of selenium compared to placebo in these studies likewise showed significant overall eye improvement upon evaluation at 6 months (RR 1.70; 95% CI: 1.11, 2.60) and 12 months (RR 1.75; 95% CI: 1.17, 2.62) of treatment.[23]

Quality of Life Improvement

Furthermore, the use of selenium compared to placebo led to a significant improvement in quality of life (QOL) at 6 months (RR 3.80; 95% CI: 1.79, 5.28) and at 12 months (RR 1.83; 95% CI: 1.25, 2.66) of treatment, as assessed by the GO-QOL questionnaire.[23]

Tables 23 and 24 summarize the efficacy outcomes of these studies.

Table 23. Selenium vs Placebo for the treatment of Graves' Disease with Mild Graves' Ophthalmopathy

Critical Outcomes	No. and Type of Studies (Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Clinical Activity Score (6 months)	2 RCTs (n=134)	MD -1.64	-1.88, -1.40	Beneficial	Low
Clinical Activity Score (12 months)	1 RCT (n=104)	MD -1.20	-1.93, -0.47	Beneficial	Moderate
Overall Eye Evaluation Improvement (6 months)	1 RCT (n=104)	RR 1.70	1.11, 2.60	Beneficial	Moderate

Overall Eye Evaluation Improvement (12 months)	1 RCT (n=104)	RR 1.75	1.17, 2.62	Beneficial	Moderate
Quality of Life Improvement (6 months)	1 RCT (n=99)	RR 3.08	1.79, 5.28	Beneficial	Moderate
Quality of Life Improvement (12 months)	1 RCT (n=99)	RR 1.83	1.25, 2.66	Beneficial	Moderate

Table 24. Selenium vs Placebo for the treatment of Graves' Disease with Mild Graves' Ophthalmopathy - Subgroup analysis

Critical Outcomes	Subgroup	No. and Type of Studies (Total Participants)	Effect Size	95% CI	Interpretation	Certainty of Evidence
Clinical Activity Score	6 months	2 RCTs (n=134)	MD -1.64	-1.88, -1.40	Beneficial	Low
	12 months	1 RCT (n=104)	MD -1.20	-1.93, -0.47	Beneficial	Moderate
Overall Eye Evaluation Improvement	6 months	1 RCT (n=104)	RR 1.70	1.11, 2.60	Beneficial	Moderate
	12 months	1 RCT (n=104)	RR 1.75	1.17, 2.62	Beneficial	Moderate
Quality of Life Improvement	6 months	1 RCT (n=99)	RR 3.08	1.79, 5.28	Beneficial	Moderate
	12 months	1 RCT (n=99)	RR 1.83	1.25, 2.66	Beneficial	Moderate

Safety

RCTs have found no adverse events in either the selenium treatment group nor the placebo groups (n=134).[22,23] However, in the study of Almanza-Monterrubio (2020), one patient had gastrointestinal issues in the first month of the trial and this patient was excluded from the study and was not included in the analysis.[22]

Certainty of evidence

The study of Almanza-Monterrubio (2020) had high risk of attrition bias.[22] Both studies were imprecise due to low event rate.[22,23]. The overall certainty of evidence was then downgraded to low due to serious risk of bias and imprecision.

Recommendations from Other Groups

The European Group on Graves' Orbitopathy 2021[16] recommends that a 6-month selenium supplementation for patients with mild and active GO of recent onset, because it improves eye manifestations and QoL and usually prevents GO progression to more severe forms.

Ongoing Studies and Research Gaps

There is an ongoing RCT on selenium supplementation among patients with GD and mild GO in the Philippines. As of February 27, 2023, the final analysis was still unavailable. There is a paucity of RCTs on GD with GO with larger sample sizes.

Additional Considerations for Decision-making

Cost

There were no economic studies regarding the use of selenium among patients with GO. At any rate, selenium is readily accessible as a dietary supplement at dosages of either 100 or 200 mcg. Each tablet costs around PhP4.00 to PhP8.00, respectively. Estimated costs for a 6 month-treatment course ranges from Php 712.00 to Php 1,424.00. However, caution should be exercised in the use of unregistered selenium preparations.[25]

Patient's Values and Preference, Equity, Acceptability and Feasibility

There were no studies looking into patient values and preference, equity, acceptability and feasibility.

Consensus Issues

It is important to consider the classification of GO based on both clinical activity score and EUGOGO classification. GO can be categorized as active or inactive, as well as mild, moderate to severe, or sight-threatening.

For patients with mild and active GO, the Consensus Panel recommends selenium supplementation for a period of six months. This is due to selenium's multiple mechanisms of action, including its significant impact on reducing TRAb and thyroid peroxidase antibodies. Selenium supplementation is particularly beneficial for patients with mild GO, but it may not effectively improve structural changes that occur during the active phase of the condition.

Selenium supplementation is generally considered safe and well-tolerated when taken in prescribed doses, with minimal known negative effects. It is easily accessible as an over-the-counter supplement. However, caution is essential while purchasing selenium products, as some unregistered supplements may exist in the market. To ensure safety and efficacy, obtaining medical recommendations before starting any supplement is crucial.

Certain circumstances may warrant caution or preclude the use of selenium supplements. Individuals with already elevated selenium levels in their body or a history of allergic reactions to selenium or related compounds should avoid selenium supplementation. Additionally, despite promising clinical improvement results, further evidence is needed to fully understand the comprehensive effects and risks associated with selenium supplementation.

Clinical Question No. 15 Should we routinely treat non-pregnant adults and children with persistent biochemically confirmed subclinical hyperthyroidism?

Recommendation No. 15A
Among adult patients with persistent biochemically confirmed subclinical hyperthyroidism ≥ 65 years and serum TSH levels <0.1 mIU/L, we suggest routine treatment *(Very low certainty of evidence; Weak recommendation)* **i.e., ATD, RAI, etc*

Recommendation No. 15B
Among adult patients with persistent subclinical hyperthyroidism ≥ 65 years and serum TSH levels greater than or equal to 0.1 mIU/L, we suggest against routine treatment* due to insufficient evidence *(Very low certainty of evidence; Weak recommendation)* **i.e., ATD, RAI, etc*

Recommendation No. 15C
Among adult non-pregnant patients with subclinical hyperthyroidism who are <65 years, we suggest against routine treatment* due to insufficient evidence *(Very low** certainty of evidence; Weak recommendation)* **i.e., ATD, RAI, surgery, etc* *Treatment should be individualized and may be considered for certain conditions such as TSH levels (< 0.1 mIU/L), signs and symptoms of the patients, and presence of comorbidities (eg cardiovascular disease, osteoporosis).*

Recommendation No. 15D
Among children with subclinical hyperthyroidism, we suggest against routine treatment* due to insufficient evidence *(Very low certainty of evidence; Weak recommendation)* ** i.e., ATD, RAI, surgery, etc*

Introduction

Subclinical hyperthyroidism is biochemically defined as TSH levels below the reference range with normal serum T4 and T3.[50] Its prevalence among adults in the Philippines is 5.33%.[2] In pediatric patients, the prevalence is around 0.5%. Similar to overt hyperthyroidism, subclinical hyperthyroidism can also be caused by endogenous or exogenous causes (ie excess thyroid hormone intake).[51] Since subclinical hyperthyroidism is considered a mild form of hyperthyroidism, the deleterious effects seen in overt hyperthyroidism might also occur in subclinical hyperthyroidism such as cardiovascular disease, osteoporosis, and increase in overall mortality.[52-55]

Because serum TSH can be transiently reduced, serum TSH together with T4 and T3 should be repeated after one to three months or earlier if with cardiovascular disease to confirm the diagnosis.[209]

The management options for persistent endogenous subclinical hyperthyroidism include ATD, RAI, and no treatment. The management will depend on the presence of risk factors such as age of more than 65 years or comorbidities such as heart disease or osteoporosis.[56]

Recent meta-analyses indicated that patients with persistent subclinical hyperthyroidism having serum TSH levels <0.1 mIU/l are at an increased risk of coronary artery disease, atrial fibrillation, heart failure, fractures, and mortality. A systematic review and meta-analysis of 22 observational studies (Sohn et al 2021) reported an association of overt and subclinical hyperthyroidism with the risk of cardiovascular events and cardiovascular mortality.[57] A meta-analysis of 12 cohort studies (Xu et al 2020) reported an association of subclinical hyperthyroidism with osteoporosis.[58]

A review of the management of subclinical hyperthyroidism in children stated that the management is uncertain and routine treatment is not recommended for all patients whose TSH is mildly decreased (0.1-0.45 mU/L). Treatment should be considered in the presence of TSH <0.1 mU/L, especially for those with symptoms suggestive of hyperthyroidism.[59]

Summary of Efficacy and Safety

Efficacy Outcomes

Cardiovascular function

In a prospective observational study (Sgarbi et al, 2003) involving 10 patients with endogenous subclinical hyperthyroidism (median TSH 0.05, range 0.05–0.07) rendered euthyroid with methimazole (median dose 12.5 mg daily; range, 5–30 mg daily) treated for a median duration of 9.1 months (range, 7–13 months), the patients had a significant reduction in heart rate, total number of beats during 24 hours, number of atrial premature beats, and ventricular premature beats. There was also a decrease in left ventricular mass index compared to 10 age and sex-matched controls.[61] In another prospective observational study (Faber et al, 2001), 6 patients with subclinical hyperthyroidism (age 47-81 years; serum TSH 0.006-0.090 mU/l) given 131I had significant reductions in both heart rate and cardiac output.[60]

Bone mineral density

In a prospective non-randomized study (Faber et al 1998) involving postmenopausal women with nodular goiter and subclinical hyperthyroidism (TSH <0.2mU/l), 16 were treated with RAI (median dose 555 MBq), whereas 12 were followed without treatment. BMD at the spine tended to increase (not significant) after RAI to a median of 101.5% (expressed as a percentage of the base-line value) after 2 years. In contrast, the untreated group experienced a continued fall in BMD to 95.5% after 2 years ($p < 0.02$). BMD of the hip also increased in the RAI-treated group to 101.7% after 2 years, while it decreased to 98.0% after 2 years in the untreated group ($p < 0.01$).[62]

In another study (Mudde et al 1994), methimazole treatment in 8 postmenopausal women with endogenous subclinical hyperthyroidism led to a significant improvement in their distal forearm bone mineral density after two years compared to nontreated controls.[64]

Safety Outcomes

No adverse events (e.g., death, cardiovascular complications, agranulocytosis, arthritis, or hepatic events) occurred in either group during five years of follow-up.

Table 25. Summary of findings on treatment of non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism

Outcomes	No. of participants (studies) Follow-up	Certainty of the evidence (GRADE)	Interpretation	Anticipated absolute effects	
				Risk with No Treatment	Risk difference with Treatment
Cardiovascular Function (Methimazole vs No Treatment)	20 (1 observational study [61])	⊕◯◯◯ Very low[a,b]	Benefit (favors treatment)	Mean LV mass index: 79.1g/m^2	mean 7.7 lower (58.3 to 90.8)
Cardiovascular Function (before and after radioiodine therapy)	6 (1 observational study [60])	⊕◯◯◯ Very low[a,b]	Benefit (favors treatment)	Mean cardiac output: 8.53L/min	mean 2.95 lower (3.64 to 7.92)
Distal Forearm Bone Mineral Density (Methimazole vs No Treatment)	16 (1 RCT [64])	⊕◯◯◯ Very low[b,c]	Benefit (favors treatment)	Mean bone mineral density: 95%*	mean 5% higher
Hip Bone Mineral Density (Radioactive Iodine Vs. No Treatment)	28 (1 observational study [62])	⊕◯◯◯ Very low[a,b]	Benefit (favors treatment)	Mean bone mineral density: 98%*	mean 3.7 higher (100 to 102.8%)

**expressed as a percentage of the base-line value*

Recommendations from Other Groups

The American Thyroid Association recommends treatment of subclinical hyperthyroidism when TSH is persistently <0.1 mU/L in all individuals ≥ 65 years of age; in patients with heart disease or osteoporosis; in postmenopausal women who are not on estrogen or bisphosphonate; and in individuals with significant hyperthyroid symptoms.

When TSH is persistently <0.1mU/L, treatment may be considered in asymptomatic individuals <65 years of age even without the conditions listed above. When TSH is persistently below the lower limit of normal but ≥ 0.1 mU/L, treatment may be considered in individuals ≥ 65 years of age and in patients with cardiac disease, osteoporosis, or symptoms of hyperthyroidism. When TSH is persistently below the lower limit of normal but ≥ 0.1 mU/L, asymptomatic patients under age 65 years without cardiac disease or osteoporosis can be observed without further investigation of the etiology or treatment.[10]

Additional Considerations for Decision-making

Cost

An overall cost was included in the study of Azizi et. al. on the treatment of subclinical hyperthyroidism in the elderly. For the management of hyperthyroidism and related complication, the overall 5-year cost was US$ 7025 ± 89 (Php 389,850) for radioactive iodine and US$ 7009 ± 97 (Php 388,907) for methimazole-treated groups.

Patient's Values and Preference, Equity, Acceptability and Feasbility

We did not find any study that looked into patient values and preferences.

Consensus Issues

Subclinical hyperthyroidism is a commonly encountered condition in clinical practice and requires careful consideration due to its potential to lead to cardiac complications and overt hyperthyroidism. However, not all patients with subclinical hyperthyroidism should immediately undergo routine treatment. Factors like age (especially for patients over 65 years old), TSH levels (< 0.1 mIU/L), the presence of signs and symptoms, and coexisting medical conditions should be carefully evaluated to determine the appropriate course of action. Early intervention is especially critical for symptomatic and elderly patients, as it has been shown to significantly reduce the risk of complications. By closely monitoring and appropriately treating subclinical hyperthyroidism based on individual patient characteristics, healthcare professionals can ensure the best possible outcomes and improve overall patient well-being.

For asymptomatic children diagnosed with subclinical hyperthyroidism, a conservative approach of observation and close monitoring is generally recommended. However, if the condition progresses to overt hyperthyroidism, medical treatment becomes necessary, unless contraindications are present, in which case alternative treatment options should be explored.

The medications required to manage subclinical hyperthyroidism are widely available, accessible, and cost-effective. Nevertheless, it is crucial to exercise discretion in determining when to initiate treatment, considering that treatment may come with potential side effects. Balancing the necessity of treatment with the likelihood of side effects is essential to minimize any additional costs and to ensure the overall well-being of the patients.

By carefully assessing each individual case and adopting an informed and prudent approach to treatment, healthcare providers can optimize the management of subclinical hyperthyroidism, ensuring effective care while minimizing potential risks and expenses.

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Barriers and Facilitators

After discussions with the multistakeholder group throughout the CPG development process, information/description of the types of facilitators and barriers have emerged. Additional feedback were sought from other key stakeholders through dialogues or external communications. These methods included the identification of facilitators (i.e., support of government for medications and services, advocacy groups activity) and barriers (i.e., out-of-pocket mode of healthcare payment, availability of specific machines/laboratory tests/reagents, etc.). This information influenced the value judgment of the consensus panel during the discussions and formulation of the recommendation statements and the strength of each recommendation.

Implementation Tools

The diagnostic algorithms for patients (i.e., pregnant, non-pregnant, adult, and/or children) are illustrated below. This may serve as a guide in the context of patient care/management at the level of the target users (i.e., primary care, specialists).

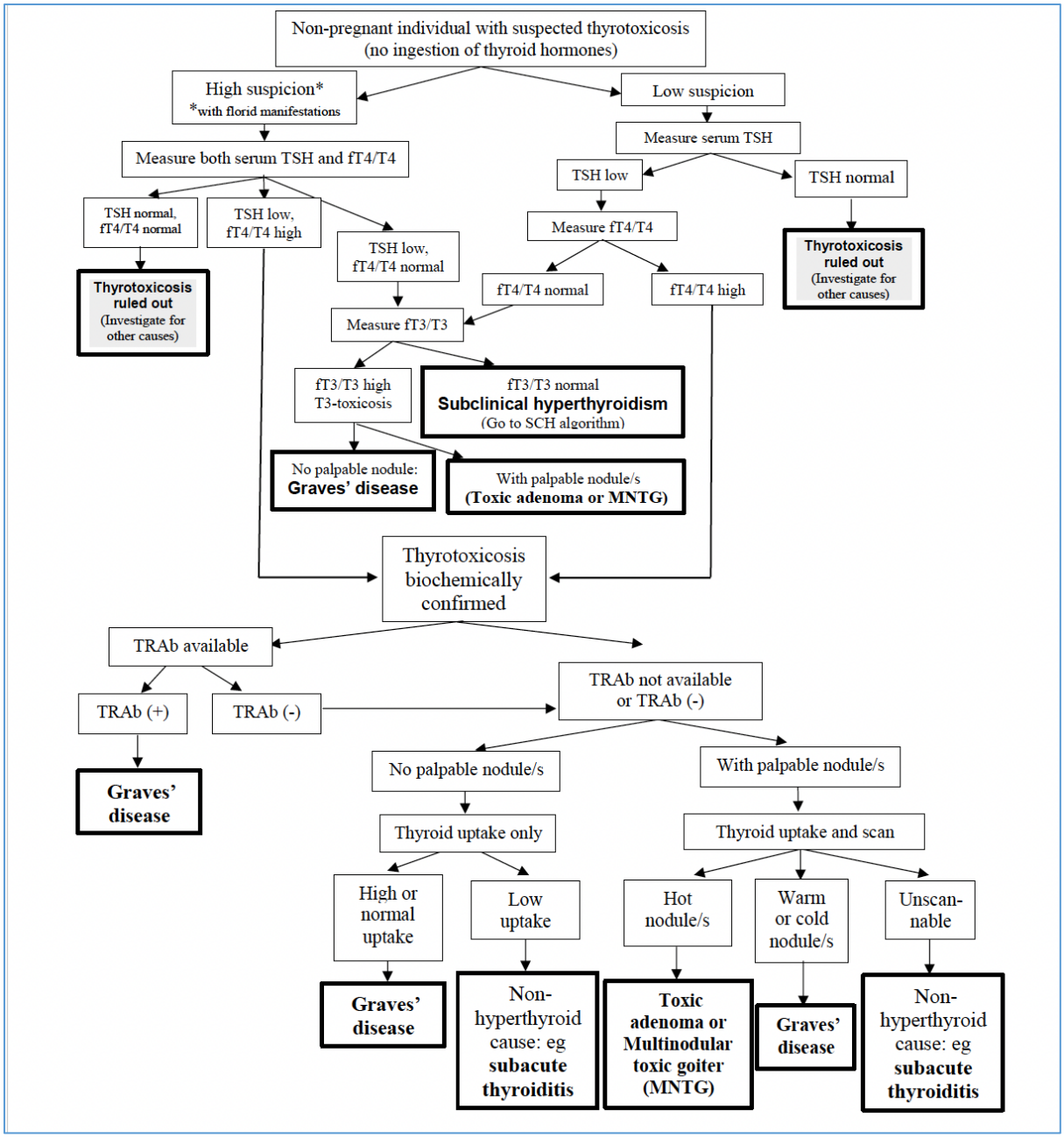

Figure 1. Diagnostic algorithm for a nonpregnant patient with suspected thyrotoxicosis

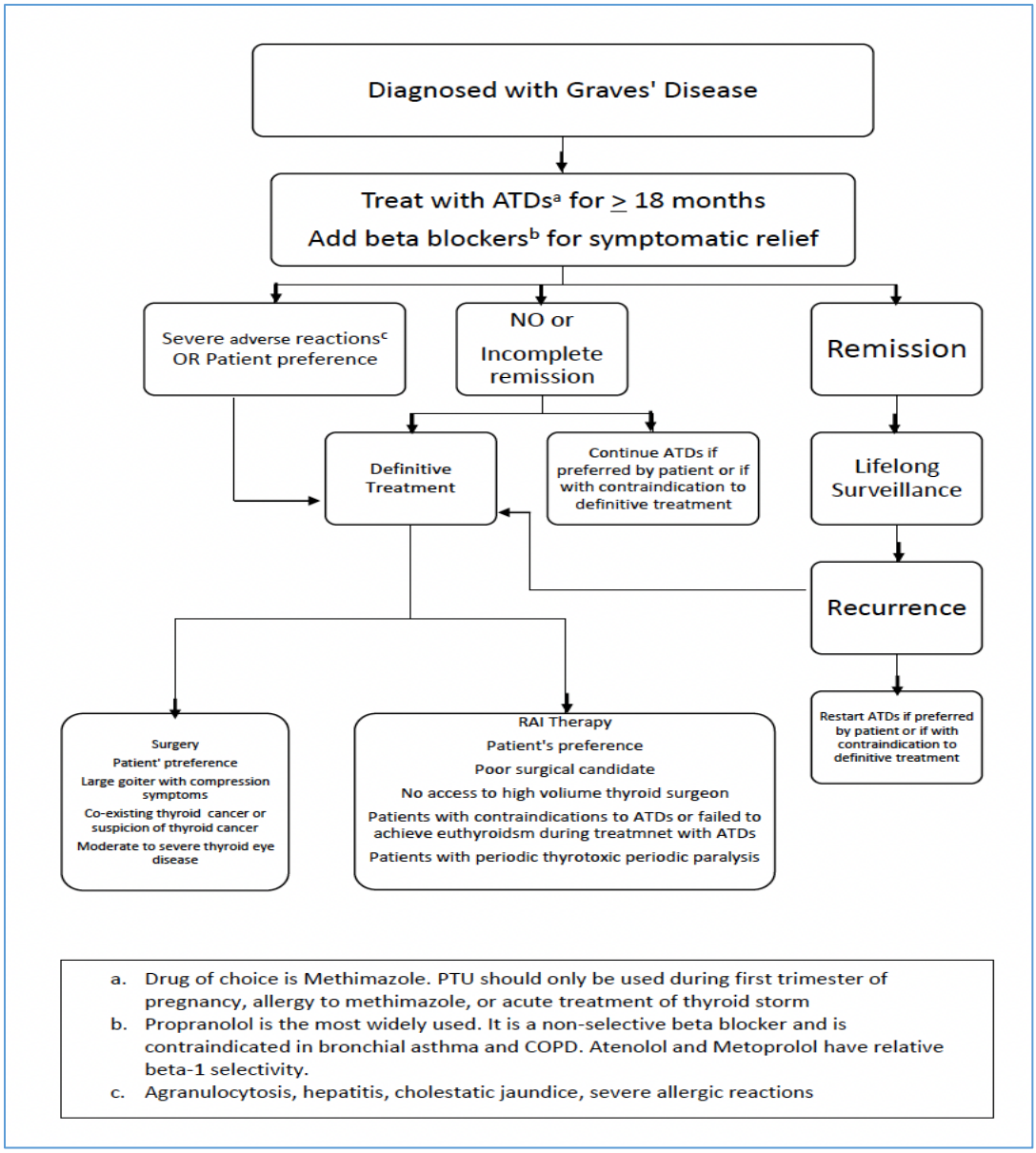

Figure 2. Treatment algorithm for a nonpregnant adult patient with Graves' disease

Research Implications

Research gaps were identified during the conduct of Consensus Panel meetings regarding the diagnosis and management of hyperthyroidism.

Very low certainty of evidence was found on the routine use of paired testing as initial evaluation of thyroid function and T3 testing on top of TSH and fT4/T4 among individuals suspected to have thyrotoxicosis. In differentiating Graves' disease from the thyrotoxic phase of subacute thyroiditis, the certainty of evidence was considered very low as well regarding the routine use of radioactive iodine uptake (I-131) (RAIU) among non-pregnant adults and routine use of 99m technetium pertechnetate thyroid uptake among pediatric patients. Likewise, the routine performance of a thyroid scan to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter) and the use of beta-blockers (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors among children and non-pregnant adults also has very low certainty of evidence. As for women with Graves' hyperthyroidism requiring ATD, there was low certainty of evidence for switching of methimazole/carbimazole to propylthiouracil. The use of ATD as first-line drug for Graves' disease for pediatric patients and routine treatment (i.e., ATD, RAI, surgery, etc) of non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism also had very low certainty of evidence.

On the other hand, low certainty of evidence was found on the use of (1) TRAb assay among adult and pediatric patients to confirm Graves' disease; (2) routine use of thyroid ultrasound among individuals with hyperthyroidism; (3) methimazole as initial treatment among children children and non-pregnant adolescents with Graves' hyperthyroidism; (4) propylthiouracil and (5) methimazole during the first trimester among adult pregnant patients with Graves' hyperthyroidism; (6) ATDs as first-line treatment; (7) total thyroidectomy instead of RAI among non-pregnant adults with Graves' disease; (8) selenium supplementation for six months among patients with mild and active Graves' orbitopathy.

Moderate certainty of evidence was found on the use of routine 99m technetium pertechnetate thyroid uptake among pregnant adults with biochemically confirmed thyrotoxicosis; and use of methimazole as an initial treatment among non-pregnant adults with Graves' hyperthyroidism who require antithyroid therapy.

This CPG underscores the importance of supplementing our understanding with local data regarding the cost-effectiveness of the interventions discussed herein. Furthermore, the inclusion of data pertaining to the indirect costs associated with these interventions is imperative for a comprehensive analysis.

Resource Implications

For this CPG, cost information was sought whenever available including economic evaluations. A systematic review of existing literature was sought to determine eligible studies or references that can be used as basis for the recommendations. The different stakeholders also gave their value judgments based on their experiences and value judgments. Information on the cost of the drug and/or procedure was sought out including a comparison between private and public institution rates. Equity and ability of patients to pay for the services/medications were part of the considerations in the final recommendation statements and strength of recommendation. Other issues regarding costs (if any) were also highlighted in the consensus statements per review question.

Search Strategies

Clinical Question No. 1 Should we use history and PE findings alone (i.e., Pretibial myxedema, goiter, exophthalmos) to diagnose Graves' disease?

Database	Search Strategy	Date and time of search	Results	
			Yield	Eligible
Efficacy				
PubMed	(("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND ("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("euthyroid"[All Fields] OR "euthyroidal"[All Fields] OR "euthyroidic"[All Fields] OR "euthyroidism"[All Fields] OR "euthyroids"[All Fields] OR "normal tests"[All Fields] OR "resolution of symptoms"[All Fields] OR ("QoL"[All Fields] OR "quality of life"[All Fields]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) Filters: Clinical Trial, Meta-Analysis, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review	January 6, 2023 5:32PM	12	2
Cochrane	(Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND ((euthyroidism OR "normal tests" OR "resolution of symptoms") OR (QoL OR "quality of life")) Filter: Cochrane Reviews, Trials	January 6, 2023 5:37PM	14	0
Safety				
PubMed	(("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND ("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ((("cardiovascular system"[MeSH Terms] OR	January 6, 2023 5:46PM	1	0

	("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR "CV"[All Fields] OR ("heart"[MeSH Terms] OR "heart"[All Fields] OR "hearts"[All Fields] OR "heart s"[All Fields]) OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields])) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields] OR ("outcome"[All Fields] OR "outcomes"[All Fields]) OR ("outcome"[All Fields] OR "outcomes"[All Fields]))) OR ("congest heart fail"[Journal] OR "chf"[All Fields] OR "congestive heart failure"[All Fields])) OR ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields] OR ("agranulocytosis"[MeSH Terms] OR "agranulocytosis"[All Fields] OR "agranulocytoses"[All Fields]) OR ("hepatotoxic"[All Fields] OR "hepatotoxicities"[All Fields] OR "hepatotoxicity"[All Fields] OR "hepatotoxity"[All Fields] OR "liver injury"[All Fields]) OR ("allergie"[All Fields] OR "hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "allergies"[All Fields] OR "allergy"[All Fields] OR "allergy and immunology"[MeSH Terms] OR ("allergy"[All Fields] AND "immunology"[All Fields]) OR "allergy and immunology"[All Fields] OR ("allergie"[All Fields] OR "hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "allergies"[All Fields] OR "allergy"[All Fields] OR "allergy and immunology"[MeSH Terms] OR ("allergy"[All Fields] AND "immunology"[All Fields]) OR "allergy and immunology"[All Fields])) OR ("vasculitide"[All Fields] OR "vasculities"[All Fields] OR "vasculitis"[MeSH Terms] OR "vasculitis"[All Fields] OR "vasculitides"[All Fields]))))) AND (meta-analysis[Filter] OR systematicreview[Filter]) Filters: Meta-Analysis, Systematic Review			
Cochrane	(Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND (Mortality OR ((cardiovascular OR CV OR heart OR cardiac) AND (disease OR outcome OR outcomes) OR (CHF OR "congestive heart failure")) OR (safety OR agranulocytosis OR (hepatotoxicity OR "liver injury") OR (allergy OR allergies) OR vasculitis) Filter: publication date from Jan 2020 to present, in Trials	January 6, 2023 5:51PM	4	0
Children subgroup				
PubMed	((("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND	January 6, 2023 6:13PM	1	0

	("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) OR "school age"[All Fields]) AND ("school performance"[All Fields] OR "academic performance"[All Fields] OR ("grade"[All Fields] OR "graded"[All Fields] OR "grades"[All Fields] OR "grading"[All Fields] OR "gradings"[All Fields]) OR ("growth and development"[MeSH Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms] OR "growths"[All Fields]) OR ("develop"[All Fields] OR "develope"[All Fields] OR "developed"[All Fields] OR "developer"[All Fields] OR "developer s"[All Fields] OR "developers"[All Fields] OR "developing"[All Fields] OR "developments"[All Fields] OR "develops"[All Fields] OR "growth and development"[MeSH Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "development"[All Fields]))) NOT ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields] OR ("pregnant"[All Fields] OR "pregnants"[All Fields]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR systematicreview[Filter]) Filters: Clinical Trial, Meta-Analysis, Observational Study, Pragmatic Clinical Trial, Systematic Review			
Cochrane	Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND (child OR children OR pediatric OR "school age") AND (“school performance” OR “academic performance” OR grades OR growth OR development) NOT (pregnancy OR pregnant) Filter: Cochrane Reviews, Trials	January 6, 2023 6:18PM	2	0
Pregnant women subgroup				
PubMed	(("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH	January 6, 2023 6:20PM	0	0

	Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND ("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields] OR ("pregnant"[All Fields] OR "pregnants"[All Fields]))) AND (meta-analysis[Filter] OR systematicreview[Filter]) Filters: Meta-Analysis, Systematic Review			
Cochrane	Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND (pregnancy OR pregnant) Filter: publication date from Jan 2020 to present, in Trials	January 6, 2023 6:25PM	3	0

Clinical Question No. 2 Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?

Search number	Query	Results
21	#17 AND #20	74
20	#18 OR #19	148
19	#1 AND #16	69
18	#1 AND #15	142
17	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	4,830,260
16	#9 OR #10 OR #11 OR #12 OR #13 OR #14	4,897
15	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	22,660
14	"thyroid associated ophthalmopathy"	736
13	"thyroid related eye disease"	13
12	"thyroid eye disease"	1,197
11	"graves ophthalmopathy"	4,055
10	"Graves' ophthalmopathy"	45
9	"Graves Ophthalmopathy"[Mesh]	2,793
8	"graves' hyperthyroidism"[Title/Abstract]	838
7	"Graves' hyperthyroidism"[Title/Abstract]	6
6	"graves hyperthyroidism"[Title/Abstract]	838
5	"Graves' disease"[Title/Abstract]	608
4	"graves disease"[Title/Abstract]	12,943
3	"graves' disease"[Title/Abstract]	12,943
2	"Graves Disease"[Mesh]	18,319
1	selenium[Title/Abstract]	33,227

A.2 Search strategy and yield (as of September 17, 2022),CENTRAL
selenium in Title Abstract Keyword AND "Graves ophthalmopathy" in Title Abstract Keyword - (Word variations have been searched)
Result: 10

A.3 Search strategy and yield (as of September 17, 2022), Google Scholar

allintitle: selenium graves ophthalmopathy
Result: 11

A.4 Search strategy and yield (as of September 17, 2022), Herdin Plus
selenium AND "graves ophthalmopathy" OR "thyroid eye disease"
Result: 1

A.5 Search strategy and yield (as of September 17, 2022), Journal of the ASEAN Federation of Endocrine Societies JAFES
Selenium
Result: 1

Clinical Question No. 3 Should beta-blockers be used as an adjunct for individuals with thyrotoxicosis?

National Institute for Health and Care Excellence (NICE)
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	10 (3 Guidance, 1 Advice, 5 Research recommendations)	1

MEDLINE
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
(thyrotoxicosis) AND (guideline[Publication Type])	14	5

Philippine College of Endocrinology Diabetes and Metabolism
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	0	0

Scottish Paediatric Endocrine Group
Date of search: September 4, 2022

QUERY	RESULTS	YIELD
Thyrotoxicosis	1	1

European Thyroid Association
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Pediatric	1	1

American Thyroid Association
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Pregnancy	1	1

Clinical trial, RCT, and meta-analyses search

ClinicalTrials.gov
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	13	0

Cochrane library
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	235 trials, 0 reviews, 0 protocols, 0 editorials	18
Thyrotoxicosis (custom search for years 2016 to 2022)	61	0

HERDIN PLUS
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	43	0

MEDLINE
Date of search: January 4, 2023

#	Query	Results
1	"thyrotoxicosis"[MeSH Terms] OR "thyrotoxicosis"[All Fields] OR "thyrotoxicoses"[All Fields]	10,213
2	"adrenergic beta antagonists"[Pharmacological Action] OR "adrenergic beta antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta antagonists"[All Fields]) OR "adrenergic beta antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields]	105,859
3	"propranolol"[MeSH Terms] OR "propranolol"[All Fields] OR "propanolol"[All Fields] OR "bisoprolol"[MeSH Terms] OR "bisoprolol"[All Fields] OR "atenolol"[MeSH Terms] OR "atenolol"[All Fields] OR "metoprolol"[MeSH Terms] OR "metoprolol"[All Fields] OR "practolol"[MeSH Terms] OR "practolol"[All Fields] OR "nadolol"[MeSH Terms] OR "nadolol"[All Fields] OR "sotalol"[MeSH Terms] OR "sotalol"[All Fields] OR "sotalol s"[All Fields] OR "oxprenolol"[MeSH Terms] OR "oxprenolol"[All Fields]	65,594
4	#2 OR #3	120,238

5	#1 AND #4	784
6	(("adrenergic beta antagonists"[Pharmacological Action] OR "adrenergic beta antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta antagonists"[All Fields]) OR "adrenergic beta antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields] OR ("propranolol"[MeSH Terms] OR "propranolol"[All Fields] OR "propanolol"[All Fields] OR ("bisoprolol"[MeSH Terms] OR "bisoprolol"[All Fields]) OR ("atenolol"[MeSH Terms] OR "atenolol"[All Fields]) OR ("metoprolol"[MeSH Terms] OR "metoprolol"[All Fields]) OR ("practolol"[MeSH Terms] OR "practolol"[All Fields]) OR ("nadolol"[MeSH Terms] OR "nadolol"[All Fields]) OR ("sotalol"[MeSH Terms] OR "sotalol"[All Fields] OR "sotalol s"[All Fields]) OR ("oxprenolol"[MeSH Terms] OR "oxprenolol"[All Fields]))) AND ("thyrotoxicosis"[MeSH Terms] OR "thyrotoxicosis"[All Fields] OR "thyrotoxicoses"[All Fields])) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (fft[Filter]) AND (humans[Filter]))	22

Clinical Question No. 4 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

A. Efficacy Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	"Antithyroid Agents" [Mesh]	6,272
12	"Methimazole" [Mesh]	3,407
13	"Carbimazole" [Mesh]	1,118
14	"Propylthiouracil" [Mesh]	4,320
15	PTU	2.255
16	"thionamide*"	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99

B. Safety Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233

9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118
14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255
16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99
20	Mortality	1,491,781
21	Cardiovascular risk	415,032
22	Cardiac risk	393,316
23	#20 OR #21 OR #22	1,905,960
24	#18 AND #23	41

C. Children

Search Number	Query	Results
1	“Graves Disease” [Mesh]	18,479
2	“Graves Disease”	20,512
3	“Hyperthyroidism” [Mesh]	45,587
4	“toxic goiter”	1,031
5	“Iodine Radioisotopes” [Mesh]	52,054
6	“radioactive iodine”	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118
14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255

16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	Child OR children OR pedia* OR school age children	3.508,134
20	#18 AND #19 NOT pregnant NOT pregnancy, filters: SR, MA, RCT, CT, Pragmatic clinical trial, Observational study, Comparative Study, Guideline, Practice Guideline	17
21	#18 AND #19 NOT pregnant NOT pregnancy ANG growth OR school performance	17

Clinical Question No. 5 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

A. Efficacy Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	"Antithyroid Agents" [Mesh]	6,272
12	"Methimazole" [Mesh]	3,407
13	"Carbimazole" [Mesh]	1,118
14	"Propylthiouracil" [Mesh]	4,320
15	PTU	2.255
16	"thionamide*"	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99

B. Safety Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555

8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118
14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255
16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99
20	Mortality	1,491,781
21	Cardiovascular risk	415,032
22	Cardiac risk	393,316
23	#20 OR #21 OR #22	1,905,960
24	#18 AND #23	41

C. Children

Search Number	Query	Results
1	“Graves Disease” [Mesh]	18,479
2	“Graves Disease”	20,512
3	“Hyperthyroidism” [Mesh]	45,587
4	“toxic goiter”	1,031
5	“Iodine Radioisotopes” [Mesh]	52,054
6	“radioactive iodine”	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118

14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255
16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	Child OR children OR pedia* OR school age children	3.508,134
20	#18 AND #19 NOT pregnant NOT pregnancy, filters: SR, MA, RCT, CT, Pragmatic clinical trial, Observational study, Comparative Study, Guideline, Practice Guideline	17
21	#18 AND #19 NOT pregnant NOT pregnancy ANG growth OR school performance	17

Clinical Question No. 6 Should we routinely treat non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism?

Medline

#	Query	Results
1	(subclinical hyperthyroidism) OR (Subclinical Hyperthyroism[MeSH Major Topic])	2,231
2	(Antithyroid drug) OR (Antithyroid Drug[MeSH Major Topic])	17,050
3	(Radioactive Iodine) OR (Radioactive Iodine[MeSH Major Topic])	16,322
4	#1 AND (#2 OR #3)	260
5	No Treatment	12,873,670
6	#1 AND ((#2 OR #3) OR #5)	1,288
7	Randomized Controlled Trial OR RCT OR systematic review or metaanalysis	1,125,389
8	#1 AND ((#2 OR #3) OR #5) AND #7	89

HERDIN

#	Query	Results
1	subclinical hyperthyroidism	8
2	Antithyroid drug	10
3	Radioactive Iodine	69
4	Subclinical Hyperthyroidism AND Antithyroid drugs OR Radioactive Iodine AND No Treatment	0

COCHRANE LIBRARY

#	Query	Results
1	subclinical hyperthyroidism	114
2	Antithyroid drug	431
3	(Radioactive Iodine) OR (Radioactive Iodine[MeSH Major Topic])	487
4	Subclinical Hyperthyroidism AND Antithyroid drugs OR Radioactive Iodine AND Randomized controlled trial	200

Clinical Question No. 7 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves' disease versus thyrotoxic phase of subacute thyroiditis?

MEDLINE (PubMed)

#	Query	Results
1	((radioactive iodine[Title/Abstract]) OR (technetium[Title/Abstract])) AND (uptake[Title/Abstract])	5,026
2	thyroid uptake[Title/Abstract]	895
3	#1 or #2	5,761
4	graves disease[MeSH Terms]	18,433
5	"thyroiditis"[MeSH Terms]	15,431
6	graves disease[Title/Abstract]	13,078
7	thyroiditis[Title/Abstract]	16,576
8	#4 or #5 or #6 or #7	40,478
9	"sensitivity and specificity"[MeSH Terms]	642,037
10	"diagnosis, differential"[MeSH Terms]	466,654
11	sensitiv*[Title/Abstract]	1,604,438
12	specific*[Title/Abstract]	3,632,294
13	diagnos*[Title/Abstract]	2,960,927
14	#9 or #10 or #11 or #12 or #13	7,552,933
15	#3 and #8	539
16	#14 and #15	286

Cochrane CENTRAL

#	Query	Results
1	((radioactive iodine or technetium) and uptake):ti,ab,kw	341
2	(thyroid uptake):ti,ab,kw	373
3	#1 or #2	620
4	MeSH descriptor: [Graves Disease] explode all trees	470
5	(graves disease):ti,ab,kw	2546
6	(thyroiditis):ti,ab,kw	481
7	#5 or #6	2963
8	#3 and #7	60

Clinical Question No. 8 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves' disease versus thyrotoxic phase of subacute thyroiditis?

MEDLINE (PubMed)

#	Query	Results
1	((radioactive iodine[Title/Abstract]) OR (technetium[Title/Abstract])) AND (uptake[Title/Abstract])	5,026
2	thyroid uptake[Title/Abstract]	895
3	#1 or #2	5,761
4	graves disease[MeSH Terms]	18,433
5	"thyroiditis"[MeSH Terms]	15,431
6	graves disease[Title/Abstract]	13,078
7	thyroiditis[Title/Abstract]	16,576
8	#4 or #5 or #6 or #7	40,478
9	"sensitivity and specificity"[MeSH Terms]	642,037
10	"diagnosis, differential"[MeSH Terms]	466,654
11	sensitiv*[Title/Abstract]	1,604,438
12	specific*[Title/Abstract]	3,632,294
13	diagnos*[Title/Abstract]	2,960,927
14	#9 or #10 or #11 or #12 or #13	7,552,933
15	#3 and #8	539
16	#14 and #15	286

Cochrane CENTRAL

#	Query	Results
1	((radioactive iodine or technetium) and uptake):ti,ab,kw	341
2	(thyroid uptake):ti,ab,kw	373
3	#1 or #2	620
4	MeSH descriptor: [Graves Disease] explode all trees	470
5	(graves disease):ti,ab,kw	2546
6	(thyroiditis):ti,ab,kw	481
7	#5 or #6	2963
8	#3 and #7	60

Clinical Question No. 9 Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(((Thyrotoxicosis [Mesh]) OR (Thyrotoxicosis [tiab])) AND ((Immunoglobulins, Thyroid-Stimulating [Mesh]) OR (Thyrotropin receptor antibody [tiab]) OR (TRAb [tiab]) OR (TSH receptor antibody [tiab]))) AND ((sensitivity and specificity[MeSH]) OR (diagnosis, differential[MeSH]) OR (sensitiv*[tiab]) OR (specific*[tiab]) OR (diagnos*[tiab])) Filters: January 30, 2012 to January 17, 2023	January 17, 2023, 03:47 AM	179	8
CENTRAL	Thyrotropin receptor antibody:ti,ab,kw OR TRAb:ti,ab,kw OR TSH receptor antibody:ti,ab,kw AND MeSH descriptor:[Thyrotoxicosis] explode all trees OR Thyrotoxicosis:ti,ab,kw Filters: none	January 18, 2023, 10:00 AM	14	0
Herdin Plus	TRAb	January 18, 2023, 3:00pm	3	0
Google Scholar	Advanced search tab: allintitle: TRAb Graves'	January 19, 2023, 8:30AM	129	2
ClinicalTrials.gov	TSH Receptor Antibody	November 30, 2022	20	0
chinaxiv.org	TSH Receptor Antibody	January 15, 2022	0	0
Medrxiv.org	TSH Receptor Antibody	January 15, 2022	0	0

Clinical Question No. 10 Should we do routine paired testing (T4/T4 plus TSH) versus TSH testing alone as initial evaluation of thyroid function among patients with suspected thyrotoxicosis?

MEDLINE via Pubmed (as of September 10, 2022)

Keywords	Strategy	Yields	Hits
TSH, T4, thyroid stimulating hormone, thyroxine, thyroid hormone	(((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract])	163,970	-
	Filter: meta-analysis	648	-
Thyrotoxicosis, hyperthyroidism, hyperthyroid*, thyrotoxic*	(((((thyrotoxicosis[MeSH Terms]) OR (hyperthyroidism[MeSH Terms])) OR (thyrotox*[MeSH Terms])) OR (hyperthyroid*[MeSH Terms])) OR (hyperthyroid*[Title/Abstract])) OR (thyrotoxic*[Title/Abstract]) ((((((thyrotoxicosis[MeSH Terms]) OR (hyperthyroidism[MeSH Terms])) OR (thyrotox*[MeSH Terms])) OR (hyperthyroid*[MeSH Terms])) OR (hyperthyroid*[Title/Abstract])) OR (thyrotoxic*[Title/Abstract])) AND ((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract]))	54,949	
	Filter: systematic review	81	
	((((((((((diagnosis) OR (diagnos*)) OR (diagnos*[Title/Abstract])) OR (diagnos*[MeSH Terms])) OR (laboratory[MeSH Terms])) OR (predictor[Title/Abstract])) OR (odds ratio[Title/Abstract])) OR (sensitivity[Title/Abstract])) OR (likelihood[Title/Abstract])) OR (positive predictive value[Title/Abstract]))) AND (((thyrotox*[MeSH Terms]) OR (thyrotoxicosis[MeSH Terms])) OR (thyrotoxic*[Title/Abstract]))	6,098	
	((((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract])) OR (thyrotropin	164,285	

	assay[Title/Abstract])) OR (thyrotropin assay[MeSH Terms])) OR (thyroid stimulating hormone test[MeSH Terms])		
Clinical practice guideline, practice guideline, thyrotoxicosis	Filter: systematic review	698	6 (2 in pregnancy)
Diagnosis, diagnostic test, Sensitivity, specificity, PPV, NPV, likelihood ratio*, accuracy	(((diagnosis[Title/Abstract]) OR (diagnostic test[Title/Abstract])) OR (test[Title/Abstract])) OR (diagnostic test[MeSH Terms])	3,353,172	-
	((((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract])) OR (thyrotropin assay[Title/Abstract])) OR (thyrotropin assay[MeSH Terms])) OR (thyroid stimulating hormone test[MeSH Terms])	164,285	
	Filter: systematic review	698	
	((((((((((diagnosis) OR (diagnos*)) OR (diagnos*[Title/Abstract])) OR (diagnos*[MeSH Terms])) OR (laboratory[MeSH Terms])) OR (predictor[Title/Abstract])) OR (odds ratio[Title/Abstract])) OR (sensitivity[Title/Abstract])) OR (likelihood[Title/Abstract])) OR (positive predictive value[Title/Abstract]))) OR ((((((((odds ratio[Title/Abstract]) OR (sensitivity[Title/Abstract])) OR (likelihood[Title/Abstract])) OR (positive predictive value[Title/Abstract])) OR (negative predictive value[Title/Abstract])) OR (specificity[MeSH Terms])) OR (sensitivity[MeSH Terms])) OR (specificity[Title/Abstract]))) AND ((((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR	479	

	(T4[Title/Abstract])) OR (thyrotropin assay[Title/Abstract])) OR (thyrotropin assay[MeSH Terms])) OR (thyroid stimulating hormone test[MeSH Terms]))Filters: Meta-Analysis		
Antithyroid drug, radioactive iodine	(((((antithyroid drug) OR (antithyroid drugs[MeSH Terms])) OR (agents, antithyroid[MeSH Terms])) OR (metabolite[Title/Abstract])) OR (radioactive iodine[Title/Abstract])) OR (radioactive iodine[MeSH Terms])Filters: Meta-Analysis, Randomized Controlled Trial	4,355	
TSH, T4, paired, sequential	"paired"[Title/Abstract] AND ("sequen*"[Title/Abstract] AND "sequential"[Title/Abstract]) AND ("T4"[All Fields] OR "TSH"[All Fields] OR ("thyrotropin"[MeSH Terms] OR "thyrotropin"[All Fields] OR ("thyroid"[All Fields] AND "stimulating"[All Fields] AND "hormone"[All Fields]) OR "thyroid stimulating hormone"[All Fields]) OR "thyrotropin"[MeSH Terms] OR "thyrotoxic*"[MeSH Terms])	5	0

CENTRAL

Keywords	Strategy	Yields	Hits
Accuracy, specificity, sensitivity	(accuracy):ti,ab,kw OR sensitivity OR specificity	94,588	-
Free serum T4, thyroxine, thyroid stimulating hormone, TSH test, thyrotropin,	MeSH descriptor: [Diagnostic Techniques and Procedures] in all MeSH products OR free serum T4 OR thyroxine OR MeSH descriptor: [Thyroxine] explode all trees OR thyroid stimulating hormone OR MeSH descriptor: [Thyrotropin] explode all trees OR TSH test	248,970	
thyrotoxicosis	MeSH descriptor: [Thyrotoxicosis] explode all trees	40	-
	((accuracy):ti,ab,kw OR sensitivity OR specificity) AND (MeSH descriptor: [Diagnostic Techniques and Procedures] in all MeSH products OR free serum T4 OR thyroxine OR MeSH descriptor: [Thyroxine] explode all trees OR thyroid stimulating hormone OR MeSH descriptor: [Thyrotropin] explode all trees OR TSH test) AND MeSH descriptor: [Thyrotoxicosis] explode all trees	1	-
Antithyroid drug, radioactive iodine	MeSH descriptor: [Antithyroid Agents] explode all trees OR antithyroid drug OR radioactive iodine	834	-

thyrotoxicosis	thyrotoxicosis OR MeSH descriptor: [Thyrotoxicosis] explode all trees	261	
	MeSH descriptor: [Antithyroid Agents] explode all trees OR antithyroid drug OR radioactive iodine AND thyrotoxicosis OR MeSH descriptor: [Thyrotoxicosis] explode all trees	73 7 reviews, 66 trials	

ClinicalTrials.gov (as of September 10, 2022)

Keywords	Query	Results
Thyrotoxicosis, antithyroid drugs	Thyrotoxicosis, hyperthyroidism, antithyroid drugs	2
Thyrotoxicosis, antithyroid drugs	Thyrotoxicosis, hyperthyroidism, radioactive iodine	1

HERDIN (as of September 10, 2022)

Keywords	Query	Results
Thyrotoxicosis	Thyrotoxicosis	43
Antithyroid drug	Antithyroid drug	10
Radioactive iodine	Radioactive iodine	66
Thryoxine	Thyroxine	65

Clinical Question No. 11 Should we routinely do T3 testing on top of TSH and T4/fT4 testing in the workup of individuals suspected to have thyrotoxicosis?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed MEDLINE	(("Thyrotoxicosis"[MeSH Terms] OR "Thyrotoxicosis"[Title/Abstract] OR "Hyperthyroidism"[Title/Abstract] OR "Hyperthyroidism"[MeSH Terms]) AND ("Triiodothyronine"[MeSH Terms] OR "T3"[Title/Abstract]) AND ("T4"[Title/Abstract] OR "fT4"[Title/Abstract] OR "Thyroxine"[MeSH Terms]) AND ("Thyrotropin"[MeSH Terms] OR "TSH"[Title/Abstract]) AND "Thyroid Function Tests"[MeSH Terms]) AND (clinicaltrial[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter])	April 11, 2023 10:57 AM	104	25
EMBASE	('thyrotoxicosis'/exp OR 'thyreotoxicosis' OR 'thyrotoxicosis' OR 'hyperthyroidism'/exp) AND (t3:ti,ab OR 'liothyronine'/exp) AND ('randomized controlled trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'observational study'/exp)	April 11, 2023 10:57 AM	21	14
Herdin.ph	“thyroid test”	April 10, 2023 9:15 PM	91	2
ClinicalTrials.gov	“thyroid” and “T3”	April 11, 2023 11:00 AM	29	0

Clinical Question No. 12 Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?

#	Query	Results
1	Thyrotoxicosis	10,298
2	Hyperthyroidism	53,506
3	Thyroid nodules	16,754
4	Nodular goiter	5,938
5	Multinodular goiter	3,089
6	Toxic goiter	3,274
7	Graves' disease	24,870
8	Plummer disease	1,428
9	Toxic adenoma	5,424
10	Thyroid scan	13,440
11	Thyroid scintigraphy	11,328
12	Thyroid scanning	12,674
13	#1 or #2	54,978
14	#3 or #4 or #5	22,239
15	#6 or #7 or #8 or #9	32,704
16	#10 or #11 or #12	16,893
17	#13 and #14 and #15 and #16	393

Clinical Question No. 13 Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	Search: Hyperthyroidism AND Thyroidectomy AND Radioactive Iodine Filters: Free full text, Full text ((("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("thyroidectomy"[MeSH Terms] OR "thyroidectomy"[All Fields] OR "thyroidectomies"[All Fields]) AND (("radioactively"[All Fields] OR "radioactivity"[MeSH Terms] OR "radioactivity"[All Fields] OR "radioactive"[All Fields] OR "radioactivities"[All Fields]) AND ("halogenation"[MeSH Terms] OR "halogenation"[All Fields] OR "iodination"[All Fields] OR "iodin"[All Fields] OR "iodinate"[All Fields] OR "iodinated"[All Fields] OR "iodinates"[All Fields] OR "iodinating"[All Fields] OR "iodinations"[All Fields] OR "iodine"[MeSH Terms] OR "iodine"[All Fields] OR "iodides"[MeSH Terms] OR "iodides"[All Fields] OR "iodines"[All Fields])))) AND ((ffrft[Filter]) AND (fft[Filter]))	August 20, 2022 2:00 PM	105	4
COCHRANE	Hyperthyroidism (MESH) and Thyroidectomy (MESH) and Radioactive iodine (MESH)	August 20, 2022 2:30PM	7	1
HERDIN	Hyperthyroidism AND Thyroidectomy AND (RAI or Radioactive iodine)	August 20, 2022 2:38PM	8	2
ClinicalTrials.gov	Hyperthyroidism / Thyrotoxicosis	August 20, 2022 2:15PM	17	0

Clinical Question No. 14 Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	("thyrotoxicosis"[MeSH Terms] OR "hyperthyroidism"[MeSH Terms] OR "graves disease"[MeSH Terms]) AND "thyroid nodule"[MeSH Terms] AND ((("thyroid gland"[MeSH Terms] OR ("thyroid"[All Fields] AND "gland"[All Fields]) OR "thyroid gland"[All Fields] OR "thyroid"[All Fields] OR "thyroid usp"[MeSH Terms] OR ("thyroid"[All Fields] AND "usp"[All Fields]) OR "thyroid usp"[All Fields] OR "thyroids"[All Fields] OR "thyroid s"[All Fields] OR "thyroidal"[All Fields] OR "thyroideal"[All Fields] OR "thyroidism"[All Fields] OR "thyroiditis"[MeSH Terms] OR "thyroiditis"[All Fields] OR "thyroiditides"[All Fields]) AND ("ultrasonography"[MeSH Terms] OR "ultrasonics"[MeSH Terms])) OR (("thyroid gland"[MeSH Terms] OR ("thyroid"[All Fields] AND "gland"[All Fields]) OR "thyroid gland"[All Fields] OR "thyroid"[All Fields] OR "thyroid usp"[MeSH Terms] OR ("thyroid"[All Fields] AND "usp"[All Fields]) OR "thyroid usp"[All Fields] OR "thyroids"[All Fields] OR "thyroid s"[All Fields] OR "thyroidal"[All Fields] OR "thyroideal"[All Fields] OR "thyroidism"[All Fields] OR "thyroiditis"[MeSH Terms] OR "thyroiditis"[All Fields] OR "thyroiditides"[All Fields]) AND "ultrasonography"[MeSH Terms]) OR (("neck"[MeSH Terms] OR	January 26, 2023 04:09AM	91	3

	"neck"[All Fields]) AND ("ultrasonography"[MeSH Terms] OR "ultrasonics"[MeSH Terms])) OR (("neck"[MeSH Terms] OR "neck"[All Fields]) AND "ultrasonography"[MeSH Terms]))			
PubMed	(((((hyperthyroidism[MeSH Terms]) OR (thyrotoxicosis[MeSH Terms])) OR (Graves Disease[MeSH Terms])) AND (((children[MeSH Terms]) OR (adolescent[MeSH Terms])) OR (young[MeSH Terms]))) AND ((((Thyroid ultrasound[MeSH Terms]) OR (thyroid ultrasonography[MeSH Terms])) OR (neck ultrasound[MeSH Terms])) OR (neck ultrasonography[MeSH Terms]))) AND (thyroid nodules[MeSH Terms])	March 30, 2023 08:10PM	15	0
Cochrane Library	thyroid ultrasound AND thyroid nodules AND hyperthyroidism Filters: 2018 to 2023	January 26, 2023 05:00AM	11	0
ClinicalTrials.gov	Ultrasonography, thyroid ultrasound, neck ultrasound, hyperthyroidism, thyrotoxicosis	March 3, 2023	0	0

Clinical Question No. 15 Should we use history and PE findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves' disease (GD) versus non-Graves' disease (i.e., other etiology) among non-pregnant patients with biochemically confirmed hyperthyroidism?

Appendix 1: Search strategy for MEDLINE

Search number	Query	Results
32	(((diagnost* accura*[Title/Abstract])) OR ((specificity[Title/Abstract]))) AND (((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND (#1 OR #2 OR #3 OR #4))	546
31	((diagnost* accura*[Title/Abstract])) OR ((specificity[Title/Abstract]))	751,550
30	(diagnost* accura*[Title/Abstract])	262,787
29	((specificity[Title/Abstract])) AND (((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND (#1 OR #2 OR #3 OR #4))	429
28	(specificity[Title/Abstract])	558,188
26	(sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnose[Title/Abstract] OR diagnosed[Title/Abstract] OR diagnoses[Title/Abstract] OR diagnosing[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnostic[Title/Abstract] OR diagnosis[MeSH:noexp] OR (diagnostic equipment[MeSH:noexp] OR diagnostic errors[MeSH:noexp] OR diagnostic imaging[MeSH:noexp] OR diagnostic services[MeSH:noexp]) OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp])	6,437,668
24	((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND (#1 OR #2 OR #3 OR #4)	19,823
23	(graves disease) AND (Diagnosis/Narrow[filter])	578
22	(((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND ((sensitivity and specificity[MeSH Terms]) OR (predict* OR diagnos* OR accura*))) AND (#1 OR #2 OR #3 OR #4)	7,677
21	(physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	1,415,493
20	physical examination[MeSH Terms]	1,373,283
19	#18 AND #17 AND #5	3,209

18	#6 OR #7 OR #8 OR #9 OR #11 OR #12 OR #13 OR #14 OR #15	28,028
17	(sensitivity and specificity[MeSH Terms]) OR (predict* OR diagnos* OR accura*)	8,280,802
16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	43,108
15	acropachy	1,067
14	thyroid orbitopathy	5,800
13	thyroid ophthalmopathy	5,584
12	Graves' orbitopathy	5,897
11	Graves' ophthalmopathy	5,276
10	proptosis	29,211
9	exophthalm*	10,047
8	thyroid dermopathy	9,972
7	Grave* dermopathy	2,394
6	pretibial myxedema	446
5	#1 OR #2 OR #3 OR #4	24,720
4	exophthalmic goiter[MeSH Terms]	18,771
3	(diffuse toxic goiter[Title/Abstract]) OR (toxic diffuse goiter[Title/Abstract])	547
2	disease, graves'[MeSH Terms]	18,771
1	Graves[Title/Abstract]	17,517

Cochrane Library

ID	Search	Hits
#1	("Graves disease"):ti,ab,kw (Word variations have been searched)	699
#2	diffuse toxic goiter	30
#3	("exophthalmic goiter"):ti,ab,kw	2
#4	MeSH descriptor: [Graves Disease] explode all trees	543
#5	MeSH descriptor: [Sensitivity and Specificity] this term only	10929
#6	diagnostic accuracy	13041
#7	sensitivity	77820

#8	specificity	24239
#9	#1 OR #2 OR #3 OR #4	839
#10	#6 OR #7 OR #8	87365
#11	#9 AND #10	104

Search Strategies

Clinical Question No. 1 Should we use history and PE findings alone (i.e., Pretibial myxedema, goiter, exophthalmos) to diagnose Graves' disease?

Database	Search Strategy	Date and time of search	Results	
			Yield	Eligible
Efficacy				
PubMed	(("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND ("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("euthyroid"[All Fields] OR "euthyroidal"[All Fields] OR "euthyroidic"[All Fields] OR "euthyroidism"[All Fields] OR "euthyroids"[All Fields] OR "normal tests"[All Fields] OR "resolution of symptoms"[All Fields] OR ("QoL"[All Fields] OR "quality of life"[All Fields]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR pragmaticclinicaltrial[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter]) Filters: Clinical Trial, Meta-Analysis, Pragmatic Clinical Trial, Randomized Controlled Trial, Systematic Review	January 6, 2023 5:32PM	12	2
Cochrane	(Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND ((euthyroidism OR "normal tests" OR "resolution of symptoms") OR (QoL OR "quality of life")) Filter: Cochrane Reviews, Trials	January 6, 2023 5:37PM	14	0
Safety				
PubMed	(("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND ("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("mortality"[MeSH Terms] OR "mortality"[All Fields] OR "mortalities"[All Fields] OR "mortality"[MeSH Subheading] OR ((("cardiovascular system"[MeSH Terms] OR	January 6, 2023 5:46PM	1	0

	("cardiovascular"[All Fields] AND "system"[All Fields]) OR "cardiovascular system"[All Fields] OR "cardiovascular"[All Fields] OR "cardiovasculars"[All Fields] OR "CV"[All Fields] OR ("heart"[MeSH Terms] OR "heart"[All Fields] OR "hearts"[All Fields] OR "heart s"[All Fields]) OR ("cardiacs"[All Fields] OR "heart"[MeSH Terms] OR "heart"[All Fields] OR "cardiac"[All Fields])) AND ("disease"[MeSH Terms] OR "disease"[All Fields] OR "diseases"[All Fields] OR "disease s"[All Fields] OR "diseased"[All Fields] OR ("outcome"[All Fields] OR "outcomes"[All Fields]) OR ("outcome"[All Fields] OR "outcomes"[All Fields]))) OR ("congest heart fail"[Journal] OR "chf"[All Fields] OR "congestive heart failure"[All Fields])) OR ("safety"[MeSH Terms] OR "safety"[All Fields] OR "safeties"[All Fields] OR ("agranulocytosis"[MeSH Terms] OR "agranulocytosis"[All Fields] OR "agranulocytoses"[All Fields]) OR ("hepatotoxic"[All Fields] OR "hepatotoxicities"[All Fields] OR "hepatotoxicity"[All Fields] OR "hepatotoxity"[All Fields] OR "liver injury"[All Fields]) OR ("allergie"[All Fields] OR "hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "allergies"[All Fields] OR "allergy"[All Fields] OR "allergy and immunology"[MeSH Terms] OR ("allergy"[All Fields] AND "immunology"[All Fields]) OR "allergy and immunology"[All Fields] OR ("allergie"[All Fields] OR "hypersensitivity"[MeSH Terms] OR "hypersensitivity"[All Fields] OR "allergies"[All Fields] OR "allergy"[All Fields] OR "allergy and immunology"[MeSH Terms] OR ("allergy"[All Fields] AND "immunology"[All Fields]) OR "allergy and immunology"[All Fields])) OR ("vasculitide"[All Fields] OR "vasculities"[All Fields] OR "vasculitis"[MeSH Terms] OR "vasculitis"[All Fields] OR "vasculitides"[All Fields]))))) AND (meta-analysis[Filter] OR systematicreview[Filter]) Filters: Meta-Analysis, Systematic Review			
Cochrane	(Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND (Mortality OR ((cardiovascular OR CV OR heart OR cardiac) AND (disease OR outcome OR outcomes) OR (CHF OR "congestive heart failure")) OR (safety OR agranulocytosis OR (hepatotoxicity OR "liver injury") OR (allergy OR allergies) OR vasculitis) Filter: publication date from Jan 2020 to present, in Trials	January 6, 2023 5:51PM	4	0
Children subgroup				
PubMed	((("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND	January 6, 2023 6:13PM	1	0

	("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields] OR ("child"[MeSH Terms] OR "child"[All Fields] OR "children"[All Fields] OR "child s"[All Fields] OR "children s"[All Fields] OR "childrens"[All Fields] OR "childs"[All Fields]) OR ("paediatrics"[All Fields] OR "pediatrics"[MeSH Terms] OR "pediatrics"[All Fields] OR "paediatric"[All Fields] OR "pediatric"[All Fields]) OR "school age"[All Fields]) AND ("school performance"[All Fields] OR "academic performance"[All Fields] OR ("grade"[All Fields] OR "graded"[All Fields] OR "grades"[All Fields] OR "grading"[All Fields] OR "gradings"[All Fields]) OR ("growth and development"[MeSH Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "growth"[All Fields] OR "growth"[MeSH Terms] OR "growths"[All Fields]) OR ("develop"[All Fields] OR "develope"[All Fields] OR "developed"[All Fields] OR "developer"[All Fields] OR "developer s"[All Fields] OR "developers"[All Fields] OR "developing"[All Fields] OR "developments"[All Fields] OR "develops"[All Fields] OR "growth and development"[MeSH Subheading] OR ("growth"[All Fields] AND "development"[All Fields]) OR "growth and development"[All Fields] OR "development"[All Fields]))) NOT ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancy s"[All Fields] OR ("pregnant"[All Fields] OR "pregnants"[All Fields]))) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR observationalstudy[Filter] OR pragmaticclinicaltrial[Filter] OR systematicreview[Filter]) Filters: Clinical Trial, Meta-Analysis, Observational Study, Pragmatic Clinical Trial, Systematic Review			
Cochrane	Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND (child OR children OR pediatric OR "school age") AND (“school performance” OR “academic performance” OR grades OR growth OR development) NOT (pregnancy OR pregnant) Filter: Cochrane Reviews, Trials	January 6, 2023 6:18PM	2	0
Pregnant women subgroup				
PubMed	(("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("methimazol"[All Fields] OR "methimazole"[MeSH Terms] OR "methimazole"[All Fields] OR "MMZ"[All Fields] OR "MMI"[All Fields] OR ("carbimazole"[MeSH	January 6, 2023 6:20PM	0	0

	Terms] OR "carbimazole"[All Fields] OR "carbimazol"[All Fields] OR "CBZ"[All Fields])) AND ("propylthiouracil"[MeSH Terms] OR "propylthiouracil"[All Fields] OR "PTU"[All Fields]) AND ("pregnancy"[MeSH Terms] OR "pregnancy"[All Fields] OR "pregnancies"[All Fields] OR "pregnancys"[All Fields] OR ("pregnant"[All Fields] OR "pregnants"[All Fields]))) AND (meta-analysis[Filter] OR systematicreview[Filter]) Filters: Meta-Analysis, Systematic Review			
Cochrane	Hyperthyroidism AND ((Methimazole OR MMZ OR MMI) OR (Carbimazole OR CBZ)) AND (Propylthiouracil OR PTU)) AND (pregnancy OR pregnant) Filter: publication date from Jan 2020 to present, in Trials	January 6, 2023 6:25PM	3	0

Clinical Question No. 2 Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?

Search number	Query	Results
21	#17 AND #20	74
20	#18 OR #19	148
19	#1 AND #16	69
18	#1 AND #15	142
17	("randomized controlled trial"[Publication Type] OR "controlled clinical trial"[Publication Type] OR "randomized"[Title/Abstract] OR "placebo"[Title/Abstract] OR "drug therapy"[MeSH Subheading] OR "randomly"[Title/Abstract] OR "trial"[Title/Abstract] OR "groups"[Title/Abstract]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])	4,830,260
16	#9 OR #10 OR #11 OR #12 OR #13 OR #14	4,897
15	#2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	22,660
14	"thyroid associated ophthalmopathy"	736
13	"thyroid related eye disease"	13
12	"thyroid eye disease"	1,197
11	"graves ophthalmopathy"	4,055
10	"Graves' ophthalmopathy"	45
9	"Graves Ophthalmopathy"[Mesh]	2,793
8	"graves' hyperthyroidism"[Title/Abstract]	838
7	"Graves' hyperthyroidism"[Title/Abstract]	6
6	"graves hyperthyroidism"[Title/Abstract]	838
5	"Graves' disease"[Title/Abstract]	608
4	"graves disease"[Title/Abstract]	12,943
3	"graves' disease"[Title/Abstract]	12,943
2	"Graves Disease"[Mesh]	18,319
1	selenium[Title/Abstract]	33,227

A.2 Search strategy and yield (as of September 17, 2022),CENTRAL
selenium in Title Abstract Keyword AND "Graves ophthalmopathy" in Title Abstract Keyword - (Word variations have been searched)
Result: 10

A.3 Search strategy and yield (as of September 17, 2022), Google Scholar

allintitle: selenium graves ophthalmopathy
Result: 11

A.4 Search strategy and yield (as of September 17, 2022), Herdin Plus
selenium AND "graves ophthalmopathy" OR "thyroid eye disease"
Result: 1

A.5 Search strategy and yield (as of September 17, 2022), Journal of the ASEAN Federation of Endocrine Societies JAFES
Selenium
Result: 1

Clinical Question No. 3 Should beta-blockers be used as an adjunct for individuals with thyrotoxicosis?

National Institute for Health and Care Excellence (NICE)
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	10 (3 Guidance, 1 Advice, 5 Research recommendations)	1

MEDLINE
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
(thyrotoxicosis) AND (guideline[Publication Type])	14	5

Philippine College of Endocrinology Diabetes and Metabolism
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	0	0

Scottish Paediatric Endocrine Group
Date of search: September 4, 2022

QUERY	RESULTS	YIELD
Thyrotoxicosis	1	1

European Thyroid Association
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Pediatric	1	1

American Thyroid Association
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Pregnancy	1	1

Clinical trial, RCT, and meta-analyses search

ClinicalTrials.gov
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	13	0

Cochrane library
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	235 trials, 0 reviews, 0 protocols, 0 editorials	18
Thyrotoxicosis (custom search for years 2016 to 2022)	61	0

HERDIN PLUS
Date of search: January 4, 2023

QUERY	RESULTS	YIELD
Thyrotoxicosis	43	0

MEDLINE
Date of search: January 4, 2023

#	Query	Results
1	"thyrotoxicosis"[MeSH Terms] OR "thyrotoxicosis"[All Fields] OR "thyrotoxicoses"[All Fields]	10,213
2	"adrenergic beta antagonists"[Pharmacological Action] OR "adrenergic beta antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta antagonists"[All Fields]) OR "adrenergic beta antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields]	105,859
3	"propranolol"[MeSH Terms] OR "propranolol"[All Fields] OR "propanolol"[All Fields] OR "bisoprolol"[MeSH Terms] OR "bisoprolol"[All Fields] OR "atenolol"[MeSH Terms] OR "atenolol"[All Fields] OR "metoprolol"[MeSH Terms] OR "metoprolol"[All Fields] OR "practolol"[MeSH Terms] OR "practolol"[All Fields] OR "nadolol"[MeSH Terms] OR "nadolol"[All Fields] OR "sotalol"[MeSH Terms] OR "sotalol"[All Fields] OR "sotalol s"[All Fields] OR "oxprenolol"[MeSH Terms] OR "oxprenolol"[All Fields]	65,594
4	#2 OR #3	120,238

5	#1 AND #4	784
6	(("adrenergic beta antagonists"[Pharmacological Action] OR "adrenergic beta antagonists"[MeSH Terms] OR ("adrenergic"[All Fields] AND "beta antagonists"[All Fields]) OR "adrenergic beta antagonists"[All Fields] OR ("beta"[All Fields] AND "blockers"[All Fields]) OR "beta blockers"[All Fields] OR ("propranolol"[MeSH Terms] OR "propranolol"[All Fields] OR "propanolol"[All Fields] OR ("bisoprolol"[MeSH Terms] OR "bisoprolol"[All Fields]) OR ("atenolol"[MeSH Terms] OR "atenolol"[All Fields]) OR ("metoprolol"[MeSH Terms] OR "metoprolol"[All Fields]) OR ("practolol"[MeSH Terms] OR "practolol"[All Fields]) OR ("nadolol"[MeSH Terms] OR "nadolol"[All Fields]) OR ("sotalol"[MeSH Terms] OR "sotalol"[All Fields] OR "sotalol s"[All Fields]) OR ("oxprenolol"[MeSH Terms] OR "oxprenolol"[All Fields]))) AND ("thyrotoxicosis"[MeSH Terms] OR "thyrotoxicosis"[All Fields] OR "thyrotoxicoses"[All Fields])) AND ((clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter]) AND (fft[Filter]) AND (humans[Filter]))	22

Clinical Question No. 4 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

D. Efficacy Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	"Antithyroid Agents" [Mesh]	6,272
12	"Methimazole" [Mesh]	3,407
13	"Carbimazole" [Mesh]	1,118
14	"Propylthiouracil" [Mesh]	4,320
15	PTU	2.255
16	"thionamide*"	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99

E. Safety Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233

9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118
14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255
16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99
20	Mortality	1,491,781
21	Cardiovascular risk	415,032
22	Cardiac risk	393,316
23	#20 OR #21 OR #22	1,905,960
24	#18 AND #23	41

F. Children

Search Number	Query	Results
1	“Graves Disease” [Mesh]	18,479
2	“Graves Disease”	20,512
3	“Hyperthyroidism” [Mesh]	45,587
4	“toxic goiter”	1,031
5	“Iodine Radioisotopes” [Mesh]	52,054
6	“radioactive iodine”	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118
14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255

16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	Child OR children OR pedia* OR school age children	3.508,134
20	#18 AND #19 NOT pregnant NOT pregnancy, filters: SR, MA, RCT, CT, Pragmatic clinical trial, Observational study, Comparative Study, Guideline, Practice Guideline	17
21	#18 AND #19 NOT pregnant NOT pregnancy ANG growth OR school performance	17

Clinical Question No. 5 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

D. Efficacy Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	"Antithyroid Agents" [Mesh]	6,272
12	"Methimazole" [Mesh]	3,407
13	"Carbimazole" [Mesh]	1,118
14	"Propylthiouracil" [Mesh]	4,320
15	PTU	2.255
16	"thionamide*"	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99

E. Safety Outcomes

Search Number	Query	Results
1	"Graves Disease" [Mesh]	18,479
2	"Graves Disease"	20,512
3	"Hyperthyroidism" [Mesh]	45,587
4	"toxic goiter"	1,031
5	"Iodine Radioisotopes" [Mesh]	52,054
6	"radioactive iodine"	6,547
7	RAI	18,555

8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118
14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255
16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	#10 AND #17, filters: CT, MA, RCT, SR	99
20	Mortality	1,491,781
21	Cardiovascular risk	415,032
22	Cardiac risk	393,316
23	#20 OR #21 OR #22	1,905,960
24	#18 AND #23	41

F. Children

Search Number	Query	Results
1	“Graves Disease” [Mesh]	18,479
2	“Graves Disease”	20,512
3	“Hyperthyroidism” [Mesh]	45,587
4	“toxic goiter”	1,031
5	“Iodine Radioisotopes” [Mesh]	52,054
6	“radioactive iodine”	6,547
7	RAI	18,555
8	#1 OR #2 OR #3 OR #4	49,233
9	#5 OR #6 OR #7	72,346
10	#8 AND #9	5,210
11	“Antithyroid Agents” [Mesh]	6,272
12	“Methimazole” [Mesh]	3,407
13	“Carbimazole” [Mesh]	1,118

14	“Propylthiouracil” [Mesh]	4,320
15	PTU	2.255
16	“thionamide*”	426
17	#11 OR #12 OR #13 OR #14 OR #15 OR #16	12,725
18	#10 AND #17	1,106
19	Child OR children OR pedia* OR school age children	3.508,134
20	#18 AND #19 NOT pregnant NOT pregnancy, filters: SR, MA, RCT, CT, Pragmatic clinical trial, Observational study, Comparative Study, Guideline, Practice Guideline	17
21	#18 AND #19 NOT pregnant NOT pregnancy ANG growth OR school performance	17

Clinical Question No. 6 Should we routinely treat non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism?

Medline

#	Query	Results
1	(subclinical hyperthyroidism) OR (Subclinical Hyperthyroism[MeSH Major Topic])	2,231
2	(Antithyroid drug) OR (Antithyroid Drug[MeSH Major Topic])	17,050
3	(Radioactive Iodine) OR (Radioactive Iodine[MeSH Major Topic])	16,322
4	#1 AND (#2 OR #3)	260
5	No Treatment	12,873,670
6	#1 AND ((#2 OR #3) OR #5)	1,288
7	Randomized Controlled Trial OR RCT OR systematic review or metaanalysis	1,125,389
8	#1 AND ((#2 OR #3) OR #5) AND #7	89

HERDIN

#	Query	Results
1	subclinical hyperthyroidism	8
2	Antithyroid drug	10
3	Radioactive Iodine	69
4	Subclinical Hyperthyroidism AND Antithyroid drugs OR Radioactive Iodine AND No Treatment	0

COCHRANE LIBRARY

#	Query	Results
1	subclinical hyperthyroidism	114
2	Antithyroid drug	431
3	(Radioactive Iodine) OR (Radioactive Iodine[MeSH Major Topic])	487
4	Subclinical Hyperthyroidism AND Antithyroid drugs OR Radioactive Iodine AND Randomized controlled trial	200

Clinical Question No. 7 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves' disease versus thyrotoxic phase of subacute thyroiditis?

MEDLINE (PubMed)

#	Query	Results
1	((radioactive iodine[Title/Abstract]) OR (technetium[Title/Abstract])) AND (uptake[Title/Abstract])	5,026
2	thyroid uptake[Title/Abstract]	895
3	#1 or #2	5,761
4	graves disease[MeSH Terms]	18,433
5	"thyroiditis"[MeSH Terms]	15,431
6	graves disease[Title/Abstract]	13,078
7	thyroiditis[Title/Abstract]	16,576
8	#4 or #5 or #6 or #7	40,478
9	"sensitivity and specificity"[MeSH Terms]	642,037
10	"diagnosis, differential"[MeSH Terms]	466,654
11	sensitiv*[Title/Abstract]	1,604,438
12	specific*[Title/Abstract]	3,632,294
13	diagnos*[Title/Abstract]	2,960,927
14	#9 or #10 or #11 or #12 or #13	7,552,933
15	#3 and #8	539
16	#14 and #15	286

Cochrane CENTRAL

#	Query	Results
1	((radioactive iodine or technetium) and uptake):ti,ab,kw	341
2	(thyroid uptake):ti,ab,kw	373
3	#1 or #2	620
4	MeSH descriptor: [Graves Disease] explode all trees	470
5	(graves disease):ti,ab,kw	2546
6	(thyroiditis):ti,ab,kw	481
7	#5 or #6	2963
8	#3 and #7	60

Clinical Question No. 8 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves' disease versus thyrotoxic phase of subacute thyroiditis?

MEDLINE (PubMed)

#	Query	Results
1	((radioactive iodine[Title/Abstract]) OR (technetium[Title/Abstract])) AND (uptake[Title/Abstract])	5,026
2	thyroid uptake[Title/Abstract]	895
3	#1 or #2	5,761
4	graves disease[MeSH Terms]	18,433
5	"thyroiditis"[MeSH Terms]	15,431
6	graves disease[Title/Abstract]	13,078
7	thyroiditis[Title/Abstract]	16,576
8	#4 or #5 or #6 or #7	40,478
9	"sensitivity and specificity"[MeSH Terms]	642,037
10	"diagnosis, differential"[MeSH Terms]	466,654
11	sensitiv*[Title/Abstract]	1,604,438
12	specific*[Title/Abstract]	3,632,294
13	diagnos*[Title/Abstract]	2,960,927
14	#9 or #10 or #11 or #12 or #13	7,552,933
15	#3 and #8	539
16	#14 and #15	286

Cochrane CENTRAL

#	Query	Results
1	((radioactive iodine or technetium) and uptake):ti,ab,kw	341
2	(thyroid uptake):ti,ab,kw	373
3	#1 or #2	620
4	MeSH descriptor: [Graves Disease] explode all trees	470
5	(graves disease):ti,ab,kw	2546
6	(thyroiditis):ti,ab,kw	481
7	#5 or #6	2963
8	#3 and #7	60

Clinical Question No. 9 Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	(((Thyrotoxicosis [Mesh]) OR (Thyrotoxicosis [tiab])) AND ((Immunoglobulins, Thyroid-Stimulating [Mesh]) OR (Thyrotropin receptor antibody [tiab]) OR (TRAb [tiab]) OR (TSH receptor antibody [tiab]))) AND ((sensitivity and specificity[MeSH]) OR (diagnosis, differential[MeSH]) OR (sensitiv*[tiab]) OR (specific*[tiab]) OR (diagnos*[tiab])) Filters: January 30, 2012 to January 17, 2023	January 17, 2023, 03:47 AM	179	8
CENTRAL	Thyrotropin receptor antibody:ti,ab,kw OR TRAb:ti,ab,kw OR TSH receptor antibody:ti,ab,kw AND MeSH descriptor:[Thyrotoxicosis] explode all trees OR Thyrotoxicosis:ti,ab,kw Filters: none	January 18, 2023, 10:00 AM	14	0
Herdin Plus	TRAb	January 18, 2023, 3:00pm	3	0
Google Scholar	Advanced search tab: allintitle: TRAb Graves'	January 19, 2023, 8:30AM	129	2
ClinicalTrials.gov	TSH Receptor Antibody	November 30, 2022	20	0
chinaxiv.org	TSH Receptor Antibody	January 15, 2022	0	0
Medrxiv.org	TSH Receptor Antibody	January 15, 2022	0	0

Clinical Question No. 10 Should we do routine paired testing (T4/T4 plus TSH) versus TSH testing alone as initial evaluation of thyroid function among patients with suspected thyrotoxicosis?

MEDLINE via Pubmed (as of September 10, 2022)

Keywords	Strategy	Yields	Hits
TSH, T4, thyroid stimulating hormone, thyroxine, thyroid hormone	(((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract])	163,970	-
	Filter: meta-analysis	648	-
Thyrotoxicosis, hyperthyroidism, hyperthyroid*, thyrotoxic*	(((((thyrotoxicosis[MeSH Terms]) OR (hyperthyroidism[MeSH Terms])) OR (thyrotox*[MeSH Terms])) OR (hyperthyroid*[MeSH Terms])) OR (hyperthyroid*[Title/Abstract])) OR (thyrotoxic*[Title/Abstract]) ((((((thyrotoxicosis[MeSH Terms]) OR (hyperthyroidism[MeSH Terms])) OR (thyrotox*[MeSH Terms])) OR (hyperthyroid*[MeSH Terms])) OR (hyperthyroid*[Title/Abstract])) OR (thyrotoxic*[Title/Abstract])) AND ((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract]))	54,949	
	Filter: systematic review	81	
	((((((((((diagnosis) OR (diagnos*)) OR (diagnos*[Title/Abstract])) OR (diagnos*[MeSH Terms])) OR (laboratory[MeSH Terms])) OR (predictor[Title/Abstract])) OR (odds ratio[Title/Abstract])) OR (sensitivity[Title/Abstract])) OR (likelihood[Title/Abstract])) OR (positive predictive value[Title/Abstract]))) AND (((thyrotox*[MeSH Terms]) OR (thyrotoxicosis[MeSH Terms])) OR (thyrotoxic*[Title/Abstract]))	6,098	
	((((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract])) OR (thyrotropin	164,285	

	assay[Title/Abstract])) OR (thyrotropin assay[MeSH Terms])) OR (thyroid stimulating hormone test[MeSH Terms])		
Clinical practice guideline, practice guideline, thyrotoxicosis	Filter: systematic review	698	6 (2 in pregnancy)
Diagnosis, diagnostic test, Sensitivity, specificity, PPV, NPV, likelihood ratio*, accuracy	(((diagnosis[Title/Abstract]) OR (diagnostic test[Title/Abstract])) OR (test[Title/Abstract])) OR (diagnostic test[MeSH Terms])	3,353,172	-
	((((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR (T4[Title/Abstract])) OR (thyrotropin assay[Title/Abstract])) OR (thyrotropin assay[MeSH Terms])) OR (thyroid stimulating hormone test[MeSH Terms])	164,285	
	Filter: systematic review	698	
	((((((((((diagnosis) OR (diagnos*)) OR (diagnos*[Title/Abstract])) OR (diagnos*[MeSH Terms])) OR (laboratory[MeSH Terms])) OR (predictor[Title/Abstract])) OR (odds ratio[Title/Abstract])) OR (sensitivity[Title/Abstract])) OR (likelihood[Title/Abstract])) OR (positive predictive value[Title/Abstract]))) OR ((((((((odds ratio[Title/Abstract]) OR (sensitivity[Title/Abstract])) OR (likelihood[Title/Abstract])) OR (positive predictive value[Title/Abstract])) OR (negative predictive value[Title/Abstract])) OR (specificity[MeSH Terms])) OR (sensitivity[MeSH Terms])) OR (specificity[Title/Abstract]))) AND ((((((((((TSH[Title/Abstract]) OR (thyroid stimulating hormone[MeSH Terms])) OR (thyroxine[MeSH Terms])) OR (thyroid hormone[MeSH Terms])) OR (thyroid stimulating hormone[Title/Abstract])) OR (thyroxine[Title/Abstract])) OR (thyroid hormone[Title/Abstract])) OR	479	

	(T4[Title/Abstract])) OR (thyrotropin assay[Title/Abstract])) OR (thyrotropin assay[MeSH Terms])) OR (thyroid stimulating hormone test[MeSH Terms]))Filters: Meta-Analysis		
Antithyroid drug, radioactive iodine	(((((antithyroid drug) OR (antithyroid drugs[MeSH Terms])) OR (agents, antithyroid[MeSH Terms])) OR (metabolite[Title/Abstract])) OR (radioactive iodine[Title/Abstract])) OR (radioactive iodine[MeSH Terms])Filters: Meta-Analysis, Randomized Controlled Trial	4,355	
TSH, T4, paired, sequential	"paired"[Title/Abstract] AND ("sequen*"[Title/Abstract] AND "sequential"[Title/Abstract]) AND ("T4"[All Fields] OR "TSH"[All Fields] OR ("thyrotropin"[MeSH Terms] OR "thyrotropin"[All Fields] OR ("thyroid"[All Fields] AND "stimulating"[All Fields] AND "hormone"[All Fields]) OR "thyroid stimulating hormone"[All Fields]) OR "thyrotropin"[MeSH Terms] OR "thyrotoxic*"[MeSH Terms])	5	0

CENTRAL

Keywords	Strategy	Yields	Hits
Accuracy, specificity, sensitivity	(accuracy):ti,ab,kw OR sensitivity OR specificity	94,588	-
Free serum T4, thyroxine, thyroid stimulating hormone, TSH test, thyrotropin,	MeSH descriptor: [Diagnostic Techniques and Procedures] in all MeSH products OR free serum T4 OR thyroxine OR MeSH descriptor: [Thyroxine] explode all trees OR thyroid stimulating hormone OR MeSH descriptor: [Thyrotropin] explode all trees OR TSH test	248,970	
thyrotoxicosis	MeSH descriptor: [Thyrotoxicosis] explode all trees	40	-
	((accuracy):ti,ab,kw OR sensitivity OR specificity) AND (MeSH descriptor: [Diagnostic Techniques and Procedures] in all MeSH products OR free serum T4 OR thyroxine OR MeSH descriptor: [Thyroxine] explode all trees OR thyroid stimulating hormone OR MeSH descriptor: [Thyrotropin] explode all trees OR TSH test) AND MeSH descriptor: [Thyrotoxicosis] explode all trees	1	-
Antithyroid drug, radioactive iodine	MeSH descriptor: [Antithyroid Agents] explode all trees OR antithyroid drug OR radioactive iodine	834	-

thyrotoxicosis	thyrotoxicosis OR MeSH descriptor: [Thyrotoxicosis] explode all trees	261	
	MeSH descriptor: [Antithyroid Agents] explode all trees OR antithyroid drug OR radioactive iodine AND thyrotoxicosis OR MeSH descriptor: [Thyrotoxicosis] explode all trees	73 7 reviews, 66 trials	

ClinicalTrials.gov (as of September 10, 2022)

Keywords	Query	Results
Thyrotoxicosis, antithyroid drugs	Thyrotoxicosis, hyperthyroidism, antithyroid drugs	2
Thyrotoxicosis, antithyroid drugs	Thyrotoxicosis, hyperthyroidism, radioactive iodine	1

HERDIN (as of September 10, 2022)

Keywords	Query	Results
Thyrotoxicosis	Thyrotoxicosis	43
Antithyroid drug	Antithyroid drug	10
Radioactive iodine	Radioactive iodine	66
Thryoxine	Thyroxine	65

Clinical Question No. 11 Should we routinely do T3 testing on top of TSH and T4/fT4 testing in the workup of individuals suspected to have thyrotoxicosis?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed MEDLINE	(("Thyrotoxicosis"[MeSH Terms] OR "Thyrotoxicosis"[Title/Abstract] OR "Hyperthyroidism"[Title/Abstract] OR "Hyperthyroidism"[MeSH Terms]) AND ("Triiodothyronine"[MeSH Terms] OR "T3"[Title/Abstract]) AND ("T4"[Title/Abstract] OR "fT4"[Title/Abstract] OR "Thyroxine"[MeSH Terms]) AND ("Thyrotropin"[MeSH Terms] OR "TSH"[Title/Abstract]) AND "Thyroid Function Tests"[MeSH Terms]) AND (clinicaltrial[Filter] OR observationalstudy[Filter] OR practiceguideline[Filter] OR randomizedcontrolledtrial[Filter] OR review[Filter] OR systematicreview[Filter])	April 11, 2023 10:57 AM	104	25
EMBASE	('thyrotoxicosis'/exp OR 'thyreotoxicosis' OR 'thyrotoxicosis' OR 'hyperthyroidism'/exp) AND (t3:ti,ab OR 'liothyronine'/exp) AND ('randomized controlled trial'/exp OR 'controlled clinical trial (topic)'/exp OR 'observational study'/exp)	April 11, 2023 10:57 AM	21	14
Herdin.ph	“thyroid test”	April 10, 2023 9:15 PM	91	2
ClinicalTrials.gov	“thyroid” and “T3”	April 11, 2023 11:00 AM	29	0

Clinical Question No. 12 Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?

#	Query	Results
1	Thyrotoxicosis	10,298
2	Hyperthyroidism	53,506
3	Thyroid nodules	16,754
4	Nodular goiter	5,938
5	Multinodular goiter	3,089
6	Toxic goiter	3,274
7	Graves' disease	24,870
8	Plummer disease	1,428
9	Toxic adenoma	5,424
10	Thyroid scan	13,440
11	Thyroid scintigraphy	11,328
12	Thyroid scanning	12,674
13	#1 or #2	54,978
14	#3 or #4 or #5	22,239
15	#6 or #7 or #8 or #9	32,704
16	#10 or #11 or #12	16,893
17	#13 and #14 and #15 and #16	393

Clinical Question No. 13 Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
Medline	Search: Hyperthyroidism AND Thyroidectomy AND Radioactive Iodine Filters: Free full text, Full text ((("hyperthyroidal"[All Fields] OR "hyperthyroidic"[All Fields] OR "hyperthyroidism"[MeSH Terms] OR "hyperthyroidism"[All Fields] OR "hyperthyroid"[All Fields] OR "hyperthyroids"[All Fields] OR "hyperthyroidisms"[All Fields]) AND ("thyroidectomy"[MeSH Terms] OR "thyroidectomy"[All Fields] OR "thyroidectomies"[All Fields]) AND (("radioactively"[All Fields] OR "radioactivity"[MeSH Terms] OR "radioactivity"[All Fields] OR "radioactive"[All Fields] OR "radioactivities"[All Fields]) AND ("halogenation"[MeSH Terms] OR "halogenation"[All Fields] OR "iodination"[All Fields] OR "iodin"[All Fields] OR "iodinate"[All Fields] OR "iodinated"[All Fields] OR "iodinates"[All Fields] OR "iodinating"[All Fields] OR "iodinations"[All Fields] OR "iodine"[MeSH Terms] OR "iodine"[All Fields] OR "iodides"[MeSH Terms] OR "iodides"[All Fields] OR "iodines"[All Fields])))) AND ((ffrft[Filter]) AND (fft[Filter]))	August 20, 2022 2:00 PM	105	4
COCHRANE	Hyperthyroidism (MESH) and Thyroidectomy (MESH) and Radioactive iodine (MESH)	August 20, 2022 2:30PM	7	1
HERDIN	Hyperthyroidism AND Thyroidectomy AND (RAI or Radioactive iodine)	August 20, 2022 2:38PM	8	2
ClinicalTrials.gov	Hyperthyroidism / Thyrotoxicosis	August 20, 2022 2:15PM	17	0

Clinical Question No. 14 Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?

DATABASE	SEARCH STRATEGY / SEARCH TERMS	DATE AND TIME OF SEARCH	RESULTS	
			Yield	Eligible
PubMed	("thyrotoxicosis"[MeSH Terms] OR "hyperthyroidism"[MeSH Terms] OR "graves disease"[MeSH Terms]) AND "thyroid nodule"[MeSH Terms] AND ((("thyroid gland"[MeSH Terms] OR ("thyroid"[All Fields] AND "gland"[All Fields]) OR "thyroid gland"[All Fields] OR "thyroid"[All Fields] OR "thyroid usp"[MeSH Terms] OR ("thyroid"[All Fields] AND "usp"[All Fields]) OR "thyroid usp"[All Fields] OR "thyroids"[All Fields] OR "thyroid s"[All Fields] OR "thyroidal"[All Fields] OR "thyroideal"[All Fields] OR "thyroidism"[All Fields] OR "thyroiditis"[MeSH Terms] OR "thyroiditis"[All Fields] OR "thyroiditides"[All Fields]) AND ("ultrasonography"[MeSH Terms] OR "ultrasonics"[MeSH Terms])) OR (("thyroid gland"[MeSH Terms] OR ("thyroid"[All Fields] AND "gland"[All Fields]) OR "thyroid gland"[All Fields] OR "thyroid"[All Fields] OR "thyroid usp"[MeSH Terms] OR ("thyroid"[All Fields] AND "usp"[All Fields]) OR "thyroid usp"[All Fields] OR "thyroids"[All Fields] OR "thyroid s"[All Fields] OR "thyroidal"[All Fields] OR "thyroideal"[All Fields] OR "thyroidism"[All Fields] OR "thyroiditis"[MeSH Terms] OR "thyroiditis"[All Fields] OR "thyroiditides"[All Fields]) AND "ultrasonography"[MeSH Terms]) OR (("neck"[MeSH Terms] OR	January 26, 2023 04:09AM	91	3

	"neck"[All Fields]) AND ("ultrasonography"[MeSH Terms] OR "ultrasonics"[MeSH Terms])) OR (("neck"[MeSH Terms] OR "neck"[All Fields]) AND "ultrasonography"[MeSH Terms]))			
PubMed	(((((hyperthyroidism[MeSH Terms]) OR (thyrotoxicosis[MeSH Terms])) OR (Graves Disease[MeSH Terms])) AND (((children[MeSH Terms]) OR (adolescent[MeSH Terms])) OR (young[MeSH Terms]))) AND ((((Thyroid ultrasound[MeSH Terms]) OR (thyroid ultrasonography[MeSH Terms])) OR (neck ultrasound[MeSH Terms])) OR (neck ultrasonography[MeSH Terms]))) AND (thyroid nodules[MeSH Terms])	March 30, 2023 08:10PM	15	0
Cochrane Library	thyroid ultrasound AND thyroid nodules AND hyperthyroidism Filters: 2018 to 2023	January 26, 2023 05:00AM	11	0
ClinicalTrials.gov	Ultrasonography, thyroid ultrasound, neck ultrasound, hyperthyroidism, thyrotoxicosis	March 3, 2023	0	0

Clinical Question No. 15 Should we use history and PE findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves' disease (GD) versus non-Graves' disease (i.e., other etiology) among non-pregnant patients with biochemically confirmed hyperthyroidism?

Appendix 1: Search strategy for MEDLINE

Search number	Query	Results
32	(((diagnost* accura*[Title/Abstract])) OR ((specificity[Title/Abstract]))) AND (((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND (#1 OR #2 OR #3 OR #4))	546
31	((diagnost* accura*[Title/Abstract])) OR ((specificity[Title/Abstract]))	751,550
30	(diagnost* accura*[Title/Abstract])	262,787
29	((specificity[Title/Abstract])) AND (((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND (#1 OR #2 OR #3 OR #4))	429
28	(specificity[Title/Abstract])	558,188
26	(sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnose[Title/Abstract] OR diagnosed[Title/Abstract] OR diagnoses[Title/Abstract] OR diagnosing[Title/Abstract] OR diagnosis[Title/Abstract] OR diagnostic[Title/Abstract] OR diagnosis[MeSH:noexp] OR (diagnostic equipment[MeSH:noexp] OR diagnostic errors[MeSH:noexp] OR diagnostic imaging[MeSH:noexp] OR diagnostic services[MeSH:noexp]) OR diagnosis, differential[MeSH:noexp] OR diagnosis[Subheading:noexp])	6,437,668
24	((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND (#1 OR #2 OR #3 OR #4)	19,823
23	(graves disease) AND (Diagnosis/Narrow[filter])	578
22	(((physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)) AND ((sensitivity and specificity[MeSH Terms]) OR (predict* OR diagnos* OR accura*))) AND (#1 OR #2 OR #3 OR #4)	7,677
21	(physical examination[MeSH Terms]) OR (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)	1,415,493
20	physical examination[MeSH Terms]	1,373,283
19	#18 AND #17 AND #5	3,209

18	#6 OR #7 OR #8 OR #9 OR #11 OR #12 OR #13 OR #14 OR #15	28,028
17	(sensitivity and specificity[MeSH Terms]) OR (predict* OR diagnos* OR accura*)	8,280,802
16	#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15	43,108
15	acropachy	1,067
14	thyroid orbitopathy	5,800
13	thyroid ophthalmopathy	5,584
12	Graves' orbitopathy	5,897
11	Graves' ophthalmopathy	5,276
10	proptosis	29,211
9	exophthalm*	10,047
8	thyroid dermopathy	9,972
7	Grave* dermopathy	2,394
6	pretibial myxedema	446
5	#1 OR #2 OR #3 OR #4	24,720
4	exophthalmic goiter[MeSH Terms]	18,771
3	(diffuse toxic goiter[Title/Abstract]) OR (toxic diffuse goiter[Title/Abstract])	547
2	disease, graves'[MeSH Terms]	18,771
1	Graves[Title/Abstract]	17,517

Cochrane Library

ID	Search	Hits
#1	("Graves disease"):ti,ab,kw (Word variations have been searched)	699
#2	diffuse toxic goiter	30
#3	("exophthalmic goiter"):ti,ab,kw	2
#4	MeSH descriptor: [Graves Disease] explode all trees	543
#5	MeSH descriptor: [Sensitivity and Specificity] this term only	10929
#6	diagnostic accuracy	13041
#7	sensitivity	77820

#8	specificity	24239
#9	#1 OR #2 OR #3 OR #4	839
#10	#6 OR #7 OR #8	87365
#11	#9 AND #10	104

CLINICAL PRACTICE GUIDELINES FOR HYPERTHYROIDISM

AGREE-II[1] SELF-ASSESSMENT

The following AGREE-II Tool Self-Assessment was done by the Steering Committee Members of the CPG Task Force.

Dr. Nicodemus

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: 14/3

Comments

The ultimate goal of this CPG is to define best practices in screening, diagnosis, and treatment of hyperthyroidism and its associated conditions among patients through a comprehensive and systematic assessment of the benefit, harm, and cost of select screening, diagnosis, and treatment interventions

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: 15
Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: 14
Comments

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: ____/____
Comments

All relevant stakeholders are included

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: ____/____

Comments

The CP includes not just doctors of different specialties and fields, but also patient representative

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: ____/____

Comments

This CPG is primarily intended to be used by primary care workers (i.e., specialists, physicians, allied healthcare) or in the primary care setting. Under UHC, primary care worker refers to a health care worker, who may be a health professional or community health worker/volunteer, certified by DOH to provide primary care services, while primary care facility refers to the institution that primarily delivers primary care services which shall be licensed or registered by the DOH.

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	x 7

Page No. / Paragraph No.: 16/2
Comments

A systematic search of local and international electronic databases (i.e.,MEDLINE, CENTRAL, Google Scholar, HERDIN, and clinicaltrials.gov, UpToDate) from database inception was done until September 30, 2022 by the Evidence Review Experts (ERE). For therapeutic interventions, at least two reviewers looked for direct evidence from randomized controlled trials (RCT), systematic reviews (SR), and/or meta-analyses. In their absence, quasi-randomized and observational studies will be assessed for possible inclusion. For diagnostic interventions, RCTs and/or diagnostic test accuracy (DTA) reviews reporting clinical outcomes of benefit or harm of these diagnostic strategies or interventions and resulting treatment will be sought. If no direct evidence is found, observational studies that reported sensitivity, specificity, and other diagnostic accuracy estimates were sought

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	x 7

Page No. / Paragraph No.: 16/3
Comments

For each research question, the scope (inclusion and exclusion criteria) of the literature search will be dictated by the population, intervention, comparator, outcomes, and methodology

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	x 7

Page No. / Paragraph No.: ____/____
Comments

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	x 7

Page No. / Paragraph No.: ____/____

Comments

The certainty of the evidence (CoE) for each outcome of interest was assessed using GRADEPro, which considers the risk of bias and the presence or absence of any indirectness, imprecision, inconsistency, and other considerations (i.e., publication bias). The overall certainty of the evidence was based on the lowest certainty rating of the top seven (7) critical and important outcomes. The rating of importance of outcomes into critical, important, or relevant was decided on by the multi-sectoral consensus panel.

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Comments

CP members voted on the direction (for or against) and strength (strong or weak) of the final recommendation based on the certainty of the evidence, balance between benefits and harms, values, preferences, and burden on patients, cost and resource implications, equity, acceptability, feasibility, and appropriateness

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: ____/____
Comments

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: 18/7
Comments

The recommendations herein shall hold until such time that new evidence on screening strategies, diagnostic tests, medicines, and surgical interventions for hyperthyroidism emerges or other contingencies compel the updating of this CPG (i.e., usually after three to five years).

The Hyperthyroidism Task Force intends to review this CPG no later than 2025

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	**X 7**

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	**X 7**

Comments

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	**X 7**

Page No. / Paragraph No.: ____/____
Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	X 6	☐ 7

Comments

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Comments

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Comments

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	X 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: ____/____
Comments

23. Competing interests of guideline development group members have been recorded and addressed.

Strongly disagree Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: ____/____
Comments

Dr. Cunanan

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: __2__/_1 and 4___ 13/3

Comments

- intended to be used by primary care providers such as specialists and general practitioners
- not intended to cover the entirety of the screening, diagnosis, and management of hyperthyroidism. It provides recommendations on interventions where variability in clinical practice and some controversies in decision-making exists.

The ultimate goal of this CPG is to define best practices in screening, diagnosis, and treatment of hyperthyroidism and its associated conditions among patients through a comprehensive and systematic assessment of the benefit, harm, and cost of select screening, diagnosis, and treatment interventions. Specifically, this CPG aims to determine the (1) effectiveness, safety, and cost of screening tests, diagnostic tests, and treatment interventions used in hyperthyroidism in reducing disease-specific morbidity and mortality, and all-cause mortality among Filipinos (i.e., children, nonpregnant adults, older persons, pregnant individuals); (2) certainty of the evidence for each of the selected screening test; and, (3) to develop an evidence-based recommendations through a consensus process outlined in the DOH 2018 Manual for CPG Development.

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: _10-12___/__table__

Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: __9__/__3__

Comments

screening, diagnosis, and management of hyperthyroidism among children, non-pregnant adults, and special populations (i.e., older person, and pregnant individuals)

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: __4__/____
Comments

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	√ 5	☐ 6	7

Page No. / Paragraph No.: ____/____
Comments

Members of. Taskforce included lay people (NB not in manuscript yet)

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	6	√ 7

Page No. / Paragraph No.: __2/(1) 13/(4)
Comments

primary care workers (i.e., specialists, physicians, allied healthcare) or in the primary care setting. Under UHC, primary care worker refers to a health care worker, who may be a health professional or community health worker/volunteer, certified by DOH to provide primary care services, while primary care facility refers to the institution that primarily delivers primary care services which shall be licensed or registered by the DOH

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: __15__/_3___
Comments

A systematic search of local and international electronic databases (i.e.,MEDLINE, CENTRAL, Google Scholar, HERDIN, and clinicaltrials.gov, UpToDate) from database inception was done until September 30, 2022 by the Evidence Review Experts (ERE).

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Page No. / Paragraph No.: __15__/_3-5___

Comments

Inclusion/exclusion criteria, study quality assessment

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	√ 5	☐ 6	☐ 7

Page No. / Paragraph No.: __2__/__3__

Comments

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Page No. / Paragraph No.: __15-16__/_whole pages___

Comments

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	X5	☐ 6	☐ 7

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	X 5	☐ 6	☐ 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: __17__/__3__

Comments

Ongoing external review

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Page No. / Paragraph No.: _17___/__4__

Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Comments

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: ____/____

Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	√ 5	☐ 6	☐ 7

Comments

Page 16 guideline dissemination

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	√ 4	5	☐ 6	☐ 7

Comments

Stated in guideline dissemination page 16, but is still not available

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Comments

Cost considerations included per clinical question

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Page No. / Paragraph No.: _16-17__/____

Comments

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	√ 6	☐ 7

Page No. / Paragraph No.: _17___/__6__
Comments

23. Competing interests of guideline development group members have been recorded and addressed.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	√ 7

Page No. / Paragraph No.: _17___/__7__
Comment

Dr. Fernandez

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No. 2 / 4
Comment

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 21/ 4
Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 9 / 3
Comments

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 24 /2
Comments

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 2/1, 13/4
Comments

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 15/ 3
Comments

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 22-23 / 4,5
Comments

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 2/3
Comments

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 22-24/ 7-9

Comments

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 17/3
Comments

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 17/4
Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 24/5-6
Comments

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 17/6
Comments

23. Competing interests of guideline development group members have been recorded and addressed.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 17/7
Comments

Dr. Kho

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____

Comments

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____
Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____

Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Comments

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____

Comments

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____

Comments

Dr. Tinhay

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 13 /____
Comments

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 13 19 /____
Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 13 /____
Comments

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 19 /____
Comments

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: ____/____
Comments

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 13 /____
Comments

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 15 /____
Comments

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 15 /____
Comments

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 15-16 /____
Comments

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 15 /____

Comments

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 16-17/____
Comments

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 17 /____
Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: ____/____

Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 17 /____

Comments

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 17 /____

Comments

23. Competing interests of guideline development group members have been recorded and addressed.

Strongly disagree Strongly Agree

☐ **1**	☐ **2**	☐ **3**	☐ **4**	☐ **5**	☐ **6**	☒ **7**

Page No. / Paragraph No.: ____/____
Comments

Dr. Aragon

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Page No. / Paragraph No.: __13__/____

Comments

This hyperthyroidism guideline provided clear and comprehensive guidance for the screening, diagnosis, management, and treatment of hyperthyroidism among children, adults, and pregnant and elderly populations ensuring that the healthcare professionals have a standardized and evidence-based approach to the management of this disorder.

The general and specific objectives of the guideline are clearly stated.

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Page No. / Paragraph No.: _13-14___/____

Comments

This hyperthyroidism guideline meticulously outlines and addresses a wide spectrum of health questions related to the disorder. This provided explicit and detailed information on matters such as hyperthyroidism diagnosis, various treatment modalities, complications, and options for long-term management. This specificity is essential for guiding healthcare practitioners in delivering precise and effective care.

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Page No. / Paragraph No.: _13___/____

Comments

This hyperthyroidism guideline specified a clear and well-defined target audience. They are intended to apply to a diverse population, such as healthcare providers, patients, and the general public. By specifying the audience, these guidelines ensure that relevant information is accessible to medical practitioners for accurate diagnosis and treatment, while also providing valuable information to patients and the public to promote awareness and understanding of hyperthyroidism.

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Page No. / Paragraph No.: ____/____

Comments

The inclusion of various healthcare professionals in the development of these hyperthyroidism guidelines is a crucial step toward ensuring their comprehensiveness and effectiveness. It shows a holistic approach to guideline development, incorporating the expertise of various medical fields involved in the care of patients with hyperthyroidism.

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	X ☐ 6	☐ 7

Page No. / Paragraph No.: ____/____

Comments

In the development of this hyperthyroidism guideline, the views and preferences of the target population have been sought. In doing these, it enhances the relevance and applicability of the guidelines and is more likely to align with the real-world needs and preferences of the individuals.

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Page No. / Paragraph No.: ____/____

Comments

This hyperthyroidism guideline has clearly defined its target users. These are designed to serve as a valuable resource for a diverse audience, including healthcare professionals, patients, caregivers, and anyone seeking reliable information on hyperthyroidism. This ensures that each user group can readily access the guidelines relevant to their needs, facilitating a better understanding, diagnosis, and management of hyperthyroidism.

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Page No. / Paragraph No.: _15___/____

Comments

A systematic search of local and international electronic databases (i.e.,MEDLINE, CENTRAL, Google Scholar, HERDIN, and clinicaltrials.gov, UpToDate) was done by the Evidence Review Experts (ERE). This will ensure that the guidelines are firmly grounded in the latest research and clinical data making it a reliable and trustworthy clinical guideline.

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Page No. / Paragraph No.: ____/____

Comments

This hyperthyroidism guideline has clearly described and outlined the criteria used for selecting evidence. By doing this, it provides a transparent framework that helps the users understand the basis for recommendations.

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ X 7

Page No. / Paragraph No.: ____/____

Comments

This approach of acknowledging the strengths and limitations, such as potential biases or gaps in the research provide users with a comprehensive understanding of the foundation on which the recommendations were built.

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Page No. / Paragraph No.: ____/____

Comments

This ensures that the recommendations are generated through a systematic and evidence-based approach.

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Comments

This is very important when formulating recommendations for health-related matters. The balance of benefits and risks became the basis for the draft recommendation in this Hyperthyroidism guidelines.

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Comments

In this hyperthyroidism guideline, there is a clear and explicit link between the recommendations provided and the supporting evidence. This ensures that healthcare decisions are based on a solid foundation of research leading to more effective and informed patient care.

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Page No. / Paragraph No.: __17 __/____

Comments

The manuscript of this CPG was reviewed by a clinical epidemiologist and methodology expert, a non-content clinician, and a content expert clinician. This peer review process helps ensure the quality, accuracy, and reliability of this guideline.

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ X7

Page No. / Paragraph No.: __17__/____

Comments

This ensures that this Hyperthyroidism guideline remains current and relevant as new research and evidence emerge. The Hyperthyroidism Task Force intends to review this CPG no later than 2025.

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Comments

The Hyperthyroidism CPG recommendations are specific for each population (pediatrics, adult non-pregnant, elderly population, and pregnant) since there are variations in the management which may not be applicable for other population groups. There is clarity in the medical guidelines for healthcare professionals to confidently implement best practices which translates to improved patient outcomes.

16. The different options for the management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Comments

This was discussed clearly and highlighted during the meetings with the consensus panel. This will help the healthcare providers to make well-informed decisions tailored to individual patient needs.

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Page No. / Paragraph No.: ____/____

Comments

In each of the recommendations for a specific question, you can clearly identify which recommendation pertains to a specific population. This will help simplify the decision-making process of healthcare professionals.

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Comments

The inclusion of information about facilitators and barriers to its application in this Hyperthyroidism CPG will help healthcare professionals anticipate challenges and create strategies to ensure effective implementation.

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	X☐ 6	☐ 7

Comments

This Hyperthyroidism CPG is not only valuable for its evidence-based recommendations but also for its clear guidance on how to translate these recommendations into clinical practice. It provides clinicians with advice and tools, such as diagnostic algorithms and monitoring strategies.

(Algorithms to follow)

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Comments

The Hyperthyroidism CPG has assessed whether the guidelines' recommendations can be feasibly implemented in the local healthcare system. It has considered the availability of diagnostic tools, medications, and specialist services.

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X 7

Page No. / Paragraph No.: __17__/____

Comments

The Hyperthyroidism guideline used the final Strength of Recommendation to determine key performance indicators

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐X 7

Page No. / Paragraph No.: _18___/____

Comments

The content of this Hyperthyroidism guideline remains unbiased, the views of the funding body have not influenced its development.

23. Competing interests of guideline development group members have been recorded and addressed.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	X☐ 7

Page No. / Paragraph No.: _18___/____

Comments

All the members of the CPG development groups have accomplished and signed a declaration of conflict of interests (DCOI) form before formally being assigned to the different development groups (Steering Committee, Evidence review experts, Consensus panel).

An independent COI review committee (COIRC) went through the COI forms and CVs of the Task Force members and after deliberation came up with guidelines as bases for their decision.

Dr. De La Pena

CLINICAL PRACTICE GUIDELINES FOR HYPERTHYROIDISM

AGREE-II[1] SELF-ASSESSMENT

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree						Strongly Agree
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 21 / 2

Comments

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree						Strongly Agree
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 21&22 / 4

Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☑ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: 21 / 2&3

Comments

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 23&24 / 2

Comments

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree — Strongly Agree

☐ 1	☑ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7

Page No. / Paragraph No.: ____/____

Comments

6. The target users of the guideline are clearly defined.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 21 / 4

Comments

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 23 / 3 appendix

Comments

8. The criteria for selecting the evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 23 / 4&5

Comments

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: ____/____

Comments

10. The methods for formulating the recommendations are clearly described.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 23&24/ 7,8,9

Comments

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 25 / 3

Comments

14. A procedure for updating the guideline is provided.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 25 / 4

Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

17. Key recommendations are easily identifiable.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Page No. / Paragraph No.: 17 / Table 1

Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree — Strongly Agree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☑ 6	☐ 7

Comments

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree						Strongly Agree
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree						Strongly Agree
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Comments

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☑ 6	☐ 7

Strongl

Page No. / Paragraph No.: 24 / 5

Comments

22. The views of the funding body have not influenced the content of the guideline.

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☑ 7

Strongly disagree Strongly Agree

Page No. / Paragraph No.: 25/ 5

Comments

Dr. De La Paz

DOMAIN 1. SCOPE AND PURPOSE

1. The overall objective(s) of the guideline is (are) specifically described.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _____21___/__2___

Comments

2. The health question(s) covered by the guideline is (are) specifically described.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _____21 & 22_/____4_
Comments

3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 x 4 ☐ 5 ☐ 6 ☐ 7

Page No. / Paragraph No.: __21__/__2 & 3
Comments - The target population was mentioned in the objectives part of the CPG (paragraph 2). The target populations mentioned in paragraph 3 pertains to the users of the guideline

DOMAIN 2. STAKEHOLDER INVOLVEMENT

4. The guideline development group includes individuals from all relevant professional groups.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _23 & 24_____/___2_
Comments

5. The views and preferences of the target population (patients, public, etc.) have been sought.

Strongly disagree Strongly Agree

☐ 1 x 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 ☐ 7

Page No. / Paragraph No.: _____/____

Comments There was no mention of this process during the CPG development

6. The target users of the guideline are clearly defined.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _____21__/__4__

Comments

DOMAIN 3. RIGOUR OF DEVELOPMENT

7. Systematic methods were used to search for evidence.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _____23___/___3_; appendix

Comments

8. The criteria for selecting the evidence are clearly described.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _23_____/___4 & 5_

Comments

9. The strengths and limitations of the body of evidence are clearly described.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _____/____
Comments Mentioned during the discussion of each recommendation

10. The methods for formulating the recommendations are clearly described.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _23 & 24_____/___7, 8, 9_
Comments

11. The health benefits, side effects, and risks have been considered in formulating the recommendations.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Comments

12. There is an explicit link between the recommendations and the supporting evidence.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Comments

13. The guideline has been externally reviewed by experts prior to its publication.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: 25_____/___3_
Comments

14. A procedure for updating the guideline is provided.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _____25___/_4____

Comments

DOMAIN 4. CLARITY OF PRESENTATION

15. The recommendations are specific and unambiguous.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Comments

16. The different options for management of the condition or health issue are clearly presented.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Comments

17. Key recommendations are easily identifiable.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: 18 / Table 1

Comments

DOMAIN 5. APPLICABILITY

18. The guideline describes facilitators and barriers to its application.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 x 6 ☐ 7

Comments No barriers to application/dissemination were identified

19. The guideline provides advice and/or tools on how the recommendations can be put into practice.

Strongly disagree — Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Comments

20. The potential resource implications of applying the recommendations have been considered.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Comments

21. The guideline presents monitoring and/or auditing criteria.

Strongly disagree Strongly Agree
☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 x 6 ☐ 7

Page No. / Paragraph No.: _24_____/__5__
Comments There was no mention of who or how the questionnaire will be done and who will do the monitoring and/or auditing

DOMAIN 6. EDITORIAL INDEPENDENCE

22. The views of the funding body have not influenced the content of the guideline.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _25_____/__5__

Comments

23. Competing interests of guideline development group members have been recorded and addressed.

Strongly disagree Strongly Agree

☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6 x 7

Page No. / Paragraph No.: _25_____/__6__

Comments

Recommendations from Other Groups

Clinical Questions	Group	Recommendation	Strength of Recommendation
1. Should we do routine paired testing (fT4/T4 plus TSH) versus TSH testing alone as initial evaluation of thyroid function among patients with suspected thyrotoxicosis?	American Thyroid Association 2016 and Association of Clinical Endocrinologists Taskforce on Hyperthyroidism 2011[10, 140]	On biochemical evaluation "Serum TSH measurement has the highest sensitivity and specificity of any single blood test used in the evaluation of suspected hyperthyroidism and should be used as an initial screening test. However, when hyperthyroidism is strongly suspected, diagnostic accuracy improves when both a serum TSH and free T4 are assessed at the time of the initial evaluation." In overt hyperthyroidism, usually both serum-free T4 and T3 estimates are elevated, and serum TSH is undetectable; however, in milder hyperthyroidism, serum T4 and free T4 estimates can be normal, only serum T3 may be elevated, and serum TSH will be <0.01 mU/L (or undetectable)."	Not stated
2. Should we routinely do T3 testing on top of TSH and fT4/T4 testing in the workup of individuals suspected to have thyrotoxicosis?	2019 UK NICE[79, 147]	ADULTS Consider measuring TSH alone for adults when secondary thyroid dysfunction (pituitary disease) is not suspected. If TSH is below the	No strength of recommendation; no evidence found

		reference range, measure fT4 and fT3 in the same sample. Consider measuring both TSH and fT4 for adults with suspected secondary thyroid dysfunction. If TSH is below the reference range, measure fT3 in the same sample. Consider repeating thyroid function tests if symptoms worsen or new symptoms develop (but no sooner than 6 weeks from the most recent test). CHILDREN Consider measuring both TSH and fT4 for children. If TSH is below the reference range, measure fT3 in the same sample. Consider repeating thyroid function tests if symptoms worsen or new symptoms develop (but no sooner than 6 weeks from the most recent test).	
	2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism[8]	ADULTS No explicit recommendation When hyperthyroidism is strongly suspected, diagnostic accuracy improves when both TSH and fT4 are assessed at the time of the initial evaluation. In overt hyperthyroidism, both serum free	Not a guideline recommendation; cited two observational studies for TSH[4,5]

	2022 European Thyroid Association Guideline for the Management of Pediatric Graves' Disease[44]	T4 and T3 concentrations are elevated; in milder hyperthyroidism, serum total T4 and fT4 levels can be normal and only serum fT3 may be elevated. CHILDREN No explicit recommendation statement In all pediatric patients with suspected hyperthyroidism, serum fT4, fT3, and TSH should be measured. An elevated fT3 level is a more sensitive maker of overt hyperthyroidism than fT4 and will confirm or refute the diagnosis of pediatric GD in most cases.	
	2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis[10]	No explicit recommendation statement Serum TSH should be used as an initial screening test to evaluate suspected thyrotoxicosis. When thyrotoxicosis is strongly suspected, diagnostic accuracy improves when serum TSH, free T_4, and total T_3 are assessed in the initial evaluation.	Not a guideline recommendation statement; cited two observational studies for TSH[4,5]
	2013 Korean Thyroid Association (KTA)[43]	No explicit recommendation statement Suggests both serum TSH and free T_4 at the time of initial evaluation when hyperthyroidism is strongly	Not a guideline recommendation; consensus report based only on survey of KTA members

		suspected. Total T_3 is helpful for the diagnosis of T_3-toxicosis.	
3. Should we use history and PE findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves' disease from non-Graves' disease (i.e., other etiologies) among patients with biochemically confirmed thyrotoxicosis?	American Thyroid Association 2016[10]	"All patients with known or suspected hyperthyroidism should undergo a comprehensive history and physical examination, including measurement of pulse rate, blood pressure, respiratory rate, and body weight. Thyroid size, tenderness, symmetry, and nodularity should also be assessed along with pulmonary, cardiac, and neuromuscular function and the presence or absence of peripheral edema, eye signs, or pretibial myxedema."	Not stated
	The Brazilian consensus for the diagnosis and treatment of hyperthyroidism: Brazilian Society of Endocrinology and Metabolism 2013[199]	"The diagnosis of Graves' hyperthyroidism can be established with relative confidence in patients with moderate to severe symptoms of thyrotoxicosis, recent ophthalmopathy, and diffuse goiter. In these cases, no additional tests are needed to investigate its etiology."	Not stated
4. Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?	American Thyroid Association 2016 [10]	The etiology of thyrotoxicosis should be determined. If the diagnosis is not apparent based on the clinical presentation and initial biochemical evaluation, diagnostic testing is indicated and	Strong recommendation, moderate quality of evidence

		can include, depending on available expertise and resources, (1) measurement of TRAb, (2) determination of the radioactive iodine uptake (RAIU), or (3) measurement of thyroidal blood flow on ultrasonography.	
	European Thyroid Association 2018[24]	The measurement of TSH-R-Ab is a sensitive and specific tool for rapid and accurate diagnosis and differential diagnosis of Graves' hyperthyroidism. 1, ØØØØ When technically available, differentiation of TSH-R- Ab functionality is helpful and predictive in Graves' patients during pregnancy/postpartum, as well as for extrathyroidal manifestations. 2, ØØØo	Strong recommendation, high quality of evidence Weak recommendation, moderate quality of evidence
5. Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves' disease from versus thyrotoxic phase of subacute thyroiditis? 7. Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to	European Thyroid Association[8]	Thyroid scintigraphy if thyroid nodularity coexists with hyperthyroidism	Weak recommendation, moderate-quality evidence
	American Thyroid Association[10]	If the etiology is not apparent: Measurement of TRAbs Determination of radioactive iodine uptake Measurement of thyroid blood flow on ultrasonography ^{123}I or ^{99m}Tc pertechnetate scan when the clinical presentation	Strong recommendation, moderate-quality evidence

differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?		suggests a toxic adenoma or toxic multinodular goiter	
	Indonesian Society of Endocrinology[72]	Radioactive iodine uptake when the clinical presentation of thyrotoxicosis is not diagnostic of GD. Thyroid scan if there is presence of thyroid nodularity	Not specified
6. Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves' disease from thyrotoxic phase of subacute thyroiditis?	National Institute for Health and Care Excellence (2019)[79]	For children with thyrotoxicosis: Technetium scanning if TRAbs are negative Thyroid ultrasound if there is a palpable nodule or the cause of thyrotoxicosis remains unclear following TRAbs testing and technetium scanning	Low-quality evidence
	European Thyroid Association (2018)[8]	Thyroid scintigraphy if thyroid nodularity coexists with hyperthyroidism	Weak recommendation, moderate-quality evidence
	American Thyroid Association (2016)[10]	If the etiology is not apparent: Measurement of TRAbs Determination of radioactive iodine uptake Measurement of thyroid blood flow on ultrasonography ^{123}I or ^{99m}Tc pertechnetate scan when the clinical presentation suggests a toxic adenoma or toxic multinodular goiter	Strong recommendation, moderate-quality evidence
	Indonesian Society of Endocrinology (2012)[82]	Thyroid scan if there is presence of thyroid nodularity	Not specified

8. Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?	2022 European Thyroid Association Guideline for the management of pediatric Graves' disease[9]	Young patients with a thyroid nodule/s should be evaluated by thyroid ultrasound and proceed to cytological evaluation if indicated from the sonographic findings or undergo total thyroidectomy.	Weak Recommendation, Low Quality of Evidence
9. Should beta-blockers be used as an adjunct for individuals with thyrotoxicosis?	2016 American Thyroid Association (ATA)[10]	Beta-adrenergic blockade is recommended in all patients with symptomatic thyrotoxicosis, especially elderly patients and thyrotoxic patients with resting heart rates in excess of 90 beats per minute or coexistent cardiovascular disease. Beta-adrenergic blockade is recommended for children experiencing symptoms of hyperthyroidism,	Strong recommendation, moderate-quality evidence Strong recommendation, low-quality evidence
	2016 Japan Thyroid Association [11]	Beta 1-adrenergic receptor antagonists (beta-AAs) (landiolol, esmolol (intravenous), or bisoprolol (oral)) should be selected as the first choice of treatment for tachycardia in thyroid storm. Other beta1-selective oral drugs are also recommended.	"High" strength recommendation, low-quality evidence
	2017 Guidelines of the American Thyroid Association for the	The appropriate management of abnormal maternal thyroid	Strong recommendation, moderate-quality evidence

	Diagnosis and Management of Thyroid Disease during Pregnancy and the Postpartum[12]	tests attributable to gestational transient thyrotoxicosis and/or hyperemesis gravidarum includes supportive therapy, management of dehydration, and hospitalization if needed. ATDs are not recommended, though beta-blockers may be considered.	
	2022 European Thyroid Association Guideline for the management of pediatric Graves' disease[13]	Beta-adrenergic blockade is recommended in patients presenting with marked signs of thyroid hormone excess.	Strong recommendation, moderate certainty of evidence
	NICE guidelines Guidance on thyroid disease: assessment and management (NG145)[15]	For initial treatment in primary/non-specialist care: Be aware that transient thyrotoxicosis without hyperthyroidism usually only needs supportive treatment (for example, beta-blockers).	Ungraded
	Guidelines for the treatment of childhood-onset Graves' disease in Japan, 2016[16]	For a patient with severe symptoms of thyrotoxicosis, use a β-blocker concurrently.	Consensus
	2018 Scottish Paediatric Endocrine Group Clinical Guideline on the medical management of children with thyrotoxicosis[17]	Propranolol or other beta-blockers can be used to give relief from symptoms such as anxiety, tremor and palpitations in the first few weeks of treatment.	Ungraded
10. Should we give methimazole/ carbimazole as first-line therapy instead of	Malaysia Endocrine and Metabolic Society[11]	MMZ/CBZ is the preferred agent in all patients who choose ATD therapy for GD	SOR - Weak COE - Low

propylthiouracil among individuals with hyperthyroidism?			
	European Thyroid Association [12,13]	MMZ/CBZ should be used in every non-pregnant patient who chooses ATD therapy for Graves' hyperthyroidism.	SOR - Strong COE - High
		Either CBZ or its active metabolite MMZ should be used in young people with GD. Propylthiouracil should not be used.	SOR - Strong COE - High
	American Thyroid Association [14,15]	MMZ should be used in virtually every patient who chooses ATD therapy for GD, except during the first trimester of pregnancy when PTU is preferred, in the treatment of thyroid storm, and in patients with minor reactions to MMZ who refuse RAI therapy or surgery.	SOR - Strong COE - Moderate
		For pregnant women, ATDs should be avoided in the first trimester of pregnancy, but when necessary PTU is generally favored.	SOR - Strong COE - Moderate
		Consideration can be given to discontinuing PTU after the first trimester and switching to MMZ to decrease the risk of liver failure in the mother.	No recommendation; insufficient evidence to assess benefits and risks.
11. Should we give long-duration instead of short-duration ATD treatment among individuals with Graves' hyperthyroidism?	American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis[10]	If MMZ is chosen as the primary therapy for GD, the medication should be continued for approximately 12–18 months, then discontinued if the TSH and	Strong recommendation, high-quality evidence

		TRAb levels are normal at that time.	
	European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism[8]	MMZ is administered for 12–18 months then discontinued if the TSH and TRAb levels are normal.	Strong recommendation, high-quality evidence
	European Thyroid Association Guideline for the Management of Pediatric Graves' Hyperthyroidism[9]	ATD is normally administered for at least 3 years and only stopped when TRAb levels have been low for several months. Longer courses of ATD (≥5 years) should be considered if the likelihood of remission is low on the basis of disease characteristics at presentation (1,ØØØO). The overall remission rate after ATD treatment in pediatric GD patients is between 20 and 30% after 2 years of ATD treatment and may increase with continuous ATD duration (1,ØØØØ).	Strong recommendation, moderate-quality evidence Strong recommendation, high-quality evidence
12. Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?	ADULTS		
	MEMS 2019 (Malaysia)[7]	Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: ATDs, RAI therapy, or thyroidectomy. The choice between ATD maintenance and RAI depends on several factors like comorbidities, pregnancy, contraindications to ATD, age, and presence of severe GO.	Did not use GRADE

	ETA 2018 (Europe)[8]	Patients with newly diagnosed Graves' hyperthyroidism should be treated with ATD. RAI therapy or thyroidectomy may be considered in patients who prefer this approach. There are no absolute indications for RAI therapy, but it is often recommended for patients with side effects to or recurrence after a course of ATD.	Strong recommendation, high-quality of evidence
	ATA 2016 (US)[10]	Patients with overt Graves' hyperthyroidism should be treated with any of the following modalities: RAI therapy, ATDs, or thyroidectomy. Patients choosing RAI therapy as treatment for GD would likely place relatively higher value on definitive control of hyperthyroidism, the avoidance of surgery, and the potential side effects of ATDs, as well as a relatively lower value on the need for lifelong thyroid hormone replacement, rapid resolution of hyperthyroidism, and potential worsening or development of GO. Patients choosing ATD as treatment for GD would place relatively higher value on the possibility of remission and the	Strong recommendation, moderate-quality of evidence

		avoidance of lifelong thyroid hormone treatment, the avoidance of surgery, and exposure to radioactivity and a relatively lower value on the avoidance of ATD side effects, and the possibility of disease recurrence.	
	KTA (2013) Korea[43]	The initial treatment options are ATD, RAI, or thyroidectomy The most preferred treatment modality is ATD. RAI is an option but is given more when there is recurrence after initial ATD treatment.	Not indicated
	CHILDREN		
	ETA 2022 (Europe)[44]	Either carbimazole (CBZ) or its active metabolite methimazole (MMZ) should be used in young people with GD. Propylthiouracil should not be used. RAI should be avoided in patients younger than 5 years and only used in the age group 5-10 years when surgery is not a realistic option. There is no contraindication to RAI use in patients older than 10 years/post-pubertal children.	Strong recommendation, high-quality of evidence Strong recommendation, moderate-quality of evidence
	JSPE 2016 (Japan)[45]	ATD is the primary treatment option.	Consensus

		I-131 is generally contraindicated in children 5 years or younger.	Strong recommendation, moderate-quality of evidence
	ATA 2016 (US)[10]	Children with GD should be treated with MMZ, RAI therapy, or thyroidectomy. RAI therapy should be avoided in very young children (<5 years).	Strong recommendation, moderate-quality of evidence
13. Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?	ADULTS		
	2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and other Causes of Thyrotoxicosis[167]	Recommendation on choice for therapy depends on the clinical situations that favor a particular modality.	Weak Recommendation, Low Quality Evidence
	2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism[8]	RAI therapy or thyroidectomy may be considered in patients who prefer this approach. Older patients who have had atrial fibrillation, cardiac failure, or cardiac ischemic symptoms precipitated by hyperthyroidism should undergo definitive therapy, usually RAI	Strong Recommendation, High Quality Evidence
	CHILDREN		
	2018 European Thyroid Association Guideline for the Management of Graves' Hyperthyroidism[8]	Thyroidectomy is the primary definitive therapy in childhood, but in post-pubertal children RAI can be considered.	Weak Recommendation, Low Quality Evidence
	2022 European Thyroid Association Guideline for the	RAI should be avoided in patients younger than 5 years and only	Strong Recommendation, Low Quality Evidence

	management of Pediatric Graves' disease[44]	used in the age group 5–10 years when surgery is not a realistic option. There is no contraindication to RAI use in patients older than 10 years/post-pubertal children	
14. Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?	European Group on Graves' Orbitopathy (EUGOGO) 2021[16]	Mild GO should be treated with local treatments and general measures to control risk factors; a 6-month selenium supplementation should be given to patients with mild and active GO of recent onset, because it improves eye manifestations and QoL and usually prevents GO progression to more severe forms.	Strong Recommendation, Moderate Quality of Evidence
	European Thyroid Association 2018[24]	No recommendation on selenium but mentioned that "a 6-month selenium supplementation improves mild and active GO and prevents its progression to more severe forms."	N/A
15. Should we routinely treat non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism?			

COI Declarations

Names:	Organization	Decisions	Management
Dr. Ma. Victoria Valmonte-Torres	Philippine Obstetrical and Gynecological Society (POGS)	B	May participate in the entire CPG development process but must declare COI
Ms. Marimel Lamsin	Philippine Alliance of Patient Organizations (PAPO)	B	May participate in the entire CPG development process but must declare COI
Dr. Nestor Eric R. Laplano	Philippine College of Endocrinology, Diabetes and Metabolism, Inc. (PCEDM)	B	May participate in the entire CPG development process but must declare COI

Names:	Decisions	Management
Dr. Pepito E. De la Peña	A	
Dr. Elaine C. Cunanan	B	Declare previous publications related to the CPG topic
Dr. Lora May T. Tin Hay	A	
Dr. Cecille R. dela Paz	B (Owns no more than 0.1% of the total stocks of the hospital)	Declare indirect financial COI
Dr. Sjoberg A. Kho	B	Declare previous publications related to the CPG topic
Dr. Nemencio A. Nicodemus Jr.	A	
Dr. Eve G. Fernandez	A	
Dr. Jedeane M. Aragon	A	

Names:	Decisions	Management
Dr. Anna Angelica Macalalad-Josue – ERE	B	May participate in the entire CPG development process but must declare COI
Dr. Antonio Faltado – ERE	D (Financial COI - Owns a health facility)	COIC suggest to transfer her to another Task Force with no conflict.
Dr. Sahra Mae Paragas – ERE	D (Financial COI - Advisory committee associated with a public or private sector organization – Consultancy	Disapproved for specific questions (therapeutics); may participate and review diagnostic review questions
Mr. Howell Bayona – ERE	A	
Dr. Hannah Urbanozo-Corpuz – ERE	A	

Dr. Juan Maria Ibarra O. Co	Philippine College of Physicians (PCP)	B	May participate in the entire CPG development process but must declare COI
Dr. Ryan Jeanne Ceralvo	Philippine Academy of Family Physicians (PAFP)	B	May participate in the entire CPG development process but must declare COI
Dr. Carmela Rosanne A. Remotigue	Philippine Society OF General Internal Medicine Incorporated (PSGIM)	A	
Dr. Rommel Punongbayan	Philippine College of Occupational Medicine (PCOM)	B	May participate in the entire CPG development process but must declare COI
Dr. Cynthia Feliciano	Philippine Pediatric Society (PPS)	A	
Dr. Lorna Abad	Philippine Society of Pediatric Metabolism and Endocrinology (PSPME)	B	May participate in the entire CPG development process but must declare COI
Dr. Emerita A. Barrenechea	Philippine Society of Nuclear Medicine (PSNM)	B	May participate in the entire CPG development process but must declare COI
Dr. Conrado Donato Pabico Jr.	Philippine Society Of Otolaryngology Head And Neck Surgery (PSO-HNS)	B	May participate in the entire CPG development process but must declare COI
Dr. Ida Marie T. Lim	Philippine Society of General Surgery (PSGS)	B	May participate in the entire CPG development process but must declare COI
Dr. Mark Anthony Imperial	Philippine Academy of Ophthalmology (PAO)	D	Disqualified for Diagnostics and Screening Questions, May participate for Therapy Questions but must declare COI

Dr. Erick Mendoza - ERE	B	May participate in the entire CPG development process but must declare COI
Dr. Daveric Pagsisihan – ERE	B	May participate in the entire CPG development process but must declare COI
Dr. Aivind Gabrielle Santiago – ERE	A	
Dr. Carmen Carina Cabrera – ERE	A	
Dr. Ma. Theresa Collante – ERE	B	May participate in the entire CPG development process but must declare COI
Dr. Kathryn Baltazar-Braganza – ERE	B	May participate in the entire CPG development process but must declare COI
Dr. Emilio Q. Villanueva III – ERE	D	Disapproved for specific questions (screening/diagnostic questions); may participate and review therapeutic questions
Ms. Myzelle Infantado – ERE	A	
Mr. Kerwyn Jim C. Chan – ERE	A	
Dr. Aldrich Ivan Lois D. Burog – Technical Coordinator	A	
Princess Gapuen-Ching – CPG Admin Officer	A	
Ms. Kate Dunlao – Technical Writer	A	
Dr. Mia Fojas External – Reviewer	A	
Dr. Roy Raoul Felipe - External Reviewer	B	May participate in the entire CPG development process but must declare COI
Dr. Gina Santiago Eubanas - External Reviewer	B	May participate in the entire CPG development process but must declare COI
Dr. Carol Tan-Lim CPG Moderator/Technical Facilitator	A	

Name of Reviewer: Mia Fojas

General Response (to the guideline as a whole):
Acceptable and implementable

Contents

Clinical Question No. 1 Should we give methimazole (MMZ)/carbimazole (CBZ) as first-line therapy instead of PTU among individuals with hyperthyroidism??

Recommendation No. 1A	
Among non-pregnant adults with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as an initial treatment *(Moderate certainty of evidence; Strong recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? (**YOU CAN FIND THE SEARCH STRATEGY IN THE APPENDIX**) 2. Synthesis and analysis of evidence base? **(You can refer to the main body of the manuscript that details the evidence review – benefits, harm, outcomes, and other considerations)**	1. *Adequate* 2. *Adequate*
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. The recommendation provided adequate evidence for the use or MMI / CBZ as first line therapy among individuals with hyperthyroidism. Perhaps mention "non-emergency" as some might misinterpret thyroid storm as a simple hyperthyroid state.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Acceptable.
Any comments on the "implementability" of this recommendation?	Implementable

Recommendation No. 1B	
Among children and non-pregnant adolescents' with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as initial treatment. In case methimazole is not available, we recommend the use of carbimazole (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable, despite low certainty of evidence, given currently available antithyroid medications.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Acceptable
Any comments on the "implementability" of this recommendation?	Implementable and practical.

Recommendation No. 1C	
Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of propylthiouracil during the first trimester, due to the higher risk of congenital malformation with methimazole/carbimazole. (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable, given only the currently available literature.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Acceptable
Any comments on the "implementability" of this recommendation?	Implementable and realistic.

Recommendation No. 1D	
Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of methimazole during the second and third trimester due to the lower risk of maternal liver impairment with methimazole. (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable recommendation in the light of currently available and limited literature
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree with the benefits and harms stated
Any comments on the "implementability" of this recommendation?	Implementable, no change in current practice.

Recommendation No. 1E	
Among women with Graves' hyperthyroidism requiring antithyroid therapy who are planning pregnancy, we suggest switching of methimazole/carbimazole to propylthiouracil due to the higher risk of congenital malformation with methimazole/carbimazole. (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable, despite thorough search for evidence, there is a need for more research in this aspect. Should we even have entertained this question?
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree that this should be a weak recommendation
Any comments on the "implementability" of this recommendation?	Acceptable as a Weak recommendation.

Clinical Question No. 2 Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?

Recommendation No. 2	
Among patients with mild* and active* Graves' orbitopathy, we suggest selenium supplementation for six months to improve clinical outcomes (i.e., clinical activity score, overall eye evaluation improvement, and improvement in quality of life) (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Given the current evidence, this is a good statement. The table though shows more moderate certainty of evidence and not low.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Adequate
Any comments on the "implementability" of this recommendation?	Implementable.

Clinical Question No. 3 Should beta-blockers be used as an adjunct for individuals with thyrotoxicosis?

Recommendation No. 3A	
Among non-pregnant adults with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	*** page 37 shows ongoing research and decision making on selenium in GO and not beta blockers ** Justified recommendation
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Gives more light in the manner of choosing beta blockers
Any comments on the “implementability” of this recommendation?	Very practical

Recommendation No. 3B	
Among children with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors. (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Justified, given currently available literature.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Acceptable
Any comments on the “implementability” of this recommendation?	Agree with the recommendation.

Clinical Question No. 4 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

Recommendation No. 4A	
Among non-pregnant adults with Graves' disease, we recommend antithyroid drug as first-line treatment (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	I think this statement is a redundancy and already answered in CQ 1. This will just confuse readers further.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	Among non-pregnant …… we recommend giving ATD's first prior to consideration of other interventions, such as RAI or surgery.
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	Asked and answered.

Recommendation No. 4B	
Among children with Graves' disease, we recommend antithyroid drug as first-line treatment (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 3. search of evidence? 4. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	Among children….. we recommend giving ATD's first prior to consideration of other interventions, such as RAI or surgery.
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	N/A

Clinical Question No. 5 Should we give long-duration instead of short-duration ATD treatment among individuals with Graves' disease?

Recommendation No. 5A	
Among non-pregnant adults with Graves' hyperthyroidism on ATD as first-line therapy, we suggest maintaining* antithyroid drug for at least 18 months (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Agree with Weak recommendation. Not enough long term data
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree with the rationale
Any comments on the "implementability" of this recommendation?	Implementable and useful as a guide.

Recommendation No. 5B	
Among children with Graves' disease, we suggest maintaining antithyroid drug for at least 24 months* (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable, given the very low certainty of evidence.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable, enlightens physicians regarding endpoints.

Clinical Question No. 6 Should we routinely treat non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism?

Recommendation No. 6A	
Among adult patients with persistent biochemically confirmed subclinical hyperthyroidism ≥ 65 years and serum TSH levels <0.1 mIU/L, we suggest routine treatment (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable as weak recommendaation
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	How about “we suggest routine treatment with ATD’s” perhaps add…. pending further tests determining the cause of subclinical hyperthyroidism
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the “implementability” of this recommendation?	Blurry

Recommendation No. 6B	
Among adult patients with subclinical hyperthyroidism ≥ 65 years and serum TSH levels greater than or equal to 0.1 mIU/L, we suggest against routine treatment* due to insufficient evidence (Very low** certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the “implementability” of this recommendation?	Implementable

Recommendation No. 6C	
Among adult non-pregnant patients with subclinical hyperthyroidism who are <65 years, we suggest against routine treatment* due to insufficient evidence (Very low** certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the “implementability” of this recommendation?	Implementable

Recommendation No. 6D	
Among children with subclinical hyperthyroidism, we suggest against routine treatment* (i.e., ATD, RAI, surgery, etc) due to insufficient evidence (Very low** certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes, acceptable
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the “implementability” of this recommendation?	Implementable

Clinical Question No. 7 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves' disease versus thyrotoxic phase of subacute thyroiditis?

Recommendation No. 7A	
Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we recommend using 99m technetium pertechnetate thyroid uptake (cutoff value: >1.00%) in differentiating Graves' disease versus subacute (painless) thyroiditis (Moderate certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Agree
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable

Recommendation No. 7B	
Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest against the use of radioactive iodine uptake (I-131) (RAIU) in differentiating Graves' disease versus subacute (painless) thyroiditis due to insufficient evidence (No evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Agree, since there is no literature to back this one up. Risky and may push the patient further into storm.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable and perhaps Stress on "against the use of"

Clinical Question No. 8 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves' disease versus thyrotoxic phase of subacute thyroiditis?

Recommendation No. 8	
Among non-pregnant adults with biochemically confirmed thyrotoxicosis, we suggest against routine use of 99m technetium pertechnetate thyroid uptake (cutoff value: >0.40%) in differentiating Graves' disease from thyrotoxic phase of subacute thyroiditis (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable and doing 99Tcm for such patients will be non-justifiable at this point.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable and easy.

Clinical Question No. 9 Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?

Recommendation No. 9A	
Among adult patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. More definitive than 99Tcm
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable despite being a poorly available test in the Philippines

Recommendation No. 9B	
Among pediatric patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes, agree. Similar to adults. This will be more practical and avoids unnecessarily exposing the child to radioation for diagnostic purposes.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable

Clinical Question No. 10 Should we do routine paired testing (T_4/T_4 plus TSH) versus TSH testing alone as initial evaluation of thyroid function among patients with suspected thyrotoxicosis?

Recommendation No. 10A	
Among patients with suspected thyrotoxicosis*, we recommend the routine use of TSH for initial evaluation (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree with the rationale. Budget is important for our patients
Any comments on the “implementability” of this recommendation?	Implementable.

Recommendation No. 10B	
Among patients with suspected thyrotoxicosis, we suggest against routine paired fT4/T4-TSH testing as initial evaluation/work up due to no evidence (No evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Weak recommendation
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Cost in tables are different in pages 65 and 79.
Any comments on the “implementability” of this recommendation?	Implementable

Clinical Question No. 11 Should we routinely do T3 testing on top of TSH and T4/fT4 testing in the workup of individuals suspected to have thyrotoxicosis?

Recommendation No. 11	
Among patients suspected of having thyrotoxicosis, we suggest against routine combined T3 + TSH + T4/TF4 testing as initial evaluation *(Very low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adquate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable for those who are on a budget
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree with the weak recommendation. More research needed as this type of recommendation might lead to underdiagnosis.
Any comments on the “implementability” of this recommendation?	Implementable. Physicians, however, will need to be trained further for better “clinical eyes”

Clinical Question No. 12 Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?

Recommendation No. 12	
Among patients with biochemically confirmed thyrotoxicosis and thyroid nodules, we suggest against the routine performance of a thyroid scan to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter) (No evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	The consensus mentioned "The primary reason for this caution lies on the waiting for results…" Among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules, we suggest prioritizing treatment without delays due to diagnostic exams such as thyroid scan.
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	The rationale was clear. The statement is not.
Any comments on the "implementability" of this recommendation?	Implementable

Clinical Question No. 13 Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?

Recommendation No. 13A	
Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest doing total thyroidectomy instead of RAI if a *high volume thyroid surgeon is available *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Agree on this weak recommendation. Stressing on the (in)availability of either endpoints.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable

Recommendation No. 13B	
Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest giving RAI if a high-volume thyroid surgeon is not available *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Agree on this
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the "implementability" of this recommendation?	Implementable

Recommendation No. 13C	
Among pediatric patients with hyperthyroidism who are refractory to medical management, we suggest thyroidectomy as the treatment of choice for definitive therapy in children with access to *high volume thyroid surgeons. *(Low certainty of evidence; Weak recommendation)* **more than 30 thyroidectomies per year*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Acceptable given the low certainty of evidence
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree
Any comments on the “implementability” of this recommendation?	Implementable

Clinical Question No. 14 Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?

Recommendation No. 14	
Among hyperthyroid individuals with no palpable nodules, we suggest against routine screening for nodules using thyroid ultrasound to screen due to low incidence of concomitant malignancy *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Acceptable.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree with mentioning the risk of this test in hyperthyroid individuals.
Any comments on the “implementability” of this recommendation?	Implementable

Clinical Question No. 15 Should we use history and PE findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves' disease (GD) versus non-Graves' disease (i.e., other etiology) among non-pregnant patients with biochemically confirmed hyperthyroidism?

Recommendation No. 15	
Among non-pregnant patients with biochemically confirmed hyperthyroidism, we suggest against history and physical examination (PE) findings alone to differentiate between Graves' disease (GD) versus non-Graves' disease due to harms of unnecessary treatment *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	1. Adequate 2. Adequate
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Highly acceptable due to the risks of misdiagnosis and mistreatment
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Agree with mentioning the costs. Is there evidence for cost due to "misdiagnosis"?
Any comments on the "implementability" of this recommendation?	Implementable

Name of Reviewer: Roy Raoul H. Felipe

General Response (to the guideline as a whole):

Contents

Clinical Question No. 1 Should we give methimazole (MMZ)/carbimazole (CBZ) as first-line therapy instead of PTU among individuals with hyperthyroidism??

Recommendation No. 1A	
Among non-pregnant adults with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as an initial treatment *(Moderate certainty of evidence; Strong recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although some recommendations are solidly based on low quality evidence, this one has moderate evidence. strong recommendations stem similar international guidelines.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Methimazole in the Philippines has the perfect combination of being widely available and low cost.
Any comments on the "implementability" of this recommendation?	Very much applicable and already being implemented in the Philippines.

Recommendation No. 1B	
Among children and non-pregnant adolescents' with Graves' hyperthyroidism who require antithyroid therapy, we recommend the use of methimazole as initial treatment. In case methimazole is not available, we recommend the use of carbimazole (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although insufficient evidence in children/adolescents, recommendations stem from similar international guidelines.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Recommendations is erring on the side of safety and lesser evil – since methimazole/carbimazole has better safety profile than PTU in general.
Any comments on the "implementability" of this recommendation?	Applicable and already being implemented in the Philippines.

Recommendation No. 1C	
Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of propylthiouracil during the first trimester, due to the higher risk of congenital malformation with methimazole/carbimazole. (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although insufficient evidence in pregnant, recommendations stem from similar international guidelines. Safety of fetus is prioritized.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Recommendations is erring on the side of safety and lesser evil – since methimazole/carbimazole has better safety profile than PTU in general. PTU for 1st trimester and methimazole for 2nd and 3rd.
Any comments on the "implementability" of this recommendation?	Applicable and already being implemented in the Philippines.

Recommendation No. 1D	
Among adult pregnant patients with Graves' hyperthyroidism requiring antithyroid therapy, we recommend the use of methimazole during the second and third trimester due to the lower risk of maternal liver impairment with methimazole. (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although insufficient evidence in children/adolescents, recommendations stem from similar international guidelines.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Recommendations is erring on the side of safety and lesser evil – since methimazole/carbimazole has better safety profile than PTU in general. And the findings of PTU are generally associated with 1st trimester.
Any comments on the "implementability" of this recommendation?	Applicable and already being implemented in the Philippines.

Recommendation No. 1E	
Among women with Graves' hyperthyroidism requiring antithyroid therapy who are planning pregnancy, we suggest switching of methimazole/carbimazole to propylthiouracil due to the higher risk of congenital malformation with methimazole/carbimazole. (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although insufficient evidence in pregnant, recommendations stem from similar international guidelines. Safety of fetus is prioritized.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Recommendations is erring on the side of safety and lesser evil – since methimazole/carbimazole has better safety profile than PTU in general. PTU for 1st trimester and methimazole for 2nd and 3rd.
Any comments on the "implementability" of this recommendation?	Applicable and already being implemented in the Philippines.

Clinical Question No. 2 Should patients with Graves' disease and mild Graves' ophthalmopathy (GO) be treated with selenium supplementation?

Recommendation No. 2	
Among patients with mild* and active* Graves' orbitopathy, we suggest selenium supplementation for six months to improve clinical outcomes (i.e., clinical activity score, overall eye evaluation improvement, and improvement in quality of life) (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Multiple RCT's but with very few population, all pointing to beneficial effect of selenium. Agree with low certainty of of evidence and weak recommendation
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	As above (see comment/feedback on recommendation.
Any comments on the "implementability" of this recommendation?	Low cost, low risk, potentially good benefit – in the Philippine setting.

Clinical Question No. 3 Should beta-blockers be used as an adjunct for individuals with thyrotoxicosis?

Recommendation No. 3A	
Among non-pregnant adults with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Very few RCTs available.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Strong recommendations from international guidelines, though with moderate to low evidence. Risk Benefit ratio errs on the side of high benefit, low risk.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Beta blockers in the Philippines has the perfect combination of being widely available and low cost.
Any comments on the “implementability” of this recommendation?	Very much applicable and already being implemented in the Philippines.

Recommendation No. 3B	
Among children with thyrotoxicosis, we recommend the use of beta-blockers* (i.e., atenolol, metoprolol, propranolol) for symptomatic treatment of tachycardia, palpitations, and tremors. (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Very few RCTs available.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Strong recommendations from international guidelines, though with moderate to low evidence. Risk Benefit ratio errs on the side of high benefit, low risk.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Beta blockers in the Philippines has the perfect combination of being widely available and low cost.
Any comments on the “implementability” of this recommendation?	Very much applicable and already being implemented in the Philippines.

Clinical Question No. 4 Should we give radioactive iodine (RAI) instead of ATD maintenance among nonpregnant individuals with Graves' hyperthyroidism?

Recommendation No. 4A	
Among non-pregnant adults with Graves' disease, we recommend antithyroid drug as first-line treatment (Low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Low power RCTs available.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Strong recommendations from international guidelines, though with moderate to low evidence. Risk Benefit ratio errs on the side of high benefit, low risk. Especially given cost of ATDs (minimal). Trend of international guidelines moving towards ATDs rather that RAI as first line.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	Practice depends on experience of physicians and also patient characteristics but in general ATDs has been first line in the Philippines already.

Recommendation No. 4B	
Among children with Graves' disease, we recommend antithyroid drug as first-line treatment (Very low certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 3. search of evidence? 4. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Few RCTs available.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Strong recommendations from international guidelines, and already being followed by Philippine practice.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	Applicable in the Philippines and easy to follow.

Clinical Question No. 5 Should we give long-duration instead of short-duration ATD treatment among individuals with Graves' disease?

Recommendation No. 5A	
Among non-pregnant adults with Graves' hyperthyroidism on ATD as first-line therapy, we suggest maintaining* antithyroid drug for at least 18 months (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. 1 RCT available, with low evidence.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	According to most guidelines, experience of international physicians, and as well as our own, and consistent with the few exisiting RTCs, recommendation is very much acceptable.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	

Any comments on the “implementability” of this recommendation?	Applicable and need to emphasize to physicians (GP, IM, FM) it is a case to case basis and not a blanket recommendation to keep all patients on ATDs for 18 months.

Recommendation No. 5B	
Among children with Graves’ disease, we suggest maintaining antithyroid drug for at least 24 months* (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. 1 RCT available, with low evidence.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	According to most guidelines, experience of international physicians, and as well as our own, and consistent with the few exisiting RTCs, recommendation is very much acceptable.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	

Any comments on the “implementability” of this recommendation?	Applicable and need to emphasize to physicians (GP, IM, FM) it is a case to case basis and not a blanket recommendation to keep all patients on ATDs for 24 months.

Clinical Question No. 6 Should we routinely treat non-pregnant adults and children with biochemically confirmed subclinical hyperthyroidism?

Recommendation No. 6A	
Among adult patients with persistent biochemically confirmed subclinical hyperthyroidism ≥ 65 years and serum TSH levels <0.1 mIU/L, we suggest routine treatment (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Multiple RCTs and observational studies obtained
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although some recommendations are solidly based on low quality evidence, but multiple RCTs and all guidelines concur.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	

Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Considering benefit vs. harm, the recommendation is pretty clear on who to consider treating and what risk factors to look for, as well as the consequence of treating vs. no treatment.
Any comments on the “implementability” of this recommendation?	

Recommendation No. 6B	
Among adult patients with subclinical hyperthyroidism ≥ 65 years and serum TSH levels greater than or equal to 0.1 mIU/L, we suggest against routine treatment* due to insufficient evidence (Very low** certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Multiple RCTs and observational studies obtained.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although some recommendations are solidly based on low quality evidence, but multiple RCTs and all guidelines concur.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	

Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Considering benefit vs. harm, the recommendation is pretty clear on the benefit of not treating these patients.
Any comments on the “implementability” of this recommendation?	

Recommendation No. 6C	
Among adult non-pregnant patients with subclinical hyperthyroidism who are <65 years, we suggest against routine treatment* due to insufficient evidence (Very low** certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Multiple RCTs and observational studies obtained.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although some recommendations are solidly based on low quality evidence, but multiple RCTs and all guidelines concur.

What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Considering benefit vs. harm, the recommendation is pretty clear on the benefit of not treating these patients.
Any comments on the “implementability” of this recommendation?	

Recommendation No. 6D	
Among children with subclinical hyperthyroidism, we suggest against routine treatment* (i.e., ATD, RAI, surgery, etc) due to insufficient evidence (Very low** certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines. Complete and concise.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Multiple RCTs and observational studies obtained.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Although some recommendations are solidly based on low quality evidence, but multiple RCTs and all guidelines concur.

What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Considering benefit vs. harm, the recommendation is pretty clear on the benefit of not treating these patients.
Any comments on the “implementability” of this recommendation?	

Clinical Question No. 7 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among non-pregnant adult patients with biochemically confirmed thyrotoxicosis to differentiate Graves’ disease versus thyrotoxic phase of subacute thyroiditis?

Recommendation No. 7A	
Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we recommend using 99m technetium pertechnetate thyroid uptake (cutoff value: >1.00%) in differentiating Graves’ disease versus subacute (painless) thyroiditis (Moderate certainty of evidence; Strong recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Few RCTs mentioned.

Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Given cost and benefit of using technetium, and the potential disaster of mistakenly treating a thyroiditis patient with ATD. Also given whith what is available in the Philippines, the cost and the burden of using Technetium vs. 131, recommendation is acceptable.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Considering benefit vs. harm, the recommendation is pretty clear on the benefit of using this diagnostic tool.
Any comments on the “implementability” of this recommendation?	

Recommendation No. 7B	
Among non-pregnant adults with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest against the use of radioactive iodine uptake (I-131) (RAIU) in differentiating Graves’ disease versus subacute (painless) thyroiditis due to insufficient evidence (No evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across asia. Few RCTs mentioned.

Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Given cost and benefit of using technetium, and the potential disaster of mistakenly treating a thyroiditis patient with ATD.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Yes. Given cost and benefit of using technetium, and the potential disaster of mistakenly treating a thyroiditis patient with ATD. Also given whith what is available in the Philippines, the cost and the burden of using Technetium vs. 131, recommendation is acceptable.
Any comments on the “implementability” of this recommendation?	

Clinical Question No. 8 Should thyroid uptake (i.e., Technetium 99m pertechnetate or radioactive iodine uptake) be routinely performed among children with biochemically confirmed thyrotoxicosis to differentiate Graves’ disease versus thyrotoxic phase of subacute thyroiditis?

Recommendation No. 8	
Among non-pregnant adults with biochemically confirmed thyrotoxicosis, we suggest against routine use of 99m technetium pertechnetate thyroid uptake (cutoff value: >0.40%) in differentiating Graves’ disease from thyrotoxic phase of subacute thyroiditis (Very low certainty of evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.

What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Few RCT's were noted.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Technetium scanning would be safest in children.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	Applicable and already being implemented in the Philippines.

Clinical Question No. 9 Should thyrotropin receptor antibody (TRAb) test be routinely performed among adult patients with biochemically established thyrotoxicosis to confirm Graves' disease?

Recommendation No. 9A	
Among adult patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves' disease (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:

Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. High yield and relatively low cost, will be aiding the GP IM FM towards treatment and monitoring.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the “implementability” of this recommendation?	Applicable and already being implemented in the Philippines.

Recommendation No. 9B	
Among pediatric patients with biochemically confirmed thyrotoxicosis wherein the etiology is not apparent, we suggest the use of TRAb assay to confirm Graves’ disease (Low certainty of evidence; Weak recommendation)	
	Answer/Remarks:

Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. High yield and relatively low cost, will be aiding the GP IM FM towards treatment and monitoring.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	Applicable and already being implemented in the Philippines.

Clinical Question No. 10 Should we do routine paired testing (T_4/T_4 plus TSH) versus TSH testing alone as initial evaluation of thyroid function among patients with suspected thyrotoxicosis?

Recommendation No. 10A	
Among patients with suspected thyrotoxicosis*, we recommend the routine use of TSH for initial evaluation (Very low certainty of evidence; Strong recommendation)	

	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Though no guidelines explicitly give recommendations or even have strength of recommendations.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Less burden of cost and unscrupulous use of laboratory – we promote judicious and wise decision making in requesting for tests and TSH is enough as a recommendation.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the “implementability” of this recommendation?	Applicable and already being implemented in the Philippines.

Recommendation No. 10B	
Among patients with suspected thyrotoxicosis, we suggest against routine paired fT4/T4-TSH testing as initial evaluation/work up due to no evidence (No evidence; Weak recommendation)	

	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Though no guidelines explicitly give recommendations or even have strength of recommendations.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Less burden of cost and unscrupulous use of laboratory – we promote judicious and wise decision making in requesting for tests and TSH is enough as a recommendation.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the “implementability” of this recommendation?	Applicable and already being implemented in the Philippines.

Clinical Question No. 11 Should we routinely do T3 testing on top of TSH and T4/fT4 testing in the workup of individuals suspected to have thyrotoxicosis?

Recommendation No. 11	
Among patients suspected of having thyrotoxicosis, we suggest against routine combined T3 + TSH + T4/TF4 testing as initial evaluation *(Very low certainty of evidence; Weak recommendation)*	

	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Though no guidelines explicitly give recommendations or even have strength of recommendations.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Yes. Less burden of cost and unscrupulous use of laboratory – we promote judicious and wise decision making in requesting for tests and TSH is enough as a recommendation.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the “implementability” of this recommendation?	Applicable and already being implemented in the Philippines.

Clinical Question No. 12 Should thyroid scan be routinely performed among non-pregnant patients with biochemically confirmed thyrotoxicosis and thyroid nodules to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter)?

Recommendation No. 12	
Among patients with biochemically confirmed thyrotoxicosis and thyroid nodules, we suggest against the routine performance of a thyroid scan to differentiate Graves' disease from toxic nodules (i.e., toxic adenoma, multinodular toxic goiter) (No evidence; Weak recommendation)	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Lack of availability of thyroid scan in areas outside of metro manila, and possible burden of cost added to the patient makes this recommendation justifiable.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the "implementability" of this recommendation?	

Clinical Question No. 13 Should we do thyroidectomy instead of RAI among non-pregnant patients with Graves' disease requiring definitive therapy and have no clear indications for either treatment?

Recommendation No. 13A	
Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest doing total thyroidectomy instead of RAI if a *high volume thyroid surgeon is available *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Though 1st world countries definitely have very different health care access. Multiple obsercvational studies and 1 RCT found.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	The risk of recurrence with RAI, and lack of accessibility of RAI in non-urban settings gives this recommendation its justification.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Total thyroidectomy eliminates recurrence, given a good surgeon will be performing the operation. Cost may be an issue as RAI is cheaper.
Any comments on the "implementability" of this recommendation?	

Recommendation No. 13B	
Among non-pregnant adults with Graves' hyperthyroidism requiring definitive treatment and with no clear indications for either surgery or RAI, we suggest giving RAI if a high-volume thyroid surgeon is not available *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Though 1st world countries definitely have very different health care access. Multiple obsercvational studies and 1 RCT found.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	The risk of recurrence with RAI, and lack of accessibility of RAI in non-urban settings gives this recommendation its justification.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	Total thyroidectomy eliminates recurrence, given a good surgeon will be performing the operation. Cost may be an issue as RAI is cheaper.

Any comments on the “implementability” of this recommendation?	

Recommendation No. 13C	
Among pediatric patients with hyperthyroidism who are refractory to medical management, we suggest thyroidectomy as the treatment of choice for definitive therapy in children with access to *high volume thyroid surgeons. *(Low certainty of evidence; Weak recommendation)* **more than 30 thyroidectomies per year*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe. Though 1st world countries definitely have very different health care access. Multiple obsercvational studies and 1 RCT found.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	RAI not recommended especially in pre-pubertal children due to risks.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	

Any comments on the “implementability” of this recommendation?	

Clinical Question No. 14 Should thyroid ultrasound be routinely performed among individuals with hyperthyroidism to screen for nodules?

Recommendation No. 14	
Among hyperthyroid individuals with no palpable nodules, we suggest against routine screening for nodules using thyroid ultrasound to screen due to low incidence of concomitant malignancy *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	Exhaustive search for evidence and it was tied well to come up with the recommendations as a whole. Involves recommendations and evidence across Asia, America, and Europe.
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	Given prevalence of thyroid nodules especially in Filipinos, thyroid ultrasound has low benefit and will give undue cost to patients with no risk factors and no clinical findings.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	

Any comments on the “implementability” of this recommendation?	

Clinical Question No. 15 Should we use history and PE findings alone (i.e., pretibial myxedema, exophthalmos, thyroid acropachy) to differentiate Graves’ disease (GD) versus non-Graves’ disease (i.e., other etiology) among non-pregnant patients with biochemically confirmed hyperthyroidism?

Recommendation No. 15	
Among non-pregnant patients with biochemically confirmed hyperthyroidism, we suggest against history and physical examination (PE) findings alone to difefrentiate between Graves’ disease (GD) versus non-Graves’ disease due to harms of unnecessary treatment *(Low certainty of evidence; Weak recommendation)*	
	Answer/Remarks:
Comments/feedback on this specific recommendation:	Consistent with international guidelines.
What is the level of completeness in terms of: 1. search of evidence? 2. Synthesis and analysis of evidence base?	
Is the recommendation statement above acceptable? If yes, please provide insight/justification why it is acceptable. If not acceptable, please see below.	High risk for overtreatment and also the wide confidence interval leading to low evidence makes the recommendation applicable.
What would be an alternative recommendation statement you want to suggest to be considered? Please state the recommendation statement.	
Comments on the rationale of the recommendation (i.e., consensus issues/statements discussed; evidence base of the review question that can be found in the manuscript – trade-	

offs between benefit and harm and other considerations like cost, patient preference, availability, feasibility, etc.)	
Any comments on the “implementability” of this recommendation?	