Update of the Philippine Clinical Practice Guidelines on the Diagnosis and Management of Tobacco Use and Nicotine Dependence

2021

Philippine College of Chest Physicians

Department of Health

Philippine General Hospital

COMMIT TO QUIT
NOT TO SHIFT

Update of the Clinical Practice Guidelines on the Diagnosis and Management of Nicotine Dependence 2021

This update is initiated by the Philippine College of Chest Physicians (PCCP) and the Philippine General Hospital – University of the Philippines Manila.

The final recommendations are joint statements of the Philippine College of Chest Physicians, Philippine College of Physicians, Philippine Pediatric Society, Philippine Psychiatric Association, Philippine Academy of Family Physicians, Philippine Pharmacists Association, Inc, Philippine Society of General Internal Medicine, Philippine Nurses Association, and the DOH Quitline.

This was funded by the Department of Health (DOH) and the PCCP.

DISCLAIMER

This clinical practice guidelines (CPG) is intended to serve as an update of the CPG on the diagnosis and treatment of tobacco use which was released in 2017 by the Philippine College of Chest Physicians and Council on Tobacco or Health and Air Pollution. This guideline is intended for use by specialists and primary care providers to guide them in the management of patients. This shall not restrict the specialists and primary care providers in using their clinical judgment and considering patient's values, needs, and preferences while handling individual cases. Specialists, primary care providers, and other relevant stakeholders must exercise sound clinical decision-making and must put into consideration the patients' history, current physical status, preference, and treatment response. The recommendations in this CPG should not be treated as strict rules to base legal action upon. This CPG is not intended to cover the entire diagnosis and management of tobacco use.

The members of this CPG development committee are aware of the limitations of the results and the best available evidence. The evidence summaries are based on the best available scientific evidence at the time of its formulation, hence, some aspects may not be covered in this CPG.

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EXECUTIVE SUMMARY

This CPG update of year 2021 was intended to address the current issues on the (1) pharmacologic and non-pharmacologic interventions for nicotine dependence, (2) effective intensive interventions in resource-limited settings, (3) nicotine dependence and the use of electronic nicotine delivery system (ENDS) products, and (4) effective smoking cessation & nicotine dependence strategies in the current COVID-19 pandemic setting. This is intended to supplement the prior CPG in 2017 to further guide specialists and primary care providers in the management of patients with smoking and nicotine dependence problems. Continuous smoking abstinence, which refers to non-use of combustible tobacco product over a period of 6 months, was used as the main outcome measure along with associated adverse events.

The "Grading of Recommendations, Assessment, Development, and Evaluation or GRADE Approach" and the "2018 DOH Manual for Clinical Practice Guideline Development" were used as guides for the entire development process. The approach included (1) identification of critical research questions in PICO format (population, intervention, comparison, and outcome), (2) retrieval, appraisal, and synthesis of evidence, (3) formulation of draft recommendations, (4) formulation of final recommendations using the evidence to decision framework and, (5) planning for dissemination, implementation, impact monitoring, and updating.

Recommendations are presented with the certainty of evidence (CoE) (high, moderate, low, very low) and the strength of recommendation (SOR) (strong, weak, none). Evidence with high certainty is well established and will unlikely be changed by new research findings. Strong recommendations are those which are supported by evidence with high certainty or those which the guideline development group believes will clearly benefit or harm the target population. In contrast, a weak recommendation means that the intervention is suggested and shared decision making would be necessary prior to its uptake. The absence of SOR indicates insufficient evidence to recommend for or against a particular intervention. Further clarifications of the recommendations is explained under Consensus Issues.

Table 1 shows the summary of recommendations addressing the specific questions which arose from the issues mentioned above.

Table 1. Summary of Recommendations for the Priority Clinical Questions on the diagnosis and management of tobacco use and nicotine dependence.

	Clinical Question	Recommendation	CoE	SOR
1	Among adult and adolescent smokers, should we use smoking biomarkers in determining smoking status during smoking cessation?	Among adult and adolescent smokers, there is insufficient evidence to recommend the use of smoking biological markers (exhaled carbon monoxide and salivary, blood, and urinary cotinine)	Very low	None

		in determining smoking status during smoking cessation		
2	Among adult and adolescent smokers, should we use intensive behavioral therapies over brief interventions in facilitating continuous smoking abstinence?	Among adult and adolescent smokers, we suggest the use of intensive behavioral therapies over brief interventions in facilitating continuous smoking abstinence	Low	Weak
3	Among adult and adolescent smokers who are ready to quit, is group therapy more effective than individual therapy in facilitating continuous smoking abstinence?	Among adult and adolescent smokers, we suggest the use of either group or individual therapy in facilitating continuous smoking abstinence	Low	Weak
4	Among adult and adolescent smokers, can behavioral therapy delivered remotely be used as an alternative to face-to-face in facilitating continuous smoking abstinence?	Among adult and adolescent smokers, there is insufficient evidence to recommend remotely-delivered behavioral therapy as an alternative to face-to-face counseling in facilitating continuous smoking abstinence	Very low	None
5	Among adult smokers, should we use pharmacologic therapy over no pharmacologic therapy in facilitating continuous smoking abstinence and minimizing adverse events?	Among adult smokers, we suggest the use of pharmacologic over no pharmacologic therapy in facilitating continuous smoking abstinence and in minimizing adverse events	Low	Weak
6	Among adult smokers, should we use combination pharmacologic therapies over single pharmacologic therapy, in facilitating smoking abstinence and in minimizing adverse events?	Among adult smokers, we suggest the use of combination pharmacotherapy (nicotine patch and nicotine gum, varenicline and bupropion, and varenicline and nicotine patch) over single pharmacotherapy in facilitating continuous	Low	Weak

		smoking abstinence and in minimizing adverse events		
7	Among adult smokers, should we use pharmacologic therapy alone or in combination with counseling interventions, in facilitating continuous smoking abstinence and in minimizing adverse events?	Among adult smokers, we suggest the use of pharmacologic therapy in combination with counseling interventions, in facilitating continuous smoking abstinence	Low	Weak
8	Among adult smokers, should extended duration pharmacologic therapy be used over standard duration to facilitate continuous smoking abstinence and minimize adverse events?	Among adult smokers, we recommend the use of extended duration therapy for bupropion to facilitate continuous smoking abstinence	High	Strong
9		Among adult smokers, we suggest the use of extended duration therapy for varenicline to facilitate continuous smoking abstinence	Very low	Weak
10		Among adult smokers, we suggest the use of standard duration therapy with nicotine replacement therapy over extended duration therapy to facilitate continuous smoking abstinence	Low	Weak
11	Among nonsmokers/non-tobacco product users, does the use of electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS), heat tobacco products (HTP), or vape to facilitate nicotine dependence (continued use of vape, transition to become tobacco product user, dual users of tobacco product and vape) and is associated with adverse effects?	Among nonsmokers and non-tobacco product users, we suggest against the use of electronic nicotine delivery systems, electronic non-nicotine delivery systems or vapes , heated tobacco products due to their association with subsequent cigarette smoking and association with continued electronic nicotine delivery systems/electronic non-	Very low	Weak

		nicotine delivery systems use and adverse effects		
12	Among adult and adolescent smokers, should we use ENDS/ENNDS over its non-use in facilitating smoking abstinence and in minimizing adverse events?	Among adult and adolescent smokers, there is insufficient evidence to recommend the use of electronic nicotine delivery systems/electronic non-nicotine delivery systems to facilitate continuous smoking abstinence	Low	None

**CoE – certainty of evidence; SOR – strength of recommendation*

LIST OF ABBREVIATIONS

CAR	Continuous abstinence rate
CDC	Center for Disease Control
CI	Confidence interval
DOH	Department of Health
ENDS	Electronic nicotine delivery systems
ENNDS	Electronic non-nicotine delivery systems
FDA	Food and Drug Administration
HTP	Heated tobacco products
NASEM	National Academy of Sciences, Engineering, and Medicine
NRT	Nicotine replacement therapy
OR	Odds ratio
PPM	Parts per meter
QALY	Quality-adjusted life year
RCT	Randomized controlled trial
RR	Risk ratio
THC	Tetrahydrocannabinol
WHO	World Health Organization

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DEFINITION OF TERMS

Adverse events	any undesirable experience associated with the use of medical product in a patient.
Brief interventions	are sessions lasting for <20 minutes in a single visit, regardless of number of sessions. It is given by a healthcare worker involved in the patient's routine care with no special training or equipment.
Carbon Monoxide (CO)	the result of organic matter combustion that includes tobacco products but not smokeless tobacco or electronic nicotine delivery systems (ENDS). Expired CO is measured in parts per million (ppm) by various portable instruments.
Continuous smoking abstinence rate	Period wherein a smoker no longer smokes a combustible tobacco product over 6 months.
Cotinine	the primary nicotine metabolite present in all cigarette smokers. Saliva, blood, and urine can all be tested for cotinine.
Electronic Non-nicotine Delivery Systems/ Electronic Nicotine Delivery Systems (ENNDS/ENDS)	also called as "e-cigs," "vapes," "e-hookahs," "vape pens." ENNDS/ENDS are heterogeneous class of products that use an electrically powered coil to heat and turn a liquid into an aerosol, which is inhaled by the user.
Extended duration of smoking cessation intervention	a type of intervention that is administered for a period >12 weeks.
Heated Tobacco Products (HTP)	also referred to as "heat-not-burn" products and uses electronic heating elements. HTPs comes in many forms such as (1) specially-designed sticks, plugs, or capsules containing tobacco; (2) heated liquids that create an emission that then passes through a tobacco plug to absorb flavor and nicotine from the tobacco; and (3) heats loose tobacco, either alone or together with flowers from the marijuana (cannabis) plant.
Intensive individual behavioral therapy programs	Interventions that lasts for >15 minutes (at least one session in person), with multiple sessions and administered by trained specialists NOT involved in routine care.
Nicotine Dependence	also known as Tobacco Use Disorder, a maladaptive pattern of nicotine use leading to clinically significant impairment of distress, manifested by three (or more) of the following occurring at any time in the same 12-month period: (1) tolerance, (2) withdrawal, (3) taking

	larger amounts of the substance over a longer period than was intended, (4) persistent desire for or unsuccessful efforts to cut down on its use, (5) great deal of time spent in activities necessary to obtain or use nicotine, and/or (6) abandonment or reduction of important social, occupational, or recreational activities.
Nicotine Replacement Therapy (NRT)	stop-smoking medications (nicotine gum, patches, inhalers and lozenges) containing nicotine that are intended to promote cessation by reducing craving and withdrawal symptoms in the initial period of abstinence from smoking.
Point-prevalence smoking abstinence	a smoker no longer smokes a combustible tobacco product tobacco product for the last 7 or 30 days
Smoking biomarkers	biochemical laboratory tests used to monitor tobacco exposure
Smoking status	defined based on clinical criteria or may be evaluated by biochemical laboratory tests to assess biomarkers of tobacco smoke exposure such as carbon monoxide concentration in exhaled air and level of cotinine as a result of the nicotine metabolism process.
Standard duration of smoking cessation intervention	intervention that is administered for <12 weeks.

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This 2021 update underwent external review by a pulmonologist and clinical epidemiologist. The external reviewer was not involved in the guideline development. The external reviewer was given a copy of the manuscript and in turn, he provided the guideline development group constructive feedbacks and expert advise.

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CHAPTER I. INTRODUCTION

This CPG was updated to provide physicians of various disciplines, medical practitioners, mentors and trainees answers to commonly asked questions in management of tobacco use and nicotine dependence. The recommendations in the previous CPG of 2017 are also still upheld.

An update was deemed necessary due to the significant impact of tobacco smoking in the presence of non-communicable diseases, the introduction of new products being marketed as 'safer' alternatives to tobacco smoke, and the occurrence of the COVID 19 pandemic.

Burden of Disease

According to the 2019 Philippine Health Statistics report of the Department of Health (DOH), six out of the top 10 causes of mortality are non-communicable diseases, namely ischemic heart disease (#1), malignant neoplasms (#2), cerebrovascular diseases (#3), diabetes mellitus (#5), hypertensive diseases (#6), and other heart diseases (9). Tobacco smoke is considered as one of the common preventable risk factors for these diseases. The 2021 World Health Organization (WHO) report on the global tobacco epidemic mentioned that every year, around 8 million deaths worldwide are caused by tobacco-related conditions. Smoking cessation is thus a crucial step in decreasing the prevalence of these conditions.

The 2015 Global Adult Tobacco Survey (GATS) showed that there are about 16.6 million adult smokers (all forms of tobacco products) in the country with 13.1 million of them smoking an average of 11 cigarettes per day. Surprisingly 79.6 to 96.4% of these smokers believe that smoking causes serious illness such as stroke, lung cancer and heart attack. The same report also showed that 76.7% of current smokers planned to or were thinking about quitting but only 4% were able to successfully quit. Given this data, knowledge of its ill effects is not enough to facilitate smoking cessation. It is thus very important to increase access to smoking cessation programs and services that may aid these smokers who are willing to quit and thus increase the success rate of quitting.

New Challenges

Recently, there has been an increase in marketing and availability of 'alternative' tobacco products. ENDs or Electronic Nicotine Delivery System producers (i.e., vape electronic cigarette, smokeless tobacco, Juul) are being advertised as a 'safer' alternative to conventional counseling or smoking cessation strategies. The 2015 GATS report showed that 2.8% of current smokers use electronic cigarettes. Due to the variety of forms, designs, colors and "flavors" being offered by these products, it has also caught the attention of the younger generation. In the 2019 Global Youth Tobacco Survey (GYTS), 14.1% of the surveyed students, 13 to 15 years old, are current e-cigarette users. This CPG would like to help Filipino smokers to choose to quit rather than shift.

To add to this challenge, the Philippine Senate recently approved the Senate Bill No. 2239 or Vaporized Nicotine Products Regulation Act which lowers the age restriction in using these products from 21 to 18 years old. In addition, it also transfers the regulatory role to the Department of Trade and Industry (DTI) instead of the Food and Drug Administration (FDA), which has the capacity to better assess its safety (CNN 2021). Medical groups have conducted online conferences in order to stress the harms of passing this bill emphasizing that it is more of a deregulatory measure for vaporized nicotine products (Business world online 2022).

Meanwhile, it has been almost two years since the world has been confronted with the challenges brought about by the COVID 19 pandemic. There have been multiple lock downs that made mobility difficult hence people have shifted to the online platform to avail of services. Similarly, face-to-face counseling for smoking cessation has been difficult. Because of this, efforts are being made to utilize phone consults/counseling, social media and virtual platforms for smoking cessation programs. This CPG would like to show that these can be used as alternatives given the current restrictions.

Advances in the Fight Against Tobacco Use

One of the projects launched for the smoking cessation initiative of DOH is the Quitline service. This started at Lung Center of the Philippines (LCP) last July 2017 in partnership with WHO. The primary objective of this project is to provide telephone-based counseling for smokers and thus help initiate the process for smoking cessation. Smokers who call the hotline are given information on the ill effects of smoking and are offered strategies on how to quit (such as enrollment in the smoking cessation program). Outcomes of this program were initially assessed in the paper of Batungbacal et al in 2018. It was found that there was 18% quit rate and 82% relapse rate in the DOH-LCP Quitline program during its first year. Outcome were reassessed in 2021 by Cantela et al showing an increase in quit rate to 62.7% and relapse rate to 37.3%. The study concluded that the impact of the Quitline program on achieving smoking cessation is improving through the years.

Different hospitals are also putting up their smoking cessation clinics as part of the efforts to increase the number of smokers who successfully quit. The Davao Regional Medical Center started its smoking cessation clinic services in 2017. Despite the pandemic, the City Health Office of Baguio City launched its Smoking Cessation Program which gave smokers the opportunity to gain access to these smoking cessation services thru online platforms such as Facebook, Messenger, email, and text messaging. This is part of the activities of the city's Smoke-Free Baguio Task Force which was created in 2018 thru the Smoke-free Baguio City Ordinance passed in 2017. Meanwhile, the Lung Center of the Philippines formally launched its smoking cessation clinic in November 18, 2021 and it offers individual

counseling and options for smoking cessation such as behavioral therapies and nicotine replacement therapies.

The 2021 WHO report on the global tobacco epidemic acknowledged all these efforts and cited the Philippines as one of the five countries that have achieved best-practice level in terms of tobacco use cessation services. This came in the form of health warning labels, partial restriction in the sale of ENDs (thru Executive Order 106 the prohibits the manufacture, distribution, marketing and sale of unregistered and/or adulterated ENDs/ENNDs, heated tobacco products and other novel tobacco products), increase in taxation and development of smoking cessation programs (i.e., Quit line, availability of nicotine replacement therapy, etc). There is still room for development hence the update of this CPG on tobacco and nicotine dependence to further strengthen the country's efforts to promote smoking cessation.

OBJECTIVES OF THE CLINICAL PRACTICE GUIDELINE

General Objective

The project aims to rapidly develop an update on the Philippine Clinical Practice Guidelines on the Diagnosis and Management of Tobacco Use and Nicotine Dependence.

Specific Objectives

The update on the guidelines aimed to cover the following current issues:

1. Pharmacologic and non-pharmacologic interventions for nicotine dependence
2. Effective intensive interventions in resource-limited settings
3. Nicotine dependence and the use of electronic nicotine delivery system (ENDS) products
4. Effective smoking cessation & nicotine dependence strategies in the current COVID-19 pandemic setting

Scope and Target Population

This clinical practice guideline covered smoking cessation for adults and adolescents and addressed the current issues on the (1) pharmacologic and non-pharmacologic interventions for nicotine dependence, (2) effective intensive interventions in resource-limited settings, (3) nicotine dependence and the use of electronic nicotine delivery system (ENDS) products, and (4) effective smoking cessation & nicotine dependence strategies in the current COVID-19 pandemic setting.

It is intended for use among physicians of various disciplines, medical practitioners, mentors, and trainees. Specific target beneficiaries and end-users includes (1) DOH, (2) health care practitioners and institutions, smokers and ENDS users, and the public at large.

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CHAPTER II. GUIDELINE DEVELOPMENT METHODS

Selection and Organization of the Steering Committee

The Philippine General Hospital and the Philippine College of Chest Physicians identified the Steering Committee (SC) members who led the formulation of the CPG. The SC formed two working groups, namely: (1) Technical Working Group (TWG), and (2) Consensus Panel. The TWG was composed of evidence review experts who took charge of literature search, evidence review, and synthesis. The CP is composed of 10 experts on smoking cessation, including health practitioners and a patient advocate. The CP members were nominated and authorized by their respective specialty groups to represent the voice of their organization in formulating the final recommendations. The SC identified the members of the panel according to their knowledge, expertise in the field, and absence of conflicts of interest (COI).

The "Grading of Recommendations, Assessment, Development, and Evaluation or GRADE Approach" and the "2018 DOH Manual for Clinical Practice Guideline Development" were used as guides for the entire development process.

Formulation of Clinical Questions

The SC and TWG reviewed the existing guidelines and identified priority problems that should be addressed in the current guidelines. Three questions were selected from the previous guideline for updating for the latest evidence while the remaining seven are new questions covering new modes of delivery as well as controversial topics. Table 2 below shows the list of priority clinical questions included in this CPG based on the current issues on smoking and nicotine dependence identified.

Table 2. List of priority clinical questions

1	Among adult and adolescent smokers, should we use smoking biomarkers in determining smoking status during smoking cessation?
2	Among adult and adolescent smokers, should we use intensive behavioral therapies over brief tobacco interventions in facilitating continuous smoking abstinence?
3	Among adult and adolescent smokers who are ready to quit, is group therapy more effective than individual therapy in facilitating continuous smoking abstinence?
4	Among adult and adolescent smokers, can behavioral therapy be delivered remotely be used as an alternative to face-to-face in facilitating continuous smoking abstinence?
5	Among adult smokers, should we use pharmacologic therapy over no pharmacologic therapy in facilitating continuous smoking abstinence and minimizing adverse events?
6	Among adult smokers, should we use combination pharmacologic therapies over single pharmacologic therapy, in facilitating smoking abstinence and in minimizing adverse events?

7	Among adult smokers, should we use pharmacologic therapy alone or in combination with counseling interventions, in facilitating continuous smoking abstinence and in minimizing adverse events?
8	Among adult smokers, should extended duration pharmacologic therapy be used over standard duration to facilitate continuous smoking abstinence and minimize adverse events?
9	Among nonsmokers/non-tobacco users,does the use of electronic nicotine delivery systems (ENDS) ,electronic non-nicotine delivery systems (ENNDS) or vapes, heated tobacco products (HTP) facilitate nicotine dependence (continued use of vape, transition to become tobacco product user, dual users of tobacco product and vape) and is associated with adverse effects?
10	Among adult and adolescent smokers, should we use ENDS/ENNDS over its non-use in facilitating smoking abstinence and in minimizing adverse events?

Search Strategy and Data Synthesis

The TWG members collected and synthesized the data. Questions were divided among members with at least two persons designated to work on each question. An independent electronic and systematic literature search was performed for each guideline question using at least two databases such as Cochrane Database and MEDLINE. The GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) Framework was used to determine the certainty of evidence (Tables 3 & 4). Technical advisers and CPG development experts were invited to guide and critic the evidence summaries made by the evidence reviewers.

Table 3. Certainty of Evidence in GRADE

High	We are very confident that the true effect lies close to that of the estimate of the effect. Evidence based on randomized controlled trials, further trials, further research is very unlikely to change confidence in the estimate of effect.
Moderate	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Evidence based on downgraded RCTs or upgraded observational studies, further research is likely to have impact on the confidence in the estimate of effect.
Low	Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of effect. Evidence based on observational studies, further research is very likely to have an important impact on the confidence in the estimate of effect.
Very Low	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect. Evidence based on case series or expert opinion, any estimate of effect is very uncertain.

Table 4. Strength of Recommendation

Strong	The benefits outweigh harm, there are no cost or access issues for the general population.
Weak	Best available evidence is very low to low certainty. Magnitude of benefits or risks is uncertain or closely balanced for the general population and applicable to a specific group, population or setting; benefits may not warrant the cost or resource requirements in all

Consensus Development

The CP voted on each recommendation and its strength. The panelists were guided by the evidence to decision framework which takes into consideration the (1) quality of evidence, (2) value of the outcome, (3) balance between benefit and harm and (4) cost and resource availability. The evidence for the decision framework to each guideline question is presented in the appendix.

Consensus panel meetings were held on November 23, 27, and 29, and December 16, 2021 via Zoom platform. A copy of the evidence base was electronically sent beforehand for them to review and evidence to decision framework survey was also sent via google forms for them to fill out. After the presentation of the evidence summary by the ERE, discussions, and clarifications were facilitated under the guidance of an invited technical and CPG development adviser. The voting process was conducted manually using the zoom chat box to indicate agreement (YES/AGREE), disagreement (NO/DISAGREE), or abstention. The consensus required is at least 75% of votes.

Managing of Conflicts of Interests

All members (i.e., SC, TWG, CP) involved in the development of this CPG declared all potential conflicts of interest through a standard Declaration of Conflict of Interest Form. The SC reviewed the accomplished CoI forms of each member of the task force and did not find any significant CoI.

CHAPTER III. FINAL RECOMMENDATIONS & EVIDENCE TO DECISION ISSUES

Domain 1. Diagnosis and Assessment

Research Question 1: Among adult and adolescent smokers, should we use smoking biomarkers in determining smoking status during smoking cessation?

RECOMMENDATION 1.
Among adult and adolescent smokers, there is insufficient evidence to recommend the use of smoking biological markers (exhaled carbon monoxide and salivary, blood, and urinary cotinine) in determining smoking status during smoking cessation *(Very low certainty of evidence)*

Evidence Summary
Fifteen observational studies (n=15,721) [1-15] evaluated the utility of objective measures of smoking and self-report among adult smokers. For carbon monoxide, nine studies [1,2,4,5,9–11,13,15] showed that the pooled sensitivity of carbon monoxide is 0.88 (95% CI 0.83 – 0.92) and the pooled specificity is 0.96 (95% CI 0.88 – 0.99) for detecting smoking status. The test also has a strong positive likelihood ratio of 21.7 (95% CI 7.4 - 64.3), and a moderately negative likelihood ratio of 0.13 (95% CI 0.09 – 0.18). Subgroup analysis of seven studies (n=5,926) for the pre-specified cutoff of 8-10 ppm (parts per meter) yielded a pooled sensitivity of 0.88 (95% CI 0.81 – 0.92) and pooled specificity of 0.97 (95% CI 0.91 – 0.99) for detecting smoking status [1,4,5,10,11,13,15]. The test also has a strongly positive likelihood ratio of 28.3 (95% CI 9.3 – 85.8) and a moderately negative likelihood ratio of 0.13 (95% CI 0.08 – 0.20). The certainty of the evidence for the pooled sensitivity and specificity for carbon monoxide were very low due to high risk of bias in the index test and very high heterogeneity.

For salivary cotinine, eight observational studies [1,6,8,16,11,13-15] reported a pooled sensitivity of salivary cotinine of 0.98 (95% CI 0.94 - 0.99) and a pooled specificity of 0.94 (95% CI 0.90 – 0.97) for detecting smoking status. The test has a strongly positive likelihood ratio of 16.6 (95% CI 9.3 – 29.6) and a strong negative likelihood ratio of 0.02 (95% CI 0.01 – 0.07). The certainty of evidence for the pooled sensitivity and specificity for salivary cotinine were very low due to high risk of bias in the index test and very high heterogeneity.

For blood cotinine, three observational studies [3,12,15] reported a pooled sensitivity of 0.94 (95% CI 0.63 - 0.99) and a pooled specificity of 0.97 (95% CI 0.94 – 0.99) for detecting smoking status. The test has a strongly positive

likelihood ratio of 31.2 (95% CI 17.44 – 55.79) and strong negative likelihood ratio of 0.06 (95% CI 0.01 – 0.49). Four observational studies that used the prespecified cutoff of 3-10 ng/ml reported a pooled sensitivity of cotinine that is 0.98 (95% CI 0.92 – 1.00) and a pooled specificity of 0.94 (95% CI 0.90 – 0.97) for detecting smoking status. The test has a strongly positive likelihood ratio of 17.8 (95% CI 9.6 – 32.9) - and a strong negative likelihood ratio of 0.02 (95% CI 0.01 - 0.09). The certainty of evidence for the pooled sensitivity of salivary cotinine was very low, while low for pooled specificity due to high risk of bias in the index test and flow and timing and high heterogeneity.

A single observational study [7] reported that the pooled sensitivity of urinary cotinine is 0.96 (95% CI 0.89 – 1.00) and the pooled specificity is 0.91 (95% CI 0.81 – 0.97) for detecting smoking status. The test has a strongly positive likelihood ratio of 10.66 (95% CI 4.97 – 22.89) and a strong negative likelihood ratio of 0.03 (95% CI 0.01 – 0.13). The certainty of evidence for the pooled sensitivity and specificity for salivary cotinine were low due to high risk of bias in the index test and flow and timing and heterogeneity.

For the detection of smoking status among adolescents, three observational studies reported that sensitivity ranges from 0.66 – 0.98 while specificity ranges from 0.61 – 0.85. For pregnant women, three observational studies [6,7,12] reported that sensitivity ranges from 0.87 – 0.99 while specificity ranges from 0.95 – 0.98 for detecting smoking status. The certainty of evidence for the sensitivity and specificity for salivary cotinine among the adolescent population were very low due to high risk of bias in the index test, heterogeneity, and imprecision. The certainty of evidence for the pregnant population for the sensitivity and sensitivity was very low and low, respectively due to high risk of bias in the index test, heterogeneity, and imprecision.

Other Considerations

Cost

Locally, carbon monoxide testing offered by St. Luke's Hospital - Quezon City costs Php 3,190. In a study by Kaufmann in 2010 [9], cotinine measurement by chromatography and mass spectrometry cost USD 25 (~Php 1,260.68) per sample in 2010. It may cost USD 139 (~Php 7,009.35) commercially according to LabCorp in 2021.

Recommendations from Other Groups

Current local guidelines (CCTAP, 2017) mentioned that smoking status cannot be adequately monitored on the basis of smoking biomarkers [16]. Cotinine level interpretation may be ambiguous with nicotine substitutes. The Society for Research on Nicotine and Tobacco (SNRT) Subcommittee on Biochemical Verification in 2002 recommended their use in research about harm reduction and smoking cessation in population subgroups such as adolescents, women who are pregnant, and those with smoking-related diseases [17]. Smoking biomarkers on the other hand, were not necessary for large-scale population-based investigations with limited face-to-face interaction and studies where the preferred data collection techniques were mail, telephone, or via the internet. In a recent update, it was

highlighted that using smoking biomarkers to increase scientific rigor is crucial in clinical trials. However, limitations such as cost, feasibility, and assay variability may restrict biomarker utilization. According to the Tobacco Use and Dependence Guideline (2008) [18], smoking biomarkers, referred to as "specialized assessments," may not be needed in the administration of tobacco-dependent therapy because the treatment itself is efficacious.

Consensus Issues

The validity of carbon monoxide testing is hard to justify since only the last 8 hours of carbon monoxide levels can be detected, hence the carbon monoxide testing cannot reliably assess the smoking status earlier than the 8 hours before testing. International smoking cessation programs usually utilize self-reporting as the index test and biological markers as the reference test whereas local practice tend to use self-reporting as the reference test. Biologic markers are also used in research as a confirmatory test, however, it is not considered as the standard of care due to its high cost by smoking cessation guidelines.

To date, carbon monoxide testing is still not locally available in all parts of the country, especially in distant areas which might affect health equity. In addition, carbon monoxide testing was deemed costly as well.

A better quality of evidence, cheaper cost, and availability of these diagnostic tests are needed in order to make a recommendation for or against the use of biological markers in determining smoking status during smoking cessation. The Consensus Panel deemed it not essential for a clinical smoking cessation program to have these diagnostic tools at hand to effectively implement the interventions necessary to assist the patients in achieving smoking cessation. A thorough clinical evaluation and good history taking may provide sufficient bases to assess responses of patients to smoking cessation interventions.

Domain 2. Non-pharmacologic Interventions

Research Question 2: Among adult and adolescent smokers, should we use intensive behavioral therapies over brief tobacco interventions in facilitating continuous smoking abstinence?

RECOMMENDATION 2.
Among adult and adolescent smokers, we suggest the use of intensive behavioral intervention over brief tobacco interventions in facilitating continuous smoking abstinence *(Low Certainty of evidence; Weak recommendation*

Evidence Summary

Thirty-eight randomized controlled trials (RCT) [24-61] compared individualized intensive behavioral therapy with brief tobacco intervention. Result of pooled estimates suggests that individual behavioral therapy is effective in the cessation of smoking at six months or longer (RR: 1.48; 95% CI: 1.24,1.75), however, there was a significant heterogeneity (I^2=59%). The review of individual behavioral counseling for smoking cessation published by Lancaster and Stead (2018) [60] also favored individualized behavioral therapy over brief tobacco intervention. The findings showed the same trend suggestive of efficacy based on point estimate but with significant heterogeneity. There was no harm or adverse events related to behavioral interventions that were found. The overall certainty of evidence for studies using individualized intensive behavioral therapy was moderate due to significant heterogeneity.

Other Considerations

Cost

There was no local cost-effectiveness study on the use of intensive behavioral therapies for smoking cessation. Informal survey of hospitals located in Metro Manila showed that structured individual counseling cost Php 3,000.00 - Php 4,000.00 on the initial assessment and succeeding counseling costs would depend on the extent of intervention done. Other medical practitioners would offer smoking cessation counseling with rates similar to medical consults at Php 500.00 - Php 1,500.00. Cost-effectiveness studies on spinal surgery patients [62], dental setting [63], and primary care network [64], showed cost-effectiveness at the lifetime horizon with a mean lifetime cost savings/long-term effective savings of USD 3,291 or Php 165,627.80 (standard deviation [SD], USD 868 or Php 43,684.27) [64].

Recommendations from Other Groups

The US Preventive Services Task Force [65] have found that individual counseling with a cessation specialist to be effective in increasing cigarette smoking cessation. The Surgeon General Report for Smoking Cessation [66] identified nicotine dependence treatment (both counseling and medication) as an effective intervention and recommended its inclusion for paid and covered services for

subscribers or members of health insurance packages. However, there was no evidence listed under the recommendation.

Consensus Issues

It was discussed that only less than 5% of smokers has the initiative to quit smoking by themselves and remain smoke-free for six months, whereas with intensive behavioral intervention, smoking abstinence is facilitated more through motivational interview. There were also more evidence showing that intensive behavioral therapy is associated with longer smoking cessation time. It was stressed that intensive behavioral therapy is not similar to brief tobacco interventions and more data is needed on which subgroup of smokers will benefit most from intensive behavioral therapy. Further, additional data is also needed with regard to local cost-effectiveness, acceptability, and other health-related/quality of life (QOL) outcomes (e.g. other substance abuse, depression etc.)

There were difficulties in obtaining a high level of evidence due to large heterogeneity of studies, high risk of bias and difficulty in standardizing interventions. Despite those reasons, there was a consensus to suggest intensive behavioral therapy due to the high likelihood and trend towards benefit and absence of harm. Two consensus panel members voted to strongly recommend the use of intensive behavioral therapy due to clinical experience and documented benefit; however, it was decided that more evidence is needed.

Research Question 3: Among adult and adolescent smokers who are ready to quit, is group therapy more effective than individual therapy in facilitating continuous smoking abstinence?

RECOMMENDATION 3.
Among adult and adolescent smokers, we suggest the use of either group or individual therapy in facilitating continuous smoking abstinence*(Low Certainty of evidence; Weak recommendation)*

Evidence Summary

Ten RCTs [67-76] were included in the analysis comparing group intervention with either individual intensive counseling (n=1,044) or less intensive individual counseling (n=2,119). Comparison of intensive individual therapy and intensive group therapy in terms of long-term smoking cessation at 6-12 months showed inconclusive results (RR: 0.82; 95% CI 0.57,1.19). The quality of evidence was graded moderate due to imprecision. Likewise, there were also inconclusive results when group intervention was compared with individual brief advice (RR: 1.47; 95% CI 0.85,2.54). The quality of evidence was graded low due to imprecision and inconsistency. Both findings were consistent with a previously published meta-analysis by Stead et. al. [77] in which group therapy or counseling showed to be less effective than individual therapy of the same or less intensity (brief advice/counseling).

Other Considerations

Cost

There are no cost-effectiveness studies that compared group-based to individually-administered counseling. Group-based therapy is not routinely offered locally. The cost of structured individual counseling in Manila range from Php 3,000.00 - Php 4,000.00 on the initial assessment and succeeding counseling costs would depend on the extent of intervention done. Other medical practitioners would offer smoking cessation counseling with rates similar to medical consults at Php 500.00 - Php 1,500.00. There is very limited data as of now that directly compare group therapy with individual therapy in terms of acceptability and feasibility of administration, hence, these were not considered in drafting the recommendation.

Recommendations from Other Groups

The Surgeon General's report on smoking cessation in 2020 recommended that behavioral counseling increase smoking cessation when compared to self-help materials or no intervention [78]. However, there is still no consensus whether the delivery of behavioral counseling should be given in groups or as individual treatment.

Consensus Issues

The panel discussed that both interventions are good and useful in facilitating smoking abstinence in the clinical setting. However, current data show inconclusive results in order for the panel to recommend either group or individual therapy over the other. Given the current COVID-19 situation, the use of group therapy might not be justifiable due to low level of evidence.

Research Question 4: Among adult and adolescent smokers, can behavioral therapy delivered remotely be used as an alternative to face-to-face in facilitating continuous smoking abstinence?

RECOMMENDATION 4.
Among adult and adolescent smokers, there is insufficient evidence to recommend remotely-delivered behavioral therapy as an alternative to face-to-face counseling in facilitating continuous smoking abstinence *(Very low certainty of evidence)*

Evidence Summary
Four RCTs [79-82] (n=1522) on the efficacy and safety of remote counseling as an alternative to face-to-face counseling in facilitating smoking abstinence were analyzed. The study by Berndt [79] (n=380) which analyzed the 240-day continuous abstinence rate (CAR) showed that telephone-based counseling was neither inferior nor superior (RR: 1.08; 95% CI 0.78,1.49) to face-to-face counseling.

The study by Wewers [83] (n=707) compared face-to-face counseling conducted by community health workers and those who used the Quiltline and it showed inconclusive results in terms of 12-month CAR (RR: 0.47; 95% CI 0.67,1.04) but showed a trend favoring face-to-face counseling.

The comparison of face-to-face counseling and internet-based video counseling showed that the latter was neither inferior nor superior to face-to-face counseling during the 15-week CAR (n=115) (RR: 1.03; 95% CI 0.83, 1.29) [81]. The study by Ramon [80] (n=600) also showed inconclusive results but a trend favoring face-to-face counseling over telephone-based counseling alone and face-to-face + telephone-based counseling (RR: 0.72; 95% CI 0.51,1.03) in the 50-week CAR. Pooled results of the four studies were inconclusive but there was a trend that favored face-to-face counseling (RR: 0.88; 95% CI 0.67,1.16).

Subgroup analysis based on a 6-month CAR cut-off and the type of remote intervention also showed inconclusive results but showed a trend favoring face-to-face consultations (RR: 0.79; 95% CI 0.53,1.19) [79,80,82].

The overall certainty of evidence was very low because of the risk of bias, inconsistency, and imprecision. Behavioral therapy is a generally safe intervention, there were no studies included in this review that reported safety issues and adverse events.

Other Considerations
Cost
There were no local studies available comparing the cost-effectiveness of remotely-delivered and face-to-face behavioral therapy. One study directly compared the

costs of telephone-based counseling and face-to-face counseling which used a societal perspective showing that telephone-based counseling had lower costs and higher probability of abstinence than usual care or face-to-face consultation (Table 6). Subgroup analyses showed that telephone-based counseling was more cost-effective for patients with low educational levels, and high intention to quit, while face-to-face consultation was more cost-effective for patients with high educational levels, and low intention to quit (Table 6) [83].

Table 5. Mean costs (+/- standard deviation) of telephone-based counseling and face-to-face counseling

Telephone-based counseling	**Face-to-face counseling**	**Usual care**
EUR 8,124.30+/- 8,830.70 *(Php 1,061,137.47 +/- 517,017.85)*	EUR 8,988.20 +/- 10,677.40 *(Php 526,239.12 +/- 625,138.03)*	EUR 9,181.20 +/- 11,041.00 *(Php 537,538.85 +/- 646,426.00)*

Table 6. Subgroup analyses among patients with low and high educational levels and patients with low and high intention to quit

Subgroup	**Telephone-based counseling**	**Face-to-face counseling**
Patients with *low* educational levels	EUR 6,458.00 +/- 7,076.20 *(Php 378,101.54 +/- 414,295.78)*	EUR 7,983.70 +/- 10,508.00 *(Php 467,427.88 +/- 615,220.04)*
Patients with *high* educational levels	EUR 11,058.80 +/- 10,732.80 *(Php 647,468.15 +/- 628,381.58)*	EUR 10,488.20 +/- 11,046.50 *(Php 614,107.63 +/- 646,748.01)*
Patients with low intention to quit	EUR 7,990.60 +/- 8,888.60 *(Php 467,831.86 +/- 520,407.77)*	EUR 6,860.10 +/- 8,543.50 *(Php 401,643.60 +/- 500,202.93)*
Patients with high intention to quit	EUR 8,408.90 +/- 8,906.60 *(Php 492,322.40 +/- 521,461.63)*	EUR 10,647.70 +/- 11,984.50 *(Php 623,399.16 +/- 701,665.83)*

One study [84] compared various smoking cessation interventions against unassisted intervention, including hospital counseling only, telephone counseling (Quitline), and hospital counseling plus various pharmacologic treatments using a societal perspective. Results showed that the use of Quitline did not differ in quality of adjusted life year (QALY) gained when compared to hospital counseling alone, and would have saved Baht 115 (~Php 179.22) as based on the reported 12-month abstinence rate.

These studies suggest that telephone-based counseling may be a cost-effective option to include in smoking cessation programs. Certain demographic characteristics should be taken into account in deciding its use.

Locally, the Department of Health-Lung Center of the Philippines Quitline Program is a toll-free service available to all Filipinos [85]. At the patient level, this will require having a landline or a mobile phone to avail of this service. At the provider

level, various administrative and personnel costs need to be considered in order to maintain the provision of telephone counseling services. Given the limited reach of quitlines [85,86], funding should also be considered for marketing, promotions, and information dissemination.

There are various free softwares and programs available that can be used for internet-based video counseling (e.g., Zoom, Google Meet, Doxy.me). These have corresponding subscription rates if access to additional features is desired. At the patient level, this will require having a stable internet connection, as well as a device such as a mobile phone, tablet, laptop, or computer.

Consensus Issues

It was noted that the review included only 4 studies which is insufficient to provide recommendations. Remote counseling can be a non-inferior mode of intervention in cases wherein face-to-face counseling is not feasible. Other innovative interventions may be used as a viable alternative to the usual face-to-face counseling.

Domain 3. Pharmacologic Interventions

Research Question 5: Among adult smokers, should we use pharmacologic therapy over no pharmacologic therapy in facilitating continuous smoking abstinence and minimizing adverse events?

RECOMMENDATION 5.
Among adult smokers, we suggest the use of pharmacologic over no pharmacologic therapy in facilitating continuous smoking abstinence and in minimizing adverse events *(Low certainty of evidence; Weak recommendation)*

Evidence Summary
Thirty-eight RCTs (n=27,921) [87-123] and three systematic reviews [124-126] were analyzed to determine the efficacy and safety of pharmacologic therapy over non-use of pharmacologic therapy in facilitating smoking abstinence and minimizing adverse drug reaction/s.

EFFICACY

Pharmacotherapy vs No Pharmacologic Therapy
Results of the pooled estimates (n=94,250) showed that the statistically significant benefit of using nicotine replacement therapy (NRT), varenicline, and bupropion remained consistent (RR: 1.83; 95% CI 1.75,1.91; p<0.00001) over placebo.

- *NRT of any form vs No Pharmacologic Therapy*
  Pooled analysis of 25 RCTs (n=17,452) and 4 new RCTs showed a statistically significant benefit (RR: 1.71; 95% CI 1.57,1.87) regardless of the form of NRT used. A similar pooled analysis by Hartman-Boyce (2018) showed a similar effect size (RR: 1.58; 95% CI 1.49,1.61).
- *Nicotine Gum vs No Pharmacologic Therapy*
  Eight RCTs (n=7,440) [87,91-95] showed significant benefit over control (RR: 2.31; 95% CI 1.96, 2.72, p<0.00001).
- *Nicotine Patch vs No Pharmacologic Therapy*
  Ten RCTs (n=8,090) [88, 95-103] showed a statistically significant benefit with the use of nicotine patch over control (RR: 1.64; 95% CI 1.44,1.87).
- *Nicotine Lozenge vs No Pharmacologic Therapy*
  Eight RCTs (n=3,643) [89,92,100,104-106] including two new RCTs done by Dautzenberg (2007), on nicotine lozenge was analyzed and showed a statistically significant benefit with the use of nicotine lozenges (RR: 1.53; 95% CI 1.34, 1.76).

Varenicline vs No Pharmacologic Therapy
Pooled results of twenty RCTs (n=10,469) [95,97,99,102,107-112] showed a slightly higher statistically significant benefit on the use of varenicline (RR: 2.48; 95% CI 2.27,2.72). One study by Littlewood (2016) was excluded because the number of events was not clearly stated at a time point of 6 months of abstinence but it also showed a significant benefit with the use of varenicline as compared to placebo (RR: 2.54; 95% CI 1.07,9.77, p=.037).

Bupropion vs No Pharmacologic Therapy
Results from 46 RCTs (n=17,866) showed a statistically significant benefit in using bupropion over control (RR: 1.64; 95% CI 1.52,1.77, p<0.0001).

SAFETY

NRT of any form
There was no quantitative review of the adverse effects in any of the studies included in the review, hence, a qualitative review on the adverse effects of NRTs was done. The following adverse events were noted among all forms of NRTs: headache, dizziness, nausea and vomiting, gastrointestinal symptoms, oronasal problems, hiccups and sleep problems. Cardiovascular events were seen in patch and gum forms, however, this was not serious and was very rare.

Varenicline
The most common adverse event associated with varenicline is nausea (RR: 3.27; 95% CI 3.0,3.55; I^2=27%; p=<0.00001) which was reported in 32 RCTs (n=14,963). Twenty-nine RCTs reported serious adverse events (n=15,270) associated with varenicline use (RR: 1.25; 95% CI 1.04,1.49; I^2=0%; p=<0.0001). Both outcomes indicate significant harm, however, the events were not differentiated whether they are directly related to the treatment effect for serious adverse events. Trials with an increase in adverse events associated with increased dosage found that titration reduces occurrence of nausea.

Neuropsychiatric serious adverse events (n=15 RCTs) were not worse with the use of varenicline (RR: 0.82; 95% CI 0.57,1.19, p=0.31]. On the other hand, cardiovascular serious adverse events (n=21 RCTs) including death were seen to be slightly increased with the use of varenicline use (RR: 1.36; 95% CI 0.91, 2.04, p=0.13). However, both serious adverse events did not reach statistical significance.

In conclusion, consistent with the latest available review and the new trials that emerged – varenicline use is associated with nausea and abnormal dreams but does not have significant serious adverse events that will preclude its use.

Bupropion
Twenty-two RCTs (n=10,893) reported significant harm (RR: 1.14; 95% CI 1.11,1.18; I^2= 63%; p=<0.00001) associated with the use of bupropion. As for the occurrence of serious adverse events, pooled results (n=10,625) showed that there is harm associated with its use but it was not statistically significant (RR:

1.16; 95% CI 0.90,1.48, p=025, n=10,625). In conclusion, although there is a high level of evidence that supports the use of bupropion in smoking cessation, this recommendation should be weighed with the findings that it increases the number of adverse events including psychiatric adverse effects that may cause patients to discontinue their treatments.

The overall certainty of evidence is low because of significant heterogeneity and risk of bias.

Other Considerations

Cost

There was no local cost-effectiveness data that were found. Table 7 below shows the unit costs and cost of treatment of pharmacologic therapies.

Table 7. Treatment cost of different pharmacological therapies for smoking cessation

Intervention	Dosage strength	Unit cost	Estimated Total Cost per 12 week treatment
NRTs - Gum	2 mg	Php 16.00	Php 12,960.00
	4 mg	Php 59.00	Php 47,790.00
NRTs - Patch	7 mg	Php 234.00	Php 21,060.00
	14 mg	Php 270.00	Php 24,345.00
	21 mg	Php 168.00	Php 15,120.00
NRTs - Lozenge	2 mg	Php 39.00	Php 31, 590.00
	4 mg	Php 29.00	Php 23,490.00
Varenicline	1 mg	Php 100.00	Php 18,000.00

Availability/Equity

Nicotine replacement therapies available in the country are in the forms of lozenge, gum and patch. Varenicline is available as a prescription-only drug. Bupropion is reportedly available but is not as accessible as others.

In June 2021, WHO in partnership with Johnson & Johnson, donated 315,000 NRT patches to the Lung Center of the Philippines, National Center for Mental Health, Bataan General Hospital, and Baguio General Hospital and Medical Center.

Recommendations from Other Groups

According to the American College of Chest Physicians – CHEST Foundation [127], the use of any of the US Food and Drug Administration (FDA)-approved medications for tobacco dependence improves cessation rates, regardless of the severity level of tobacco dependence. FDA-approved first-line medications for tobacco dependence includes varenicline, bupropion, and NRT products (i.e., nicotine patch, nicotine gum, nicotine lozenge, nicotine oral inhaler, nicotine nasal spray). It was noted in their report that most patients receive too little (not too much) nicotine from their

NRTs. Possible symptoms of too much nicotine includes nausea, headache, dizziness, tachycardia (patch), skin irritation, insomnia, hiccups, heartburn (gum, lozenges) nasal irritation, tearing, sneezing (nasal spray), and mouth and throat irritation (inhaler). Nausea, headache, dizziness, insomnia are also tobacco withdrawal symptoms.

The Updated Evidence Report and Systematic Review for the US Preventive Services Task Force on Interventions for Tobacco Cessation in Adults, including Pregnant Person [128] stated that there was strong evidence from systematic reviews that the combination of pharmacotherapy and behavioral support, all seven US FDA–approved medications (all forms of NRT, bupropion, varenicline), and a variety of behavioral interventions were statistically significantly associated with an increase in smokers' relative likelihood to quit smoking at 6 or more months as compared with smokers receiving usual care or a minimal stop-smoking intervention. There was also evidence of an association between the use of NRTs (RR: 1.55; 95% CI 1.49,1.61; n=64,640), bupropion (RR: 1.64; 95% CI 1.52,1.77, n=17,866), and varenicline (RR: 2.24; 95% CI 2.06,2.43; n=12,625) and smoking abstinence at 6 months or more when compared with placebo or no drug. There was no association between the use of NRT, bupropion, or varenicline and serious adverse events, including major cardiovascular adverse events or serious neuropsychiatric events, as compared with placebo or non-drug control groups that was reported.

There was sufficient evidence to infer that behavioral counseling and cessation medication interventions increase smoking cessation compared with self-help materials or no treatment according to "Smoking Cessation: A Report of the Surgeon General Executive Summary" [129].

The Official American Thoracic Society Clinical Practice Guideline on Initiating Pharmacologic Treatment in Tobacco Dependent Adults [130] recommended varenicline over a nicotine patch bupropion for tobacco-dependent adults in whom treatment is being initiated. It was noted that varenicline likely reduced the risk of serious adverse effects compared with a nicotine patch (RR: 0.72; 95% CI 0.52,1.00; ARR: 3 fewer per 1,000 patients; 95% CI 5 fewer to 0 fewer; moderate certainty in the estimated effects). The guideline also suggested that varenicline is more cost-effective compared to nicotine patch. Uptake of varenicline was noted to be lower than that of the patch, perhaps due to underprescribing or limited availability, but was considered a feasible option.

Consensus Issues

Based on the evidence presented, consensus panelists unanimously agreed that pharmacologic therapy is beneficial, however, with a low certainty of evidence and weak strength of recommendation. No other issues were raised during the discussion.

There is no available local data on the resource requirements and cost-effectiveness of pharmacotherapy for smoking cessation based on the response of the consensus panel on the evidence-to-decision table.

Research Question 6: Among adult smokers, should we use combination pharmacologic therapies over single pharmacologic therapy, in facilitating continuous smoking abstinence and in minimizing adverse events?

RECOMMENDATION 6.
Among adult smokers, we suggest the use of combination pharmacotherapy (nicotine patch and nicotine gum, varenicline and bupropion, and varenicline and nicotine patch) over single pharmacotherapy in facilitating smoking abstinence and in minimizing adverse events *(Low certainty of evidence, Weak recommendation)*

Evidence Summary
Thirteen RCTs (n=8,601) [131-142] were included in the analysis that compared combination pharmacotherapy over single pharmacotherapy in facilitating smoking abstinence. In terms of CAR at 6 months, combination pharmacotherapy is as good as or better than single pharmacotherapy (RR:1.20; 95% CI 0.97,1.48) [131-137]. A significant benefit with combination pharmacologic treatment (RR: 1.22; 95% CI 1.12,1.32) was seen on 7-day point prevalence abstinence rates at 6 months [131,133,135,138-142]. Likewise, a significant benefit was seen with the use of varenicline combined with either NRT or bupropion when compared with varenicline alone (RR: 1.10; 95% CI 0.94,1.39) [133,135,137,143] in terms of continuous abstinence rate at 6 months. Comparison of bupropion alone and bupropion with NRT in terms of continuous abstinence rate at 6 months showed inconclusive results (RR:0.87; 95% CI 0.68,1.10) [131,144]. Significant benefit was also seen with the use of combination NRT as compared to NRT alone in terms of continuous abstinence rate at 6 months (RR: 1.52; 95% CI 1.12, 2.06) [134,136].

Inconclusive results were seen on the occurrence of headache (RR: 1.12; 95% CI 0.98, 1.35) [131-135,138,139,141,145], insomnia, nausea (RR: 1.06; 95% CI 0.94, 1.21) [131,135,137-39,141,145], and vomiting (RR: 0.99; 95% CI 0.70, 1.42) [137,138,141]. On the other hand, combination therapy is attributed to a higher occurrence of insomnia (RR: 1.15; 95% CI 1.05, 1.26) [131,133,135,137-139,141,144].

The overall quality of evidence is low due to serious risk of bias.

Other Considerations
Cost
Direct cost showed combination treatment to cost more than single pharmacotherapy. Estimated total cost of combination NRT of gum and patch ranges from Php 34,020.00 to Php 72,135.00, whereas the combination of nicotine lozenge and patch ranges from Php 47,835.00 to Php 55,935.00. Individual costs

of NRTs and varenicline are tabulated in Table 7. There was no available cost for bupropion.

Availability/Equity
Among the pharmacotherapies available in the Philippines, only nicotine gum, patch, and lozenge are available. Nicotine inhalers and sprays are not available. Varenicline is widely available. Bupropion is in the Philippine market but is not readily available in all drug stores.

Patient's Values or Preferences/Social Impact
In the study of Herrera et al in a select barangay in Mandaue City, 68% of their respondents were willing to quit [146]. There was no local study found that looked specifically at patients' preferences between monotherapy and combination therapy.

Acceptability or Compliance/Feasibility
In the aforementioned study and another by Castro et. Al., efficacy of smoking cessation was strongly correlated with knowledge of smoking consequences [146,147]. According to the study of Pasaporte et. al. in the Lung Center of the Philippines, at least 87% of physicians assist their patients in smoking cessation [148].

Recommendations from Other Groups
According to 2020 Surgeon's General Report, combination NRT has superior efficacy over single NRT. Varenicline with bupropion or NRT seems to have better efficacy over varenicline alone. Bupropion combined with NRT appears to have better efficacy over bupropion alone [149].

The American Thoracic Society recommended varenicline with nicotine patch over varenicline alone, however, this was based on conditional recommendation and low level of certainty of evidence [150].

According to WHO Smoking Cessation Guidelines for Australian general practitioners, combination NRT should be offered if patients continue to experience withdrawal symptoms on one therapy. They also recommended that bupropion combined with nicotine patch should be considered where a smoker has not been successful with any of the aforementioned treatments [151].

Consensus Issues
Combination of varenicline and bupropion, and varenicline and nicotine patch were decided by the panel to be as good as or will offer significant benefit over single pharmacotherapy. This is based on the panel-agreed non-inferiority margin adjusted at 0.9. Adverse events were also noted to be minimal and minor for these combinations allowing for the adjustment of the non-inferiority margin and subsequent consideration for the use of the aforementioned combinations. Certainty of evidence remained low and strength of recommendation remained weak based on the evidence presented. There is no available local data

on the resource requirements and cost-effectiveness of combination pharmacotherapy for smoking cessation based on the response of the consensus panel on the evidence-to-decision table.

Research Question 7: Among adult smokers, should we use pharmacologic therapy alone or in combination with counseling interventions, in facilitating continuous smoking abstinence and in minimizing adverse events?

RECOMMENDATION 7.
Among adult smokers, we suggest the use of pharmacologic therapy in combination with counseling interventions, in facilitating continuous smoking abstinence *(Low certainty of evidence; Weak recommendation)*

Evidence Summary
Twenty-five studies (n=9,221) [152-205] were included in the analysis. At six months, patients who underwent counseling on top of pharmacologic smoking cessation therapy had abstinence rates that were as good as or higher than those given pharmacologic therapy alone (23.1 vs. 19.9%, RR: 1.15, 95% CI: 1.05, 1.27). This finding was consistent both for the studies that used point prevalence abstinence (RR: 1.15, 95% CI: 1.02, 1.28) [176,179,180,185,187,189,190,194, 203,204] and continuous abstinence (RR: 1.15, 95% CI: 0.93, 1.43) [177,178,179,191,193,195,196] as outcome definition. At twelve months, the findings for point prevalence and continuous abstinence were both inconclusive. However, pooled analysis of all included studies showed that smoking abstinence rates with pharmacotherapy plus counseling were as good as or higher than pharmacotherapy alone (RR: 1.07, 95% CI: 0.90, 1.27) [153,158,159,162,163,166,169,175,179,188,199,203,204].

Subgroup analysis by type of counseling revealed that interventions using a combination of multiple approaches significantly improved abstinence rates at six months (RR: 1.22; 95% CI: 1.08, 1.39) [191,193,194,195,203-205], while the findings were inconclusive for motivational interview and cognitive behavioral therapy at both time points. Test for subgroup differences revealed no significant heterogeneity between the different intervention methods (I^2=0%).

Subgroup analysis by type of counseling revealed that interventions using a combination of multiple approaches significantly improved continuous abstinence rates at six months (RR: 1.33, 95% CI: 1.11, 1.60). Findings were all inconclusive for smoking abstinence at 12 months. Test for subgroup differences revealed no significant heterogeneity between the different intervention methods (I^2=0%).

On the other hand, subgroup analysis by class of pharmacologic agent revealed a significant difference between groups (I^2=55.7%) for continuous abstinence rates at six months. For this outcome, only patients using NRT had a significant benefit with the addition of counseling (RR: 1.40, 95% CI: 1.14, 1.72). The results were inconclusive for both bupropion and varenicline. Abstinence rates at twelve months were uniformly inconclusive for all three agents, with no significant subgroup

difference detected (I^2=0%). Table 8 below shows the abstinence rates between pharmacologic therapy alone and pharmacologic therapy with counseling in adult smokers.

Table 8. Comparison of abstinence rates between pharmacologic therapy alone and pharmacologic therapy with counseling in adult smokers

Outcome	No. of studies	n	Pharma alone (%)	Pharma + counseling (%)	Risk ratio [95% CI]	Interpretation	CoE
Abstinence at 6 months							
Continuous	6	2,053	21.5	25.2	1.15 [0.93, 1.43]	As good as or better than pharmacotherapy alone	LOW
Point prevalence	14	4,646	19.1	22.3	1.15 [1.02, 1.28]	As good as or better than pharmacotherapy alone	MODERATE
Total	20	6,699	19.9	23.1	1.15 [1.05, 1.27]	As good as or better than pharmacotherapy alone	MODERATE
Abstinence at 12 months							
Continuous	4	1,287	15.6	17.1	1.14 [0.83, 1.57]	Inconclusive	MODERATE
Point prevalence	13	5,045	15.7	17.3	1.05 [0.85, 1.28]	Inconclusive	LOW
Total	17	6,332	15.7	17.3	1.07 [0.90, 1.27]	As good as or better than pharmacotherapy alone	LOW

Adverse events were not significantly different between the two groups. The adverse events enumerated in the table below are related to the use of pharmacotherapy, and the results are unable to demonstrate a benefit for counseling in reducing the incidence of these toxicities.

Table 9. Comparison of adverse events between pharmacologic therapy alone and pharmacologic therapy with counselling in adult smokers

Outcome	No. of studies	n	Pharma alone (%)	Pharma + counselling (%)	Risk ratio [95% CI]	Interpretation	CoE
Anxiety	2	429	28.3	24.6	0.83 [0.54, 1.27]	Inconclusive	LOW
Dizziness	2	429	17.3	17.2	1.00 [0.60, 1.65]	Inconclusive	LOW
Dream abnormalities	1	260	34.1	29.7	0.82 [0.48, 1.38]	Inconclusive	LOW
Dry mouth	2	429	35.0	34.5	0.98 [0.66, 1.46]	Inconclusive	LOW
Headache	2	429	30.1	24.1	0.74 [0.48, 1.14]	Inconclusive	LOW
Insomnia	2	429	32.7	32.5	0.99 [0.66, 1.48]	Inconclusive	LOW
Nausea	2	429	15.9	11.8	0.71 [0.41, 1.23]	Inconclusive	LOW
Rhinitis	1	260	25.8	21.1	0.77 [0.43, 1.37]	Inconclusive	LOW

Application-site reaction	1	260	22.0	32.0	1.67 [0.96, 2.91]	Inconclusive	LOW

The certainty of evidence for the different outcomes was downgraded by one to two levels due to risk of bias and/or imprecision. Additionally, point prevalence abstinence at 12 months was also inconsistent among the included studies, but this resolved upon sensitivity analysis after excluding studies deemed to be at high risk of bias. Certainty of evidence for adverse events was uniformly low due to lack of blinding and imprecision.

Other Considerations

Cost

No local cost evaluation studies have been performed.

Availability/Equity

Smoking cessation counseling programs are only available in select centers in the country. However, the Department of Health Quitline 1558 is a toll-free service that is equipped to provide counseling interventions nationwide.

Social Impact

No local studies have been conducted on patient values or preferences regarding counseling interventions for smoking cessation.

Feasibility

Small local studies have shown that counseling interventions are feasible and effective in promoting abstinence among Filipino smokers [206-209].

Recommendations from Other Groups

The US Preventive Services Task Force through its latest guideline on smoking cessation (2021) gave a Grade A recommendation for the provision of behavioral interventions and pharmacotherapy for cessation to all adult non-pregnant smokers [210]. Recommendation for implementation was at least four counseling sessions with 90 to 300 minutes of total contact time. Evidence for this recommendation was drawn from a 2019 meta-analysis that compared higher versus lower intensity behavioral intervention as an adjunct to pharmacotherapy, and showed that more intensive behavioral intervention increased abstinence rates (19.5 vs 17.1%, RR: 1.15, 95% CI: 1.08, 1.22) [211]. This meta-analysis analyzed both point prevalence abstinence and continuous abstinence together as a single outcome, and included studies that compared different types of behavioral intervention.

Consensus Issues

The panel has decided to suggest the combination of pharmacologic therapy and counseling based on the panel agreed non-inferiority margin adjusted at 0.9 for the outcome of continuous abstinence. This adjustment allowed for the consideration of the combination of pharmacologic and counseling interventions to be as good as or will offer significant benefit as compared to pharmacologic intervention alone.

Furthermore, the benefit of the addition of counseling intervention was more pronounced when the point prevalence abstinence outcome was used, which is an outcome deemed worthy considering also as seen in majority of the studies included in the evidence review. Certainty of evidence remained low and strength of recommendation remained weak, based on the evidence presented.

The combination of pharmacotherapy and counseling interventions is a better smoking cessation intervention than pharmacotherapy alone. It was stressed that smoking cessation interventions should not be addressed with just medications alone but, rather, should be done together with counseling to increase success in continuous smoking cessation.

There is no available local data on the resource requirements and cost-effectiveness of combination pharmacotherapy and counseling interventions for smoking cessation based on the response of the consensus panel on the evidence-to-decision table.

Research Question 8: Among adult smokers, should extended duration pharmacologic therapy be used over standard duration to facilitate continuous smoking abstinence and minimize adverse events?

RECOMMENDATION 8.
Among adult smokers, we recommend the use of extended duration therapy for bupropion to facilitate continuous smoking abstinence *(High certainty of evidence; Strong recommendation)*

RECOMMENDATION 9.
Among adult smokers, we suggest the use of extended duration therapy for varenicline to facilitate continuous smoking abstinence *(Very low certainty of evidence; Weak recommendation)*

RECOMMENDATION 10.
Among adult smokers, we suggest the use of standard duration therapy with nicotine replacement therapy over extended duration therapy to facilitate continuous smoking abstinence *(Low certainty of evidence; Weak recommendation)*

Evidence Summary
11 RCTs (n=6174) [212-225] compared extended duration and standard duration therapy. In terms of 6 months' continuous abstinence, the pooled estimate showed significant benefit of extended compared to standard duration therapy (RR: 1.77, 95% CI: 1.22, 2.57) [212-219], but with significant heterogeneity (I^2= 84%). Sub-group analysis by drug class showed benefit for extended use for bupropion (RR: 3.00, 95% CI: 2.10, 4.27) [212,219] and varenicline (RR: 2.42, 95% CI: 1.20, 4.87) [213,215,218], while it was inconclusive for NRT. Overall quality of evidence from studies on NRT was gauged to be low due to issues on blinding and imprecision. Evidence on the use of bupropion was gauged to be high, while those for varenicline were gauged to be very low due to non-blinding, inconsistency and imprecision.

For the 12 months' continuous abstinence, pooled estimate showed significant benefit of extended compared to standard duration therapy (RR: 1.21, 95% CI: 1.02, 1.43) [213,215-219]. Results of sub-group analysis by drug class were inconclusive but were uniformly in the direction favoring extended duration therapy. Overall quality of evidence from studies on NRT was downgraded to moderate due to lack of blinding in one of the studies included. Those on bupropion were deemed high, while those on varenicline very low due to non-blinding, imprecision and inconsistency.

There was no significant difference in the number of patients with adverse events between the two groups (RR: 0.00, 95% CI: -0.03, 0.03) [214,215]. However, on sub-group analysis of serious adverse drug events, there was a trend towards harm with extended duration drug therapy but this was not clinically significant (RR: 1.50, 95% CI: 0.84, 2.69) [215,220]. Moreover, the serious adverse drug events were either unrelated to treatment or occurred during the standard rather than extended phase of treatment. Overall quality of evidence for studies on adverse events of extended duration therapy was deemed moderate due to lack of blinding in some studies.

Other Considerations

Cost

There was no local cost-effectiveness or costing study comparing extended vs standard duration therapy; however, increments of cost are expected to be twice to four-fold depending on the length of extension. Refer to Domain 2 for the cost of smoking cessation behavioral therapies and to Table 7 for the cost of different pharmacotherapies for smoking cessation.

Recommendations from Other Groups

The American Thoracic Society Clinical Practice guideline on Initiating Smoking Cessation (2020) recommends the use of extended duration pharmacologic therapy to improve rates of 7-day point prevalence of smoking abstinence at 12 months, with evidence graded as moderate with a high risk of bias [221].

The 2018 American College of Cardiology Tobacco Cessation clinical pathway also recommends the use of at least 3 months of NRT, and 3-6 months of varenicline or bupropion for smoking cessation; no recommendation grade mentioned [222].

Consensus Issues

The panel noted that the evidence for extended duration of NRT has inconclusive evidence that it is superior to standard duration therapy in facilitating continuous abstinence in terms of 6 months' continuous abstinence. With this, the panel recognized the known benefit of the use of standard duration NRT in facilitating continuous smoking abstinence and decided to retain and suggest the use of standard duration over the extended duration instead. There is no available local data on the resource requirements and cost-effectiveness of standard versus extended pharmacotherapy for smoking cessation based on the response of the consensus panel on the evidence-to-decision table.

Domain 4. Vape, Electronic Nicotine Delivery System, Electronic Non-Nicotine Delivery Systems, and Heated Tobacco Products

Research Question 9: Among nonsmokers/non-tobacco users, does the use of electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS) or vapes, heated tobacco products (HTP) facilitate nicotine dependence (continued use of vape, transition to become tobacco product user, dual users of tobacco product and vape) and is associated with adverse effects?

RECOMMENDATION 11.
Among nonsmokers and non-tobacco product users, we suggest against the use of electronic nicotine delivery systems, electronic non-nicotine delivery systems or vapes, heated tobacco products due to their association with subsequent cigarette smoking and association with continued electronic nicotine delivery systems/electronic non-nicotine delivery systems use and adverse effects *(Very low certainty of evidence; Weak recommendation)*

Evidence Summary
Nineteen longitudinal cohorts (n=72,284) [226-244] were included on the use of electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS), and vape among baseline nonsmokers and its association with continued use of e-cigarettes, transition to become a cigarette smoker, dual users of tobacco product and e-cigarettes. No studies were retrieved on the use of heated tobacco products (HTP). Table 10 below summarizes the key results.

Table 10. Summary of outcomes on the use of e-cigarettes and association with future cigarette or e-cigarette smoking

Outcome (baseline compared to follow-up)	Odds ratio [95% CI]	Interpretation	Sample size
Ever e-cigarette use and its association on subsequent smoking	3.32 [2.58, 4.28]	Associated with cigarette smoking	n = 71, 992 18 studies
Ever e-cigarette use and its association on past 30-day smoking	4.37 [2.17, 8.80]	Associated with cigarette smoking	n = 17, 265 4 studies

Past 30-day e-cigarette use and its association on past 30-day smoking	3.09 [1.25, 7.66]	Associated with cigarette smoking	n = 7, 201 2 studies
Past 30-day e-cigarette use and its association on ever smoking	3.41 [1.57, 7.41]	Associated with cigarette smoking	n = 2, 163 1 study
Ever e-cigarette use and its association on past 30-day e-cigarette smoking	7.29 [4.10, 12.96]	Associated with e-cigarette smoking	n = 3, 426 1 study
Past 30-day e-cigarette use and its association on past 30-day e-cigarette smoking	7.28 [4.86, 10.91]	Associated with e-cigarette smoking	n = 5, 038 1 study
Past 30-day e-cigarette use and its association on dual use	8.86 [5.08, 15.45]	Associated with dual use	n = 5, 038 1 study

According to case reports, the use of e-cigarettes is associated with adverse events such as (1) blast injuries from explosion from assembled devices or batteries ; thermal burns from battery and assembled device explosions; cervical spine fracture (n=127) [245,246]; (2) pulmonary-related complications (i.e., e-cigarette, or vaping, product use-associated lung injury, pneumothorax, pneumonia, acute respiratory distress syndrome, pneumonitis, asthma exacerbation, diffuse alveolar hemorrhage (n=58 form individual cases; n=217 from aggregate studies [245]; (3) conjunctival intraepithelial neoplasia (n=28) [247-251]; (4) dermatitis (n=5) [245]; (5) cardiovascular-related symptoms (i.e., coronary events, supraventricular tachycardia, elevation of cardiovascular risk, increase in blood pressure) (n=2) [252-255]; (6) hepatic injury (n=1) [256]; (7) methemoglobinemia (n=1) and polycythemia (n=1) [257,258]; (8) dental caries (n=3) [259]; (9) neonatal necrotizing enterocolitis during in utero exposure (n=1) [245]; hypokalemia, lingua villosa nigra, lichenoid eruption, necrotic ulcer, and acute uvulitis (n=1 for each case) [245,260]. The use of e-cigarette is also associated with accidental or intentional ingestion and poisoning, with some resulting in death [245] and increase in medication levels of clozapine and increase seizure frequency [261].

The Center for Disease Control (CDC) has reported a total of 2,807 hospitalized cases or deaths resulting from the use of these agents in America, Puerto Rico and UR Virgin Islands [262]. Laboratory studies show that the presence of Vitamin E acetate, a component of some tetrahydrocannabinol (THC)-containing e-cigarettes, may be responsible for these cases. Use of e-cigarettes may also result in the following effects: 1) nicotine addiction; 2) developmental effects on the brain; 3) influence on the use of illicit drugs; and 5) effects on mental health. In addition, exposure to secondhand smoke may also place other people at risk [263]. According to the National Academy of Sciences, Engineering, and Medicine (NASEM), e-cigarettes and aerosols may contain certain chemicals such as tobacco-

specific nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, tobacco alkaloids, flavorings, and drugs. E-cigarettes may also contain propylene glycol, vitamin E acetate, and metals such as lead and arsenic. Acrolein, an irritant, and glycidol, a carcinogen, have also been reported as by-products of propylene glycol and glycerol thermal decomposition in e-cigarette smokers. Other compounds include tobacco-specific nitrosamines, benzene, formaldehyde, and aldehyde. According to WHO, HTPs still have an addictive potential due to the presence of nicotine. In addition, the use of these products results in the production of toxicants, including mutagenic and cytotoxic emissions in a dose-dependent manner. Among non-smokers who initiate HTP use, there is an increased risk for adverse events such as pulmonary and cardiovascular complications. Secondhand smoke may also place other people at risk--similar to tobacco and e-cigarette use [264].

Other Considerations

Cost

There is no local cost-effectiveness data on the use of e-cigarettes. Legislators passed House Bill 9007 known as the "Non-Combustible Nicotine Delivery Systems Regulation Act" to regulate the production, sale, distribution, and promotion of e-cigarettes and heat tobacco products in the Philippines in an effort to safeguard the consumers from these [265]. The estimated costs of locally available e-cigarette devices are as follows:

1. RELX Pod Pro MENTHOL PLUS For INFINITY DEVICE AND ESSENTIAL DEVICE (Vape Juice) - Php 250. 00
2. BUNDLE RELX Essential Device GREEN + 1 Pod Pro - Php 550.00
3. BUNDLE RELX Infinity Device DEEP BLUE + 1 Pod Pro - Php 1,185.00
4. JUUL Starter Kit - Php 1,750.00

Recommendations from Other Groups

The WHO prohibits the sale of ENDS and ENNDS in which the user can control device features and liquid ingredients (i.e., open systems) and ENDS with a higher abuse liability than conventional cigarettes. They also prohibited the addition of pharmacologically active substances such as cannabis and THC (in jurisdictions where they are legal), other than nicotine in electronic nicotine delivery systems, to electronic nicotine delivery systems and electronic non-nicotine delivery systems. Manufacturers and associated groups are prohibited from making claims about reduced harm of HTPs as compared with other products until further evidence on its public health impact is available. Policy-makers are also urged to clearly communicate to the public that there is currently no evidence that HTPs reduce the risks associated with tobacco products [264].

The NASEM mentioned that there is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults [266].

Consensus Issues

The panel strongly suggested against the use of ENDS, ENDDS, and HTPs among non-smokers due to the significant harms associated with its use that was stated in the case reports. It was deemed to be moderately costly as a recreational habit.

Research Question 10: Among adult and adolescent smokers, should we use electronic nicotine delivery systems/electronic non-nicotine delivery systems over its non-use in facilitating smoking abstinence and in minimizing adverse events?

RECOMMENDATION 12.
Among adult and adolescent smokers, there is insufficient evidence to recommend the use of electronic nicotine delivery systems/electronic non-nicotine delivery systems to facilitate smoking abstinence *(Low certainty of evidence)*

Evidence Summary
Seventeen randomized controlled trials (RCT) (n=11,176) [267-279] were found on the safety and efficacy of the use of ENDS/ENNDS in facilitating smoking abstinence.

ENDS
ENDS compared to NRT for smoking cessation
Three studies [267-269] evaluated smoking abstinence at 3 months comparing ENDS with nicotine replacement therapy. Pooled data from the RCTs showed that the effect of ENDS on smoking cessation is not different compared to nicotine replacement therapy (RR: 1.20; 95% CI 0.76, 1.88, I^2 74%, p=0.02). Significant heterogeneity may be secondary to the variation of cigarettes smoked per day, smoking duration and type of NRT used.

Four studies [268-271] evaluated continuous smoking abstinence for 6 months using ENDS compared to nicotine replacement therapy. Pooled data from RCTs done from 2013 and 2019 showed that the effect of ENDS on smoking cessation was similar compared with NRT (RR: 1.42; 95% CI 0.92,2.19, I^2 66%, p=0.03). Heterogeneity may also be due to differences in baseline characteristics of the included participants across the studies.

Three RCTs [267,268,271] compared adverse events between e-cigarettes and NRTs with two studies evaluating adverse events at 12 weeks and 1 study at 6 months. Pooled data shows a non-significant difference between adverse events on the two groups (RR: 1.03; 95% CI 0.91,1.18, I^2 0%, p=0.63). Most common adverse reactions reported include nausea, sleep disturbance and throat/mouth irritation and no serious adverse events were classified as probably or definitely caused by the study products.

Overall certainty of evidence was downgraded to low due to heterogeneity and imprecision for smoking abstinence and downgraded to moderate for adverse events due to imprecision.

The study by Hajek et al [268] evaluated the intervention cost of NRT compared to ENDS for smoking cessation. The mean intervention delivery cost was higher for NRT compared to ENDS (201 versus 100 euros) with the 24-hour patch and 16-hour patch as the most popular NRT among the participants.

ENDS compared to varenicline for smoking cessation
A single RCT [272] compared varenicline to ENDS for smoking cessation. Data showed higher smoking abstinence with the use of varenicline (RR: 0.31; 95% CI 0.11,0.82). There were no documented adverse events during the treatment period with either varenicline or ENDS.

ENDS compared to counseling/behavioral support or no support for smoking cessation
Six RCTs [273-278] compared ENDS to counseling/behavioral support or no support for smoking cessation. Pooled data from the studies showed that electronic cigarettes appear to be more beneficial as a smoking cessation aid compared to counseling alone or no support (RR: 2.46; 95% CI 1.44,4.19, I^2 0%, p=0.94). Certainty of evidence was downgraded to low due to imprecision with very low event count (<100) and high risk of bias (lack of blinding).

Three RCTs evaluated adverse events between the two groups with two studies [274,277] evaluating adverse events at 12 weeks while one study [276] evaluated adverse events at 24 weeks (RR: 2.16; 95% CI 0.50,9.35), I^2 70%, p=0.04). Overall certainty was also downgraded to low due to imprecision, heterogeneity and high risk of bias.

In addition to efficacy and safety, cost effectiveness was also evaluated in two of the six RCTs included [273,279]. Average cost per participant assigned to each intervention was consistently lower in the usual care group compared to the electronic cigarette group. However, mean cost for the study duration was significantly higher in the usual care group for the study of Dawkins et. al. [273] due to emergency and hospital visits offsetting the cost for the electronic cigarette arm (957 versus 682 euros at 12 weeks).

ENDS compared to ENNDS for smoking cessation
Three RCTs [271,274,275] evaluated electronic nicotine versus non-nicotine devices as smoking cessation aid for combustible cigarette smokers. Comparison between the two devices showed no significant difference in smoking cessation at 6 months (RR: 1.37; 95% CI 0.78,2.42, I^2 0%, p=0.81).

Evaluating safety of electronic cigarettes, three RCTs [271,274,278] compared ENDS with ENNDS. Pooled data from the three RCTs – with adverse events recorded at 1, 12 and 24 weeks showed no significant difference between ENDS and ENNDS in terms of adverse events (RR: 1.01; 95% CI 0.95,1.07, I^2 0%, p=0.88). Overall certainty of evidence for efficacy and safety were downgraded to low due to imprecision and risk of bias.

There are currently no published studies as of this review comparing the cost-effectiveness of either electronic delivery systems as a smoking cessation tool.

ENNDS

ENNDS compared to NRT for smoking cessation

A study done in 2019 (Lee et. al) [280] evaluated ENNDS versus NRT for smoking cessation. It showed no significant difference between the two groups (RR: 0.76; 95% CI 0.43,1.34). Adverse events were more common in the NRT group and were primarily limited to non-serious adverse events including dizziness, nausea and vomiting (RR: 0.33; 95% CI 0.12,0.87). Certainty of evidence was downgraded to low due to imprecision and risk of bias.

ENNDS compared to behavioral support only/no support

Two RCTs [274,275] evaluated ENNDS compared to behavioral support only/no support. Compiled data shows no difference for smoking cessation between the two groups (RR: 1.74; 95% CI 0.76,3.96, I^2=0%, p=0.63). Adverse events at 6 months was reported in one RCT [67] and it was statistically non-significant between the two groups (RR: 1.19; 95% CI 0.33, 4.33).

Other Considerations

Cost

The study by Hajek et. al. [268] showed that the mean intervention delivery cost was higher for NRT compared to ENDS [EUR 201 (~Php 11,670.03) versus EUR 100 (~Php 5,805.99)], with the 24-hour patch and 16-hour patch as the most popular NRT among the participants. Refer to Domain 3 for the cost of locally available NRTs. The comparison between the average cost of ENDS, counseling/behavioral support, and no support for smoking cessation per participant assigned to each intervention was consistently lower in the usual care group compared to the e-cigarette group [273-278]. However, the mean cost for the study duration was significantly higher in the usual care group for the study of Dawkins et. al. due to emergency and hospital visits offsetting the cost for the e-cigarette arm (957 versus 682 euros at 12 weeks). According to the study that evaluated the cost-effectiveness of e-cigarettes and NRT in stop-smoking services in England, using e-cigarettes as a smoking cessation aid with standard behavioral support in stop-smoking services in England is likely to be more cost-effective than using NRT in the same setting [281]. In the Philippines, there is no published study to date evaluating the safety and efficacy of ENDS/ENNDS for smoking abstinence.

E-cigarettes have been currently promoted as smoking cessation aids mainly by providing cognitive expectancies while promising reductions in craving to smoke cigarettes [282]. While proposed safe, they contain uncertain quantities of various ingredients that can alter the pharmacokinetics of nicotine and have an uncertain impact on the nature of e-cigarette use with little long-term published data known of its long-term health consequence [283]. With this, further data are needed regarding the long-term implications of using e-cigarettes as a smoking cessation aid.

Recommendations from Other Groups

The CDC currently has no recommendation on the use of e-cigarette as smoking cessation aids and continues to advocate US Food and Drug Administration (FDA)-approved smoking cessation medications and behavioral counseling as effective treatments for quitting smoking [284]. In the Philippines, DOH and FDA have released warnings regarding the health effects and safety concerns of using ENDS/ENNDS, and is currently not recommended as a smoking cessation aid [285].

Consensus Issues

Since there is insufficient evidence, the panel cannot recommend the use of ENDS/ENNDS to facilitate continuous smoking abstinence. Further data on its efficacy, safety, and cost-effectiveness as a smoking cessation tool is needed to make a recommendation for or against its use.

APPENDIX. Evidence-to-Decision (ETD) Tables

ETD 1. Among adult smokers, should we use smoking biomarkers in determining smoking status during smoking cessation?

Priority	Yes (37.5%)	Varies (27.5%), Uncertain (37.5%)			
Benefits	Small (12.5%), Moderate (25%0 to Large (12.5%)	Trivial (12.5%), Varies (12.5%), Uncertain (25%)			
Harms	Small (25%)	Trivial (50%), Uncertain (25%)			
Certainty of Evidence	Moderate (25%) to High (12.5%)	Very low (62.5%)			
Balance of effects	Favors (25%)/probably favors treatment (12.5%)	Uncertain (62.5%)			
Accuracy of the test	Accurate to very accurate			Inaccurate	Varies
Patient values and preference	Important to possible important uncertainty/variability	Probably no important uncertainty/variability			
Resource requirements	Moderate to Large			Varies to don't know	
Certainty of evidence of required resources	Moderate	Low to Very low	No included studies		
Cost-effectiveness	Favors the diagnostic test				Favors the comparison
Equity	Increased to probably increased	Reduced to probably reduced	Varies to no impact		
Acceptability	Yes to probably yes		No to probably no	varies	
Feasibility	Yes to probably yes		No to probably no	varies	

ETD 2. Among adult and adolescent smokers, should we use intensive behavioral therapies over brief tobacco interventions in facilitating smoking abstinence?

Priority	Yes (87.5%)	varies (12.5%)	
Benefits	Moderate (50%)	Trivial (12.5%), Uncertain (12.5%), Large (25%)	
Harms	Small (50%)	Uncertain (25%)	
Certainty of Evidence	Low (100%)		
Balance of effects	Favors (25%)/probably favors treatment (12.5%)	Uncertain (12.5) Probably does not favor treatment (12.5%)	
Patient values and preference	Possibly important uncertainty or variability (50%)	Probably no important uncertainty/variability (37.5%) No important uncertainty/variability (12.5%)	
Resource requirements	Moderate (25%) to Large (25%) savings	Moderate costs (25%) Large costs (12.5%) Varies (12.5%)	
Certainty of evidence of required resources	Moderate (50%)	No included studies (37.5%), Very low 12.5%	
Cost-effectiveness	No included studies (50%), Varies (25%)	Favors Comparison (12.5%)	Favors intervention (12.5%)
Equity	Increased (25%), Probably increased (12.5%), Don't know (12.5%)	Varies (12.5%) , probably reduced (25%), to probably no impact (12.5%)	
Acceptability	Yes (62.5%) to probably yes (25%)	Varies (12.5%)	
Feasibility	Yes (37.5%) to probably yes (37.5%)	Varies (25%)	

ETD 3. Among adult/adolescent smokers who are ready to quit, is group therapy more effective than individual therapy in facilitating smoking abstinence?

Priority	Yes (62.5%)		Varies (25%), Uncertain (12.5%)
Benefits	Moderate (25%)	Small (37.5%), Trivial (25%), Varies (12.5%)	
Harms	Large (12.5%)	Uncertain (62.5%), Trivial (12.5%), small (12.5%)	
Certainty of Evidence	Moderate (12.5%)	Low (75%) to very low (12.5%)	
Balance of effects	Probably favors treatment (62.5%)		Does not favor treatment (37.5%)
Patient values and preference	Important uncertainty (25%)/Probably important uncertainty (50%)		No important uncertainty (12.5%) to probably no important uncertainty (12.5%)
Resource requirements	Don't know (50%), Varies (37.5%)		Large costs (12.5%)
Certainty of evidence of required resources	Low (25%)	No included studies (75%)	
Equity	Probably reduced(37.5%), Don't know (37.5%), varies (25%)		
Acceptability	Yes (37.5%) to probably yes (25%)		Don't know (37.5%)
Feasibility	Yes (25%) to probably yes (37.5%)	Varies (12.5%), Don't know (25%)	

ETD 4. Among adult and adolescent smokers, can behavioral therapy delivered remotely be an alternative to face-to-face in facilitating smoking abstinence?

Priority	Yes (87.5%)			Uncertain (12.5)
Benefits	Large 25%	Trivial (25%), Varies (12.5%), Uncertain (50%)		
Harms	Moderate(25%), Small (12.5%)	Trivial(37.5%) Uncertain (25%)		
Certainty of Evidence	Moderate (25%)	Low (37.5%) to very low (37.5%)		
Balance of effects	Favors (12.5%)/probably favors intervention (87.5%)			
Patient values and preference	Important (12..5%) to possibly important (37.5%) uncertainty/variability	Probably no important uncertainty (37.5%), no important uncertainty (12.5%)		
Resource requirements	Moderate (12.5%) to large costs (12.5%)	Varies (37.5%), Don't know (37.5%)		
Certainty of evidence of required resources	Moderate (12.5%)	Low (50%)	No included studies (37.5%)	
Cost-effectiveness	Favors Intervention (62.5%), Probably favors intervention (25%)			Probably favors the comparison (12.5%)
Equity	Probably Increased (12.5%)	probably reduced (25%), probably no impact (12.5%)	Varies (50%), Don't Know (12.5%)	
Acceptability	Yes (37.5%), Probably Yes (37.5%)			Varies (25%)
Feasibility	Yes (25%) to probably yes (37.5%)		Varies (37.5%)	

ETD 5. Among smokers, is the use of pharmacologic therapy more effective and safe than non-use of pharmacologic therapy, in facilitating smoking abstinence and minimizing adverse drug reaction/s?

Priority	Yes (7)						
Benefits	Large (5)					Moderate (2)	
Harms	Moderate (4)				Small (3)		
Certainty of Evidence	High (4)				Moderate (3)		
Balance of effects	Favors treatment (6)						Probab. favors treatment (1)
Patient values and preference	Possibly important uncertainty/variability (3)			Probably no important uncertainty/variability (3)			No important uncertainty/ variability (1)
Resource requirements	Don't know (2)		Varies (1)	Moderate costs (2)		Large savings (1)	Negligible costs or savings (1)
Certainty of evidence of required resources	No included studies (4)				Low (2/7)		Very low (1)
Cost-effectiveness	No included studies (5)					Varies (1)	Favors the intervention (1)
Equity	Varies (2)		Probably increased (3)			Increased (2)	
Acceptability	Probably yes (4)				Yes (3)		
Feasibility	Probably yes (5)					Yes (2)	

ETD 6. Among adult smokers, should we use combination pharmacologic therapies over single pharmacologic therapy, in facilitating smoking abstinence and in minimizing adverse events?

Priority	Yes (7)						
Benefits	Large (1)	Moderate (4)				Trivial (1)	Uncertain (1)
Harms	Moderate (1)	Small (5)					Trivial (1)
Certainty of Evidence	Low (7)						
Balance of effects	Favors treatment (5)					Probab. favors treatment (1)	Uncertain (1)
Patient values and preference	Important uncertainty/ variability (1)	Possibly important uncertainty/variability (4)				Probably no important uncertainty/ variability (2)	
Resource requirements	Large costs (2)		Moderate costs (5)				
Certainty of evidence of required resources	No included studies (5)					Low (1)	Very low (1)
Cost-effectiveness	No included studies (4)				Varies (2)		Favors comparison (1)
Equity	Don't know (1)	Varies (1)	Probably increased (3/7)			Probably reduced (2)	
Acceptability	Varies (1)	Probably no (1)	Probably yes (2)	Yes (3)			
Feasibility	Probably yes (4)			Don't know (1)	Yes (2)		

ETD 7. Among adult smokers, should we use pharmacologic therapy alone or in combination with counselling interventions, in facilitating continuous smoking abstinence and in minimizing adverse events?

Priority	Yes (7)						
Benefits	Large (2)		Moderate (3)			Trivial (1)	Uncertain (1)
Harms	Small (4)				Trivial (2)		Uncertain (1)
Certainty of Evidence	Moderate (2)		Low (7)				
Balance of effects	Favors treatment (3)			Probably favors treatment (3)			Uncertain (1)
Patient values and preference	Possibly important uncertainty/variability (4)				Probably no important uncertainty/ variability (3)		
Resource requirements	Don't know (2)		Moderate costs (4)				Moderate savings (1)
Certainty of evidence of required resources	No included studies (5)					Moderate (1)	Very low (1)
Cost-effectiveness	No included studies (6)						Prob favors intervention (1)
Equity	Varies (2)		Probably reduced (1)	Probably increased (4)			
Acceptability	Probably yes (3)			Yes (4)			
Feasibility	Probably yes (3)			Yes (4)			

ETD 8. Among adult smokers, should extended duration pharmacologic therapy be used over standard duration to facilitate continuous smoking abstinence?

Priority	Yes (7)						
Benefits	Large (1)	Moderate (5)					Trivial (1)
Harms	Moderate (4)				Small (2)		Uncertain (1)
Certainty of Evidence	High (1)	Moderate (2)		Low (4)			
Balance of effects	Favors treatment (3)			Probably favors treatment (3)			Uncertain (1)
Patient values and preference	Possibly important uncertainty/variability (5)					Probably no important uncertainty/ variability (2)	
Resource requirements	Varies (2)		Large costs (2)		Moderate costs (3)		
Certainty of evidence of required resources	No included studies (5)					Low (1)	Very low (1)
Cost-effectiveness	No included studies (5)					Varies (1)	Favors comparison (1)
Equity	Reduced (1)	Probably reduced (2)		Probably increased (3)			Increased (1)
Acceptability	Varies (1)	Probably no (1)	Probably Yes (3)			Yes (2)	
Feasibility	Varies (2)		Probably no (1)	Probably Yes (2)		Yes (2)	

ETD 9. Among nonsmokers/non-tobacco product users, does the use of electronic nicotine delivery systems (ENDS), electronic non-nicotine delivery systems (ENNDS), heat tobacco products (HTP), or vape facilitate nicotine dependence (continued use of vape, transition to become tobacco product user, dual users of tobacco product and vape) and is associated with adverse effects?

Priority	Yes				
Benefits	Large	Small	Trivial, Uncertain		
Harms	Large				
Certainty of Evidence	High	Low to very low			
Balance of effects	Favors/probably favors interevention				Does not favor intervention
Patient values and preference	Important to possible important uncertainty/variability				
Resource requirements	Moderate to Large				Varies
Certainty of evidence of required resources	Low to Very low			No included studies	
Cost-effectiveness	Favors the intervention	Favors the comparison	Varies	No included studies	
Equity	Increased	Reduced, probably reduced, no impact			varies
Acceptability	Yes to probably yes	No to probably no			varies
Feasibility	Yes to probably yes			Probably no	Varies, Don't know

ETD 10. Among adult and adolescent smokers, should we use ENDS/ENNDS over its non-use in facilitating smoking abstinence and in minimizing adverse events?

Priority	Yes		No		Varies
Benefits	Large	Small	Trivial, Varies, Uncertain		
Harms	Moderate to large		Small	Uncertain	
Certainty of Evidence	Moderate	Low to very low			
Balance of effects	Favors/probably favors interevention				Does not favor intervention
Patient values and preference	Important to possible important uncertainty/variability				
Resource requirements	Moderate to large costs		Large savings	varies	
Certainty of evidence of required resources	Moderate to high		Low	No included studies	
Cost-effectiveness	No included studies			Favors the comparison	varies
Equity	Increased	Reduced, probably reduced, no impact			varies
Acceptability	Yes to probably yes		No to probably no		varies
Feasibility	Yes to probably yes			Probably no	Varies

CHAPTER IV. DISSEMINATION, IMPLEMENTATION & UPDATING OF THE GUIDELINE

Guideline Dissemination

The final recommendations will be presented to the National Practice Guideline Clearinghouse of the DOH for review, assessment, and approval. It will also be submitted to the Health Technology Assessment Council (HTAC) and will be utilized accordingly by the DOH. Future scientific fora and access to the guidelines will be ensured according to government policies with assistance from all stakeholders involved.

Guideline Monitoring and Updating

This CPG will be assessed by monitoring adherence to the recommendations, and more importantly, evaluate outcomes such as continuous smoking abstinence rates, quit rates, reduction of tobacco and vape users, and increase in enrolment of smokers in smoking cessation clinics and DOH Quitline. The SC plans to update the guideline after three (3) years, considering new evidence, availability of resources and interventions, and the results of the monitoring.

CHAPTER V. APPLICABILITY ISSUES

Issues related to equity, feasibility, and availability of the smoking cessation interventions may influence the implementation of the recommendations at a national level. The lack of availability of the interventions in other areas, especially in remote areas, may promote health inequity. Active efforts must be done to address the issues on cost, accessibility, feasibility, and equity to facilitate the implementation of the guideline.

CHAPTER VII. DECLARATION OF CONFLICTS OF INTERESTS

All members of the CPG Development Group (i.e., Steering Committee, Consensus Panel, Technical Working Group) signed a Declaration of Conflict of Interest Form. None of the members declared any significant COI.

CHAPTER VII. EDITORIAL INDEPENDENCE

The DOH and Philippine College of Chest Physicians provided funding for the creation of this CPG, however, they did not have any other influence in the CPG development process.

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