Pharmaceutical Benefits Scheme

Post-market Review

Post-market Review of medicines for smoking cessation

Report to the PBAC

ToR 4: Cost-effectiveness review of specified combinations of smoking cessation medicines and estimates for the Pharmaceutical Benefits Scheme

Contents

Abbreviations

Abbreviation	Full Name / Wording
ABS	Australian Bureau of Statistics
AMI	Acute myocardial infarction
AMH	Australian Medicines Handbook
BENESCO	Benefits of Smoking Cessation on Outcomes
BOLD	Burden of Obstructive Lung Disease
BUP	Bupropion
CA	Continuous abstinence
CER	Cost-effectiveness review
CHD	Chronic heart disease
CHE	Centre for Health Economics
COPD	Chronic obstructive pulmonary disease
DPMQ	Dispensed price for maximum quantity
ESC	Economics Sub-Committee
FEV	Forced expiratory volume
GP	General Practitioner
HILDA	Household, Income and Labour Dynamics in Australia
HSI	Heaviness of Smoking Index
ICER	Incremental cost-effectiveness ratio
ICS	Inhaled corticosteroid
ITT	Intention to treat
LABA	Long-acting beta-agonist
LAMA	Long-acting muscarinic antagonist
MBS	Medicare Benefits Schedule
NDARC	National Drug and Alcohol Research Centre
NDSHS	National Drug Strategy Household Survey
NHMRC	National Health and Medical Research Council
NMA	Network meta-analysis
NRT	Nicotine replacement therapy
NSW	New South Wales
OR	Odds Ratio
OTC	Over-the-counter
PBAC	Pharmaceutical Benefits Advisory Committee
PBS	Pharmaceutical Benefits Scheme
PMR	Post-market Review
QBM	Quit Benefit Model
RACGP	Royal Australasian College of General Practitioners
RCT	Randomised controlled trial
RPBS	Repatriation Pharmaceutical Benefits Scheme
RR	Relative risk
QALY	Quality-adjusted life-year
SDI	Smoking Duration and Intensity

TGA	Therapeutic Goods Administration
ToR	Term of reference
VAR	Varenicline

Executive summary

Background

In June 2021, the Economics Sub-Committee (ESC) of the Pharmaceutical Benefits Advisory Committee (PBAC) considered the Post-market Review (PMR) of medicines for smoking cessation report.

The ESC was asked to consider if a cost-effectiveness review (CER) of medicines for smoking cessation should be progressed under term of reference (ToR) 4 of the PMR and if considered necessary, advise on the approach to be undertaken and the potential medicine comparisons to be evaluated. In considering 'options' 2 and 3 (refer to pages 38-44 of the Report summary for the Review options) the ESC advised that a cost-effectiveness analysis of combination nicotine replacement therapy (NRT) versus NRT monotherapy and NRT in combination with varenicline (VAR) versus VAR monotherapy should be progressed under ToR 4 of the Review.

The ESC also considered a confidential submission to the Review from [redacted] that included a cost-effectiveness analysis of [redacted] The ESC noted that the [redacted] submission had not been evaluated by an external evaluation group. The ESC suggested that the department approach [redacted] to obtain supporting information to the economic model to allow an evaluation of this submission. The evaluation commentary of the [redacted] submission and any additional modelled comparisons should be provided to the ESC and the PBAC for consideration at a future meeting.

In August 2021, the Department of Health engaged the services of the Centre for Health Economics, Monash University to undertake an economic evaluation of the [redacted] submission and prepare an evaluation commentary for consideration by the ESC and the PBAC.

Due to the issues with the [redacted] submission identified in the PBAC commentary, the Centre for Health Economics (CHE), Monash University was contracted to conduct a CER of specified combinations of medicines for smoking cessation and estimates for the PBS.

Cost-effectiveness review of specified combinations of medicines for smoking cessation and estimates for the PBS

The economic analysis presented in the CER considers the relative cost-effectiveness of the following comparisons of medicines for smoking cessation:

1. varenicline monotherapy (VAR) versus NRT monotherapy (NRT)
2. Combination varenicline and NRT (VAR+NRT) versus VAR
3. VAR+NRT versus NRT
4. Combination NRT (NRT+NRT) versus VAR
5. NRT+NRT versus NRT
6. VAR+NRT and NRT+NRT versus VAR+NRT

And thus, provided evidence on the cost-effectiveness of the potential PBS listing of the following scenarios:

(i) VAR+NRT only
(ii) NRT+NRT only

(iii) both VAR+NRT and NRT+NRT

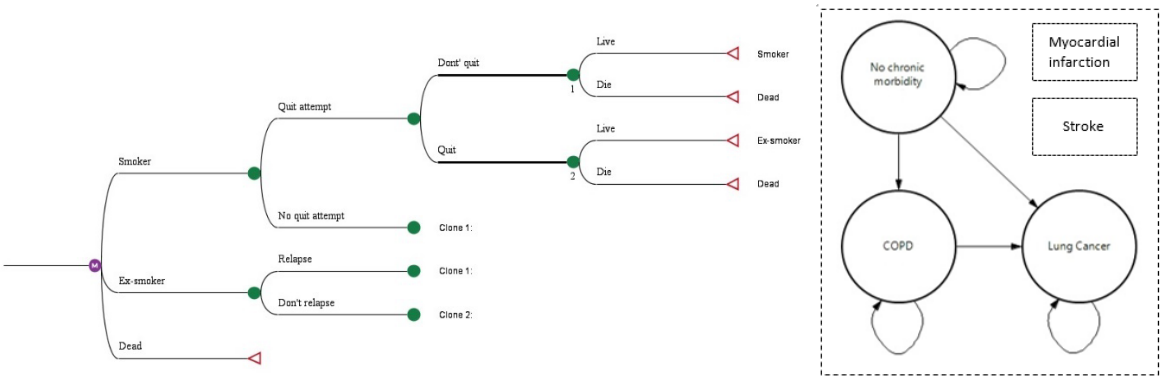
The research also provided estimates of the likely financial implications to the PBS of such listings.

Evaluating the cost-effectiveness of smoking cessation products has distinct challenges. There is often a high chance of relapse, even a year after a successful quit attempt, and individuals can have multiple assisted, and unassisted, quit attempts over their lifetime. Thus, estimating the cost-effectiveness of subsidising access to a new cessation product, or combination of products, for both current, and potentially future, quit attempts requires modelling the probable implications of changes in smoking patterns (e.g., multiple quit attempts or changes in smoking intensity) on the risk of future health events.

The Smoking Duration and Intensity (SDI) model v1.0 was recently developed to model the cost-effectiveness for a number of Australian National Health and Medical Research Council (NHMRC) funded smoking cessation trials (the model is currently not published). It was designed to consider the dynamic nature of smoking cessation and capture the relationship between smoking duration and intensity (as measured by pack-years) on the risk of key smoking-related health events in the contemporary Australian context. Importantly, this model considered the characteristics of Australian smokers currently looking to quit. This aspect of the model is vital because the population attempting to quit has likely changed over time (e.g., those still smoking are more likely to be poorer and smoking at higher intensity than those that were smoking 20 years ago) and these characteristics can influence smoking patterns and, in turn, the benefits associated with cessation.

The SDI model is a state-transition patient simulation model, consisting of health states related to smoking-status (smoker and ex-smoker), as well as smoking-related diseases (chronic obstructive pulmonary disease [COPD], lung cancer, acute myocardial infarction [AMI], and stroke). The four smoking-related diseases included in the model are consistent with those considered by other models in the literature and capture the majority (over 60%) of smoking related mortality. Figure 1 presents the model structure.

Figure 1: SDI model structure (simplified)



All patients enter the model in the smoker health state and make a pharmacologically assisted quit attempt in the first cycle. Conditional on surviving the cycle, patients who 'quit' smoking (defined as 6 months continuous abstinence [CA]) transition to the ex-smoker health state in the subsequent cycle whereas patients who don't quit remain in the smoker health state. In subsequent cycles, patients in the smoker health state have the chance to make additional quit attempts and quit smoking, and patients in the ex-smoker health state have the chance

to relapse and restart smoking. Transition probabilities for relapse and subsequent quit attempts are estimated based on Saxby et al. 2022 which uses a representative sample of Australian smokers and is calibrated with the annual quit attempts reported in the 2019 Australian National Drug Strategy Household Survey (NDSHS). These rates vary by individual characteristics including age and cigarettes smoked per day.

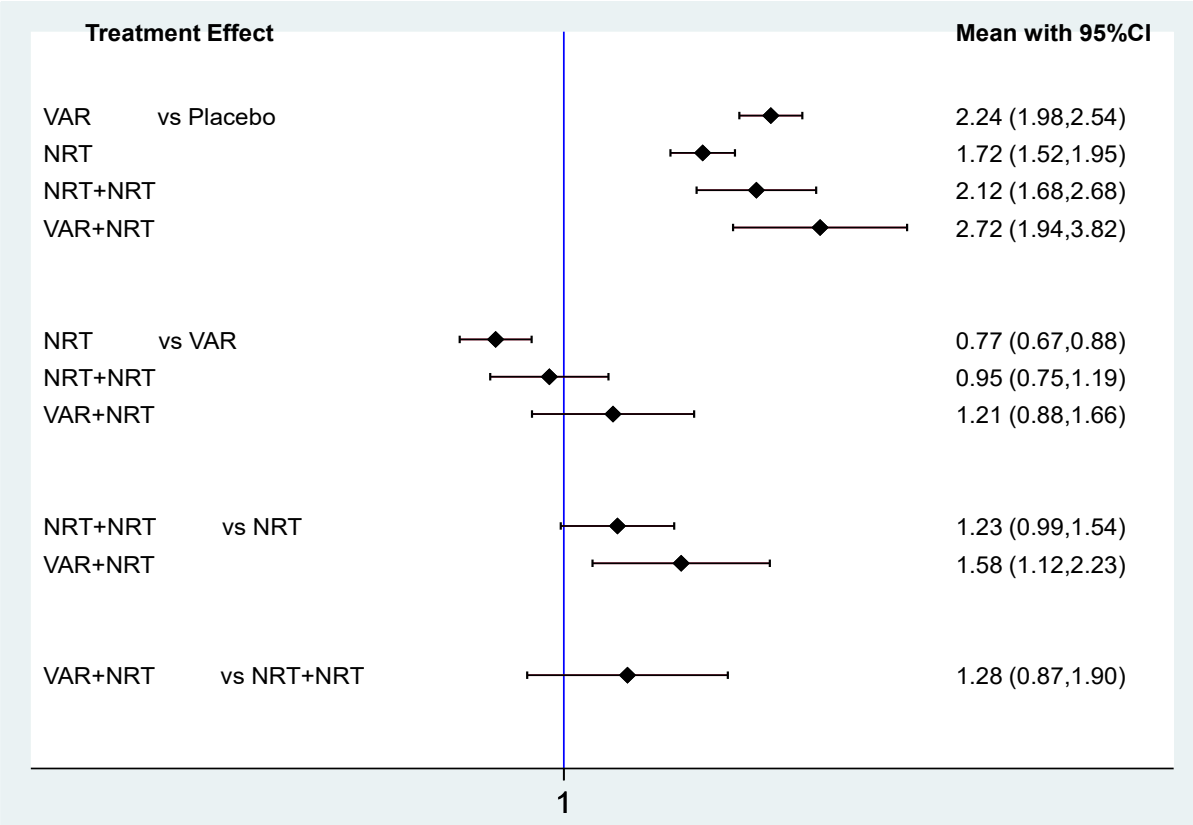
Patients may also start the model within a chronic disease health state if, for example, they have a prior history of COPD or lung cancer. Every cycle, patients without one of these comorbidities ('well') are at risk of developing either COPD or lung cancer, and patients with COPD remain at risk of developing lung cancer. For simplicity, the model does not consider COPD diagnosis or progression after a lung cancer diagnosis (this is primarily due to the short overall survival expected with lung cancer and therefore will have little impact). The COPD health state is further divided into mild, moderate, severe, and very severe disease defined by forced expiratory volume (FEV)1% predicted, which is strongly correlated with costs and outcomes. After diagnosis, patients have the chance to experience worsening COPD each cycle. In addition, all patients are at risk of having an AMI or stroke each cycle, which are modelled as transient events. The model tracks prior transient events to account for changes in risks of subsequent events and ongoing impacts on costs and quality of life. The incidence rates of smoking-related diseases vary by pack-years, years since quitting, age, and sex. The relative risk (RR) by pack-years were obtained from the literature and the underlying incidence based on Australian and international estimates. The mortality from all other causes and smoking related conditions were estimated based on the literature and Australian life tables. Costs associated with these diseases were estimated based on available Australian data and quality of life from the literature.

For this analysis, the population used in the model is a hypothetical sample of smokers with baseline characteristics representative of Australian daily smokers. Specifically, this sample was generated from the Household, Income and Labour Dynamics in Australia (HILDA) survey who reported to 'quit' smoking between 2007 and 2019. The HILDA survey is a large household-based panel study, which collects sociodemographic, economic and wellbeing information from more than 17,000 Australians each year. The HILDA quit population, which includes both shorter-term quitters (i.e., last observed smoking less than one year ago) and longer-term quitters, is a reasonable proxy for Australian smokers looking to quit smoking. The model population had a mean age of 42.0 years, with 51.7% being male, and is more likely to have lower levels of education and income compared to non-smokers. In terms of smoking characteristics, patients had smoked for on average 24.6 years with an average smoking intensity of 12.2 cigarettes per day, corresponding to 15.8 pack-years (see Section 3.4 for further details about the population).

In order to obtain consistent RR estimates of achieving 6-month CA from smoking to apply in the model for each of the alternative cessation products, combination products or unassisted quit attempts, a network meta-analysis (NMA) was estimated based on the available randomised controlled trial (RCT) evidence presented in the ToR 3 report. A summary of the findings is presented in Figure 2 below. There is substantial evidence to suggest that all products and combination products considered are more effective than an unassisted quit attempt (placebo) and that VAR is more effective than NRT (RR=0.77, 95%CI 0.67, 0.88). However, given the limited evidence on the relative effectiveness of NRT+NRT there remains substantial uncertainty about how more effective than NRT it is (RR=1.23, 95%CI 0.99, 1.54) and whether NRT+NRT is less effective than VAR (RR=0.95, 95%CI 0.75, 1.19). Also given the

limited and variable evidence for VAR+NRT there is also still considerable uncertainty on whether it is more effective than VAR (RR=1.21, 95%CI 0.88, 1.66).

Figure 2: 24-week relative risks from the network meta-analysis for smoking cessation therapies



The model uses these RR point estimates and translates what they imply for the chance of successful quitting by considering an underlying quit rate in heavy and light smokers in the VAR arm in a recent Australian RCT (1).

Given that smokers often have many assisted quit attempts during their life, when a new product is listed it may be used in the first quit attempt but also may cause a change in the use of products in subsequent quit attempts. How the listing impacts on its use throughout the treatment pathway will impact on the cost-effectiveness of providing it on the PBS. In the base case analysis, we assume the substitution rates for subsequent quit attempts outlined in Table 1. For the usual care VAR and NRT scenarios the spilt for the subsequent attempts is based on reported use of cessation products in quit attempts in the 2019 NDSHS. The substitution for the listing of the other products is based on expert opinion considering their side effect profiles. While in the base case, we assume that the listing of the new product will not cause individuals to increase their assisted quit attempts, in a sensitivity analysis we also assume that listing the new cessation product/s may encourage additional assisted quit attempts as outlined in Table 2.

Table 1: Treatments used for first and subsequent quit attempts in the model for the base case

Treatment arm	First quit attempt	Treatment used for subsequent quit attempts				
		Unassisted	NRT	VAR	VAR+NRT	NRT+NRT
VAR	VAR: 100%	58.0%	30.0%	12.0%	0%	0%
NRT	NRT: 100%	58.0%	30.0%	12.0%	0%	0%
VAR+NRT	VAR+NRT: 100%	58.0%	21.0%	8.4%	12.6%	0.0%
NRT+NRT	NRT+NRT: 100%	58.0%	15.0%	9.6%	0.0%	17.4%
VAR+NRT & NRT+NRT	VAR+NRT: 40.7%, NRT+NRT: 59.3%	58.0%	9.0%	7.2%	10.5%	15.3%

Note that the NDSHS only asked people whether they tried to quit with a cessation pill. We assume this to be VAR, given that bupropion was not in the scope of this review, and it only makes up a very small part of the cessation pill market in Australia, so this is likely to have little impact.

Table 2: Treatments used for subsequent quit attempts assuming funding leads to an increase in assisted quit attempts, considered in a sensitivity analysis

Treatment arm	Treatment used for subsequent quit attempts				
	Unassisted	NRT	VAR	VAR+NRT	NRT+NRT
VAR+NRT	57.0%	21.0%	8.4%	13.6%	0.0%
NRT+NRT	56.0%	15.0%	9.6%	0.0%	19.4%
VAR+NRT & NRT+NRT	55.75%	9.0%	7.2%	11.25%	16.8%

To evaluate the comparative cost-effectiveness of the different scenarios we simulate a hypothetical cohort of 600,000 patients through the model for each scenario for 50 years, assuming a discount rate of 5% for the base case. However, given that the costs of cessation are upfront and the benefits of cessation, especially for younger smokers, are mostly 20 to 50 years in the future the incremental cost-effectiveness ratios (ICERs) are very sensitive to the discount rate applied (see sensitivity analysis below).

A budget impact model was also constructed to estimate the likely financial implications to the PBS of such listings. The financial model used recent PBS utilisation data for smoking cessation therapies presented in the ToR 2 report and anticipated rates of substitution from monotherapy to combination therapy. The analysis relies on the number of PBS pharmacological assisted quit attempts as a reasonable basis for estimating change in the utilisation of smoking cessation therapies. Given the majority of patients do not currently use combination treatment on the PBS, the proportional use of treatments (NRT, VAR and bupropion [BUP]) by patients is a reasonable proxy for the market share of treatments by quit attempts on the PBS.

In addition to simple substitutions within the current PBS market, the financial model also accounts for growth in PBS-assisted quit attempts associated with substitutions from the non-PBS NRT market, as well as reductions in future quit attempts due to the use of more effective combination therapies. For the base case analysis however, the model assumes the proposed listing scenarios will not impact on the propensity of patients to make a first or subsequent assisted quit attempt (with either PBS or non-PBS treatments).

A key variable to consider is the number of quit attempts made using non-PBS NRT only, which is not captured by PBS data. Estimating this parameter using sales data (e.g., comparing sales for non-PBS NRT versus PBS NRT) is unreliable because it does not control for the number of patients using non-PBS NRT to supplement PBS therapies, patients using more than one non-PBS NRT product, or patients using non-PBS NRT for other reasons (i.e., occasional replacement or non-cessation purposes). Alternatively, data from the NDSHS suggests that

the number of quit attempts made using non-PBS NRT only is approximately 2.8 times the number of quit attempts using PBS-listed NRT.

Table 3 presents the assumed substitution rates in the base case analysis, informed by expert advice.

Table 3: Estimated displacement rates

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Scenario 1 (VAR + NRT listed): displacement of monotherapy for combination therapy					
PBS VAR to VAR + NRT	20%	25%	30%	30%	30%
PBS NRT to VAR + NRT	20%	25%	30%	30%	30%
Non-PBS NRT to VAR +NRT	10%	10%	10%	10%	10%
Scenario 2 (NRT + NRT listed): displacement of monotherapy for combination therapy					
PBS NRT to NRT+NRT	40%	45%	50%	50%	50%
PBS VAR to NRT + NRT	10%	15%	20%	20%	20%
Non-PBS NRT to NRT+NRT	20%	20%	20%	20%	20%
Scenario 3 (VAR+NRT & NRT+NRT listed): displacement of monotherapy for combination therapy					
PBS VAR to combination	20%	30%	40%	40%	40%
PBS VAR to VAR + NRT	15%	20%	25%	25%	25%
PBS VAR to NRT + NRT	5%	10%	15%	15%	15%
PBS NRT to combination	50%	60%	70%	70%	70%
PBS NRT to VAR + NRT	15%	20%	25%	25%	25%
PBS NRT to NRT+NRT	35%	40%	45%	45%	45%
Non-PBS NRT to combination	23%	23%	23%	23%	23%
Non-PBS NRT to VAR+NRT	5%	5%	5%	5%	5%
Non-PBS NRT to NRT+NRT	18%	18%	18%	18%	18%

The assumed substitution rates imply that combination therapy would replace monotherapy in at least 30% of total PBS-assisted quit attempts, with some substitutions more likely than others. The main justification for the relatively moderate levels of substitution assumed for the base case analysis is the current level of uncertainty around the benefits/harms of combination therapies and the uncertainty around clinical recommendations/funding restrictions (for example, combination therapy might be preferred after an unsuccessful quit attempt with monotherapy). Higher rates of substitution are considered in a sensitivity analysis.

In contrast, relatively low substitution is expected from non-PBS NRT given limited financial incentive for patients using non-PBS NRT only to switch to a PBS-listed therapy. However, more patients would likely switch from using non-PBS NRT to PBS-listed combination therapy should combination packs become available on the PBS, as this would dramatically reduce the out-of-pocket costs for patients using multiple therapies.

In terms of other healthcare costs, the financial estimates model only includes the short-term impact on medical consultations associated with the prescribing decisions. The financial model does not estimate cost savings associated with smoking-related diseases, given most benefits from smoking cessation would accrue beyond the time horizon of the financial estimates.

Key findings and results

Economic evaluation

The costs, health outcomes and ICERs for each of the stated comparisons, with a discount rate of 5%, are presented in Table 4 below. The first reported comparison compared the two

major usual care options currently available, VAR versus NRT as the first line therapy, which resulted in an ICER between $55,000 to < $75,000 per quality-adjusted life-year (QALY). The estimated ICERs for VAR+NRT versus these usual care comparators, VAR and NRT, were within the range of $35,000 to < $45,000; whilst the estimated ICERs for NRT+NRT versus VAR and NRT were within the range of $15,000 to < $25,000 and $25,000 to < $35,000 respectively. The scenario of listing both VAR+NRT and NRT+NRT compared to listing VAR+NRT alone was found to be both costlier and less effective (i.e., was dominated).

Table 4: Main cost-effectiveness analysis results (5% discount rate)

Comparison	Costs ($AU)			Health outcomes (QALYs)			ICER range ($ per QALY)
	Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
(VAR) vs (NRT) [a]							
(VAR+NRT) [b] vs (VAR)							
(VAR+NRT) [b] vs (NRT)							
(NRT+NRT) [b] vs (VAR)							
(NRT+NRT) [b] vs (NRT)							
(VAR+NRT & NRT+NRT) [b] vs (VAR+NRT) [b]							

[a] This only considered the use of NRT versus VAR on the first attempt. The assumed use of NRT and VAR for subsequent attempts was assumed to be the same in both cases.
[b] Assumptions were also made about how the listing of these new combinations would also impact on the use of products in subsequent quit attempts. These results were produced by simulating 600,000 patients through each possible scenario for 50 years. 600,000 patients were used to minimise the Monte Carlo error.

The modelling exercise also applied numerous sensitivity analyses to better understand the cost-effectiveness, some of the key ones are presented in Table 5. The results are very sensitive to the discount rate and time horizon given the majority of the health benefits from quitting smoking included in the model accrue many years in the future, especially for younger smokers (e.g., little value is placed on encouraging a 20-year-old smoker to quit and preventing them developing lung cancer at age 65). The higher the discount rate, the less importance is given to future health gains and the cost savings from lower future healthcare costs. The impact of discounting on the cost associated with future quit attempts is more complex. Overall, the impact of discounting on incremental costs is small.

The possibility that increased access to alternative smoking cessation medications would also increase the rate of future assisted (as opposed to unassisted) quit attempts was also explored (Table 6). Under the condition where assisted quit attempts increased by 1-2% depending on what treatments were listed, it was found that the ICERs increase. This was because instead of an unsuccessful quitter potentially quitting later without using treatment, they have now incurred additional costs related to quitting and these did not provide as much value for money in terms of discounted QALYs gained compared to substitution from an existing treatment.

Table 5: Selective sensitivity analysis exploring the implications of alternative assumptions

Comparison	Costs ($AU)			Health outcomes (QALYs)			ICER ($ per QALY)
	Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
0% discount rate							
(VAR+NRT) vs (VAR)	[redacted]						
(NRT+NRT) vs (NRT)							
(VAR+NRT & NRT+NRT) vs (VAR+NRT)							
3.5% discount rate							
(VAR+NRT) vs (VAR)	[redacted]						
(NRT+NRT) vs (NRT)							
(VAR+NRT & NRT+NRT) vs (VAR+NRT)							
Small reduction in unassisted quit attempts							
(VAR+NRT) vs (VAR)	[redacted]						
(NRT+NRT) vs (NRT)							
(VAR+NRT & NRT+NRT) vs (VAR+NRT)							
Time horizon, 20 years							
(VAR+NRT) vs (VAR)	[redacted]						
(NRT+NRT) vs (NRT)							
(VAR+NRT & NRT+NRT) vs (VAR+NRT)							

The value of immediate versus delayed access to VAR+NRT was considered as an additional sensitivity analysis, where VAR+NRT is available as a second line treatment (only after VAR). The results in Table 6 show that providing VAR+NRT as the first line option, as opposed to a possible second line option, generates an ICER of $45,000 to < $55,000/QALY. The extra upfront costs of providing VAR+NRT as the first line option only produces a small QALY gain when these are discounted at 5%. Compared to VAR, VAR+NRT is slightly more cost-effective as a second-line therapy after VAR ($15,000 to < $25,000/QALY), compared to a first-line therapy ($35,000 to < $45,000/QALY).

Table 6: Immediate versus delayed access to VAR+NRT, 5% discount rate

Comparison	Costs ($AU)			Health outcomes (QALYs)			ICER ($ per QALY)
	Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
(VAR+NRT) versus (VAR+NRT second line)	[redacted]						
(VAR+NRT second line) vs VAR							

[redacted]

Predicted use and budget impact analysis

Table 7 presents the estimated financial implications to the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS), Medicare Benefits Schedule (MBS) and the health system combined in each financial year to 2026-2027 for the three listing scenarios: VAR+NRT only (scenario 1), NRT+NRT only (scenario 2) and both VAR+NRT and NRT+NRT (scenario 3). Under the base case assumptions, the incremental cost to the PBS for the first five-years is approximately $60 million to < $70 million for Scenario's 1 and 2 and $90 million to < $100 million for Scenario 3. The proposed additional listings first increase costs given the substitution to more expensive therapy, but the more effective therapies are then assumed to reduce the need for future assisted quit attempts. Also, it is assumed that the substitution to the newly listed therapies will increase over time as more clinicians change their standard of care.

Table 7: Estimated incremental net cost to the PBS/RPBS (less co-payment) and MBS under the proposed listing scenarios relative to the current PBS restrictions

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Scenario 1 (VAR+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay) VAR NRT BUP MBS net cost Health budget net cost					
Scenario 2 (NRT+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay) VAR NRT BUP MBS net cost Health budget net cost					
Scenario 3 (both VAR+NRT and NRT+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay) VAR NRT BUP MBS net cost Health budget net cost					

A significant proportion of the additional costs are likely to come from those currently making attempts using over-the-counter (OTC) products or those who are already using combination products by supplementing their PBS prescription with OTC products. Further subsidising quit attempts may encourage adherence which may also increase successful quitting. These financial estimates rely heavily on the extent of the substitution away from existing products and whether these existing products are currently accessed OTC or through the PBS and there remains significant uncertainty regarding the rates of substitution we may see in practice. Assuming higher rates of substitution, such that combination therapy replaces most monotherapy on the PBS or where twice as many patients switch from non-PBS to PBS-therapy, increases these estimates by 20% to 75%. There is also a risk that the financial implications may be considerably greater than those estimated above should the proposed listing of combination therapy encourage patients to make additional assisted quit attempts.

These estimates also ignore the likely financial implications that will arise due to the current shortage of VAR. A sensitivity analysis accounting for this market shock found that the impact

on the incremental costs depends on the extent that other PBS-listed therapies (NRT and BUP) would substitute for VAR when unavailable.

Stakeholder views (forum and public consultations)

Stakeholders considered that optimising the use of smoking cessation therapies on the PBS (such as allowing combination therapy or allowing dosage or length of treatment to be tailored to the individual) would lead to more successful quit attempts and therefore cost-effectiveness would be improved.

Stakeholders noted the significant quality of life and financial burden the health consequences of smoking have on individuals and on society. Stakeholders considered that any additional costs to the PBS for optimising smoking cessation therapy would be outweighed by savings in treating smoking related diseases, such as hypertension.

Some stakeholders recommended that a CER should include the addition of the nicotine mouth spray and nicotine inhalator to the PBS.

Section 1: Context

1.1 Clinical issue

Target Population or disease

Most tobacco smokers are addicted to nicotine. This addiction is a chronic disease state that is prone to relapses and remissions (2).

Despite the long-term progress Australia has made in reducing smoking prevalence, tobacco remains the leading cause of death and disability in Australia. In 2015, cigarette smoking was responsible for 9.3% of the total burden of disease and injury, and more than 1 in every 10 (21,000) deaths (3).

The most recent available estimates of the overall social (including health) costs of tobacco use in Australia were $137 billion in 2015-16, including $19.2 billion in tangible costs and $117.7 billion in intangible costs (4).

The target population being considered in this CER are Australian smokers.

E-cigarette devices and nicotine liquids are out of scope of this PMR.

For a more detailed 'Description of the condition,' refer to page 9, section 1.4 of the Background report.

1.2 Intervention and comparator

The intervention and comparator are PBS-listed therapies (VAR and NRT), administered either as monotherapy or combination therapy.

The CER assessed the relative cost-effectiveness of the following comparisons of medicines for smoking cessation:

1. VAR versus NRT
2. VAR+NRT versus VAR
3. VAR+NRT versus NRT
4. NRT+NRT versus VAR
5. NRT+NRT versus NRT
6. VAR+NRT and NRT+NRT versus VAR+NRT

Nicotine replacement therapy

NRT patches have been designed to slowly allow nicotine to be absorbed by the body to offset the physical withdrawal symptoms of smoking cessation. It is easier to withdraw off NRT than cigarettes due to the lower levels of nicotine present. Short-acting forms of NRT (gum, inhalation cartridge, lozenge, oral spray, and sublingual tablet) provide a rapid increase in blood nicotine concentration, similar to that associated with smoking, and may be helpful for the more nicotine-dependent smokers. Nicotine patches do not produce this rapid increase, which people trying to quit may crave (5).

Varenicline

VAR is a partial agonist at α4β2 neuronal nicotinic acetylcholine receptors where it binds with high affinity and selectivity to produce an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in blockade of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity) (6).

Bupropion (not included in this cost-effectiveness review)

BUP is a selective inhibitor of the neuronal re-uptake of catecholamines (noradrenaline and dopamine) with minimal effect on the re-uptake of indolamines (serotonin) and no inhibitory effect on monoamine oxidase. The mechanism by which BUP enhances the ability of patients to abstain from smoking is unknown. However, it is presumed that this action is mediated by noradrenergic and/or dopaminergic mechanisms (7).

For a more detailed 'Description of the intervention,' refer to pages 10-11, section 1.4 of the Background report.

1.3 Purpose

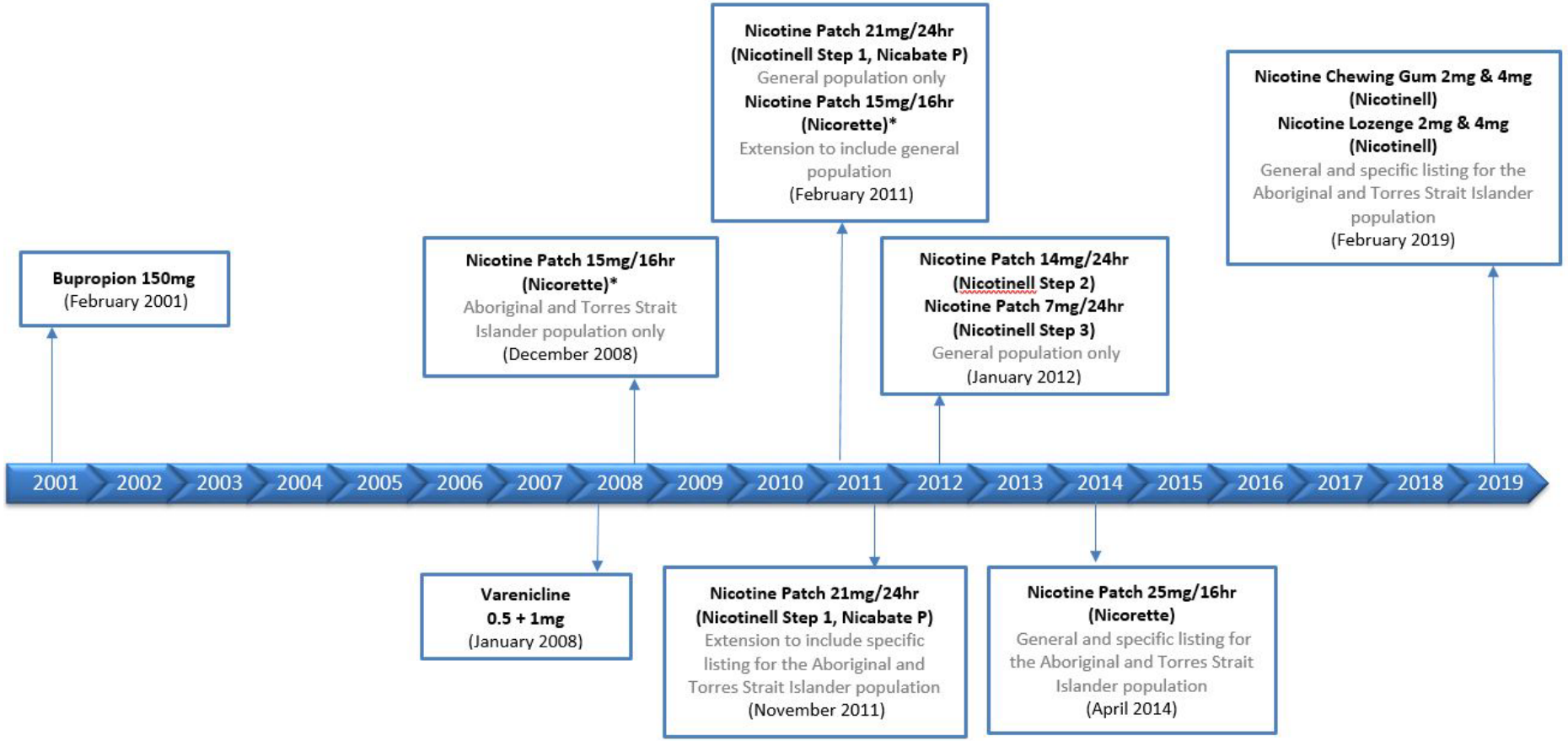
The purpose of this CER is to provide the PBAC with information on the cost-effectiveness of PBS-listed therapies for smoking cessation (VAR and NRT), at their current prices, administered either as monotherapy or combination therapy.

1.4 History of PBAC recommendations

The PBS listing dates of medicines for smoking cessation are provided in Figure 3.

For more detail refer to page 17, section 1.4 of the Background report.

Figure 3: Timeline for listing medicines for smoking cessation on the PBS



* Delisted in July 2014

1.5 Clinical management

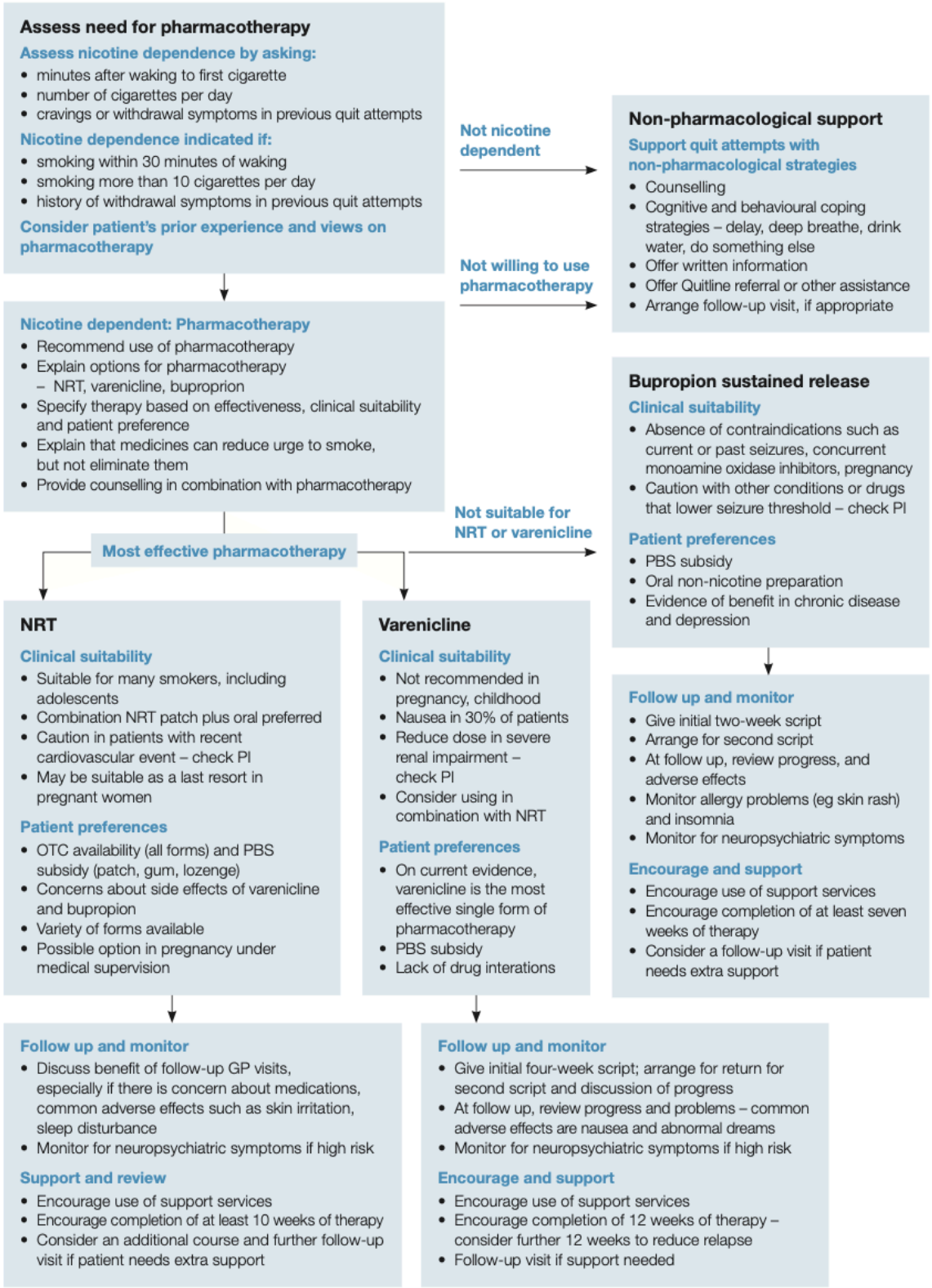
Summary of national treatment algorithm

Under ToR 1 of the PMR of medicines for smoking cessation, 12 national guidelines were identified (pages 9-11, ToR 1 report).

An explicit treatment algorithm or pathway was only included in the Royal Australian College of General Practitioners (RACGP) guidelines as provided in Figure 4 below. Following a positive assessment for nicotine dependence and a patient's willingness to use pharmacotherapy, combination NRT or VAR were considered the most effective pharmacotherapy. BUP was then considered for those who were not suitable for NRT or VAR. Counselling was recommended in combination with pharmacotherapy.

For more detail on national guidelines for smoking cessation, refer to the ToR 1 report.

Figure 4: Treatment algorithm, RACGP guidelines



Source: RACGP guidelines, Figure 2.2.

Abbreviations: GP, general practitioner; OTC, over-the-counter; PBS, Pharmaceutical Benefits Scheme; PI product information

1.6 Regulatory process

Therapeutic Goods Administration approval status

Table 8 shows the Therapeutic Goods Administration (TGA) approved indications for PBS-listed products for smoking cessation (8).

Table 8: TGA approved medicines for smoking cessation

Medicine	TGA approved indication/s
NRT	NRT is indicated for the treatment of nicotine dependence, and as an aid to smoking cessation for people over 12 years of age. NRT patches are indicated for the treatment of tobacco dependence by relieving nicotine craving and withdrawal symptoms thus facilitating smoking cessation in smokers motivated to quit. NRT lozenges are indicated for the relief of nicotine withdrawal symptoms including cravings associated with smoking cessation. Nicotine lozenges are also indicated as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping smoking. If possible, when stopping smoking, lozenges are recommended to be used in conjunction with a behavioural support program. NRT chewing gums are indicated as an aid in the cessation of smoking in smokers with nicotine dependence. Chewing gums are also indicated as part of a smoking reduction strategy by smokers who are unable or not ready to stop smoking abruptly as a step towards stopping completely.
Varenicline	VAR is indicated as an aid for smoking cessation in adults over the age of 18 years.
Bupropion	BUP is indicated as a short-term adjunctive therapy for the treatment of nicotine dependence in those over the age of 18 years who are committed to quitting smoking, when used in conjunction with counselling for smoking cessation/abstinence.

Source: TGA website

For more detail refer to page 54, section 1.5.1.1 of the ToR 1 report.

1.7 PBS restrictions

Current PBS restrictions for medicines for smoking cessation included in this cost-effectiveness review (i.e., NRT and VAR)[1]

NRT

NRT is indicated for people with nicotine dependence as a restricted benefit on the PBS General Schedule.

Under the RPBS, only the 7, 14 and 21mg/24-hour strength patches (pack size 7) are available as an Authority Required listing, with each prescription providing a maximum of 2 packs for all strengths (i.e., 14 patches) and no repeats for 7 and 14 mg/24-hour, while 2 repeats are allowed for 21 mg/24-hour strength patches The clinical criteria for this listing are:

- *Patient must have indicated they are ready to cease smoking, AND*
- *Patient must have entered a comprehensive support and counselling program.*

[1] Bupropion is not included in this CER based on options 2 and 3 from the Review options.

There are no treatment criteria with this listing, but the following note is observed:

- *Studies have shown that successful therapy with this drug is enhanced by patient participation in a support and counselling program.*

Under the General Schedule, three dosage forms of NRT are listed as a Restricted Benefit without a population criterion: patch, lozenge and chewing gum. Available strengths of NRT patches are 7, 14, 21 mg/24 hours, and 25 mg/16 hours, with each prescription providing a maximum of 1 pack (28 patches) and 2 repeats. Two strengths of NRT gum and lozenges are available (2mg and 4 mg), providing 1 pack (216 pieces) with 2 repeats. The exception is the 2mg gum, which provides a maximum of 2 packs (432 pieces) and 1 repeat. No increase in the maximum quantity, number of units or number of repeats are permitted for any listing.

To access NRT under the general population Restricted Benefit, the clinical criteria for patients' eligibility are:

- *The treatment must be as an aid to achieving abstinence from smoking, AND*
- *The treatment must be the sole PBS-subsidised therapy for this condition, AND*
- *Patient must have indicated they are ready to cease smoking, AND*
- *Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period.*

The PBS treatment criterion is: *"Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated*." Furthermore, "*details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.*"

Within the General Schedule listings for NRT patches (21 mg/24 hours and 25 mg/16 hours), lozenges (2mg and 4 mg), and chewing gum (2 and 4 mg), there are also Restricted Benefits listed with an "Aboriginal or Torres Strait Islander" population criteria. These listings have the same item codes as the listings that did not have any population criteria (except for the Nicotinell Step 1, 21mg/24 hours listings which had separate item codes for each clinical criteria), and thus have the same quantities and repeats. However, the following clinical criteria are observed:

- The treatment must be the sole PBS-subsidised therapy for this condition.

In addition, the following notes are observed:

- Only two courses of PBS-subsidised nicotine replacement therapy may be prescribed per 12-month period.
- Benefit is improved if used in conjunction with a comprehensive support and counselling program
- No increase in the maximum quantity, number of units or repeats may be authorised.

No PBS or RPBS listing covers two forms of NRT at once (i.e., no combination therapy).

The Australian Medicines Handbook (AMH) dosing recommendations and assumptions used in PBS listing decisions and the assumed equi-effective doses are displayed in Tables 9 and Table 10 respectively.

Table 9: AMH dosing recommendations and assumptions in PBS listing decisions

AMH dosing recommendations and assumptions (NRT gum, lozenge, and patch)
High dependence
Gum: 8 pieces/day for 8 weeks followed by a halving of the dose (cutting gum strip in half) for the next 4 weeks Lozenge: Waking hours from 7am to 10pm (Total = 15 hours) |10 pieces/day for 6 weeks then 5 pieces/day for 3 weeks then 3 pieces/day for 3 weeks Patch: 1 patch/day for 12 weeks
Moderate dependence
Gum: 10 pieces/day for 12 weeks Lozenge: Waking hours from 7am to 10pm (Total = 15 hours) |10 pieces/day for 6 weeks then 5 pieces/day for 3 weeks then 3 pieces/day for 3 weeks Patch: 1 patch/day for 12 weeks

Source: AMH

Table 10: Accepted equi-effective doses of NRT

Form	Strength	Dose/12weeks
High dependence		
Gum	4mg	560
Lozenge	4mg	588
Patch	21mg	84
Moderate dependence		
Gum	2mg	840
Lozenge	2mg	588
Patch	14mg	84

Source: Pharmaceutical Benefits Scheme (PBS) | Therapeutic Relativity Sheets - 1 November 2019

Varenicline

VAR is indicated for people with nicotine dependence under the PBS General schedule as an Authority Required (STREAMLINED) restriction.

Two strengths are available: 500 microgram, and 1 mg tablets. There are three different listings: commencement (500mcg & 1mg, 11/42tabs, 0 repeats); continuation (1mg, 112 tabs, 0 repeats) and completion (1mg, 56 tabs, 2 repeats).

For the commencement phase, the clinical criteria are:

- *The treatment must be as an aid to achieving abstinence from smoking, AND*
- *The treatment must be the sole PBS-subsidised therapy for this condition, AND*
- *Patient must have indicated they are ready to cease smoking, AND*
- *Patient must not receive more than 24 weeks of PBS-subsidised treatment with this drug per 12-month period.*

The PBS treatment criteria for VAR are ''*Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated*." Furthermore, details of the support and counselling program must be documented in the patient's medical records at the time treatment was initiated, and clinical review was recommended within 2 to 3 weeks of the initial prescription being requested.

For the continuation phase, the clinical criteria are the same as for the commencement phase except that the patient does not need to (re)-indicate that they are ready to cease smoking and instead the:

- *Patient must have previously received treatment with this drug during this current course of treatment.*

Furthermore, there are no clinical criteria explicitly restricting the duration of PBS-subsidised treatment during this phase of treatment, nor is further documentation of the patient's support and counselling program required in the treatment criteria.

For the completion phase, the clinical criteria is the same as the continuation phase with the following AND addition:

- *Patient must have ceased smoking in the process of completing an initial 12-weeks or ceased smoking following an initial 12-weeks of PBS-subsidised treatment with this drug in the course of treatment.*

In addition, the following notes are observed for each listing:

- A course of treatment with this drug is 12 weeks or up to 24 weeks if initial treatment of 12 weeks has been successful.
- The period between commencing varenicline and bupropion or a new course of varenicline must be at least 6 months (commencement phase only)
- A patient may only qualify for PBS-subsidised treatment under each treatment phases restriction once during a short-term course of treatment
- No increase in the maximum quantity, number of units or repeats may be authorised.

Proposed changes to PBS restrictions for medicines for smoking cessation included in this cost-effectiveness review (i.e., NRT and VAR)

Currently PBS restrictions do not allow for the use of combination NRT or NRT in combination with VAR as the restriction wording for both NRT and VAR include the clinical criterion that: *"The treatment must be the sole PBS-subsidised therapy for this condition."*

PBS-subsidised combination NRT and NRT in combination with VAR was considered by the Review reference group for the PMR of medicines for smoking cessation as shown in Review options 2 and 3 presented below (for the full Review options refer to pages 38-44 of the 'Report summary and 'options' for PBAC consideration').

Review option 2

Option 2a

- Remove the requirement for nicotine patch, lozenge, or gum to be used as monotherapy to allow for combinations of NRT patch + short acting formulations to be used concomitantly on the PBS.

AND

Option 2b

- Remove the requirement for nicotine patch, to be used as monotherapy to allow for combinations of NRT patch formulations to be used on the PBS, to allow for double patching (e.g., two 21 mg/24 hours patches daily, 21mg + 14mg/24 hour patches daily) as

second line therapy under an Authority Required restriction. Alternatively, double patching could be achieved by allowing increased quantities to be approved via a phone or online authority.

The current PBS restrictions for NRT state, "*the treatment must be the sole PBS-subsidised therapy for this condition."*

Combinations of NRT for smoking cessation have not been previously considered by the PBAC. In March 2018, the PBAC noted that the latest clinical guidelines encouraged health professionals to consider recommending the use of combination NRT (e.g., NRT patch with NRT gum or lozenges).

Review option 3

- Remove the requirement for VAR to be used as monotherapy, to allow for use in combination with NRT on the PBS.

The current PBS restrictions for VAR state, *"the treatment must be the sole PBS-subsidised therapy for this condition".* The PBAC has not previously considered a submission for the listing of VAR in combination with NRT or BUP.

Proposed restriction wording

The PMR Secretariat proposed changes to the restriction wording for NRT and VAR, should option 2a and/or 3 be recommended by the PBAC, is provided in the tables below. Italics indicate proposed additions and strikethrough indicates proposed deletions to the existing restriction wording.

Note that double patching as combination NRT therapy under Option 2b has not been proposed however, the PBAC is asked to consider whether two packs of the same NRT patch should be available on the PBS as an Authority Required benefit. This change could be implemented by removing the Administrative Advice, *"No increase in the maximum quantity or number of units may be authorised,"* from the current listings for NRT patches.

The PMR Secretariat also proposes removing the clinical criterion, "*Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period,"* from the NRT listings for the general population to allow two, 12-week courses of PBS-subsidised NRT per 12-month period – as either NRT monotherapy or as combination therapy (i.e., with another NRT product or in combination with VAR). This change would also bring the current NRT listings for the general population into line with the current NRT listings for the Aboriginal and Torres Strait Islander population.

Proposed listings for NRT – if combination NRT only (Review option 2a) and/or if NRT monotherapy in combination with varenicline (Review option 3) is recommended for PBS subsidy

Amend current nicotine listings that have two restriction summaries (one for Aboriginal and Torres Strait Islander persons and one for non-Indigenous Australians) as follows:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts.**	**Available brands**
NICOTINE					
nicotine 4 mg lozenge, 216	11619M	1	216	2	Nicotinell
nicotine 25 mg/16 hours patch, 28	10076H	1	28	2	Nicorette 16hr Invisipatch
nicotine 2 mg chewing gum, 216	11618L	2	432	1	Nicotinell
nicotine 4 mg chewing gum, 216	11612E	1	216	2	Nicotinell
nicotine 2 mg lozenge, 216	11617K	1	216	2	Nicotinell
nicotine 21 mg/24 hours patch, 28	5465P	1	28	2	Nicabate P

Delete Restriction Summary 5140 / Treatment of Concept: 5140	
Concept ID (for internal Dept. use)	~~**Category / Program:** GENERAL – General Schedule (Code GE)~~
	~~**Prescriber type:** ☒Medical Practitioners ☒Nurse practitioners~~
	~~**Restriction type:** ☒Restricted benefit~~
8619	~~**Indication:** Nicotine dependence~~
8621	~~**Population criteria:**~~
8620	~~Patient must be an Aboriginal or a Torres Strait Islander person~~
	~~**AND**~~
7890	~~**Clinical criteria:**~~
7889	~~The treatment must be the sole PBS-subsidised therapy for this condition~~
9293	~~**Administrative Advice:**~~ ~~Only 2 courses of PBS-subsidised nicotine replacement therapy may be prescribed per 12-month period.~~ ~~Benefit is improved if used in conjunction with a comprehensive support and counselling program.~~
7606	~~**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.~~
7607	~~**Administrative Advice:** No increase in the maximum number of repeats may be authorised.~~
Edit Restriction Summary 6848 / Treatment of Concept: 6848	
8619	**Indication:** Nicotine dependence
11245	**Clinical criteria:**
11244	The treatment must be as an aid to achieving abstinence from smoking
	AND
7890	**Clinical criteria:**
Remove 7889	~~The treatment must be the sole PBS-subsidised therapy for this condition~~
Insert New CC1	*The treatment must not be a PBS-benefit with other non-nicotine drugs that are PBS indicated for smoking cessation*
	AND
Insert	***Clinical criteria:***
New CC2	*The treatment must, in terms of the number of forms/presentations prescribed, be limited to up to 2 (e.g., patches plus gum is permitted, but not patches plus gum plus lozenges)*
	AND
8625	**Clinical criteria:**
8624	Patient must have indicated they are ready to cease smoking
	AND
9296	**Clinical criteria:**
Remove 9295	~~Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period~~
Insert New CC2	*Patient must not receive more than 2 x 12-week PBS-subsidised treatment courses per 12 month period*

	AND
20605	**Treatment criteria:**
20604	Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated
9299	**Prescribing Instructions:** Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.

Amend current nicotine listings that have one restriction summary to appear as follows:

MEDICINAL PRODUCT **medicinal product pack**	**PBS item code**	**Max. qty packs**	**Max. qty units**	**№. of Rpts.**	**Available brands**
NICOTINE					
nicotine 14 mg/24 hours patch, 28	5572G	1	28	2	Nicotinell Step 2
nicotine 7 mg/24 hours patch, 28	5573H	1	28	2	Nicotinell Step 3
nicotine 21 mg/24 hours patch, 28	3414Q	1	28	2	Nicotinell Step 1

Edit Restriction Summary 6848 / Treatment of Concept: 6848	
Concept ID (for internal Dept. use)	**Category / Program:** GENERAL – General Schedule (Code GE)
	Prescriber type: ☒Medical Practitioners ☒Nurse practitioners
	Restriction type: ☒Restricted benefit
8619	**Indication:** Nicotine dependence
11245	**Clinical criteria:**
11244	The treatment must be as an aid to achieving abstinence from smoking
	AND
7890	**Clinical criteria:**
Remove 7889	~~The treatment must be the sole PBS-subsidised therapy for this condition~~
Insert New CC1	*The treatment must not be a PBS-benefit with other non-nicotine drugs that are PBS indicated for smoking cessation*
	AND
Insert	***Clinical criteria:***
New CC2	*The treatment must, in terms of the number of forms/presentations prescribed, be limited to up to 2 (e.g., patches plus gum is permitted, but not patches plus gum plus lozenges)*
	AND
8625	**Clinical criteria:**
8624	Patient must have indicated they are ready to cease smoking
	AND
9296	**Clinical criteria:**
Remove 9295	~~Patient must not receive more than 12 weeks of PBS-subsidised nicotine replacement therapy per 12-month period~~
Insert New CC2	*Patient must not receive more than 2 x 12-week PBS-subsidised treatment courses per 12 month period*
	AND
20605	**Treatment criteria:**
20604	Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated
9299	**Prescribing Instructions:** Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.

Proposed listings for VAR - if NRT monotherapy in combination with varenicline (Review option 3) is recommended for PBS subsidy

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
VARENICLINE						
varenicline 500 microgram tablet [11] (&) varenicline 1 mg tablet [42], 53		9128K	1	1	0	Champix
varenicline 1 mg tablet, 56		5469W	1	56	2	Champix
varenicline 1 mg tablet, 56		9129L	2	112	0	Champix
Restriction Summary 6871 / Treatment of Concept: 6871						
	Category/Program: General Schedule					
	Prescriber types: Medica Practitioners, Nurse Practitioners					
	Restriction type: Authority Required (Streamlined) [6871]					
8619	**Indication:** Nicotine dependence					
	Treatment Phase: Commencement of a short-term (12 weeks or 24 weeks) course of treatment					
11245	**Clinical criteria:**					
11244	The treatment must be as an aid to achieving abstinence from smoking					
	AND					
7890	**Clinical criteria:**					
Remove 7889	~~The treatment must be the sole PBS-subsidised therapy for this condition~~					
	AND					
8625	**Clinical criteria:**					
8624	Patient must have indicated they are ready to cease smoking					
	AND					
20236	**Clinical criteria:**					
20235	Patient must not receive more than 24 weeks of PBS-subsidised treatment with this drug per 12-month period					
	AND					
20601	**Treatment criteria:**					
20600	Patient must be undergoing concurrent counselling for smoking cessation through a comprehensive support and counselling program or is about to enter such a program at the time PBS-subsidised treatment is initiated					
9299	**Prescribing Instructions:** Details of the support and counselling program must be documented in the patient's medical records at the time treatment is initiated.					
10230	**Prescribing Instructions:** Clinical review is recommended within 2 to 3 weeks of the initial prescription being requested.					
10231	**Administrative Advice:** A course of treatment with this drug is 12 weeks or up to 24 weeks if initial treatment of 12 weeks has been successful.					
10232	**Administrative Advice:** The period between commencing varenicline and bupropion or a new course of varenicline must be at least 6 months.					
11241	**Administrative Advice:** A patient may only qualify for PBS-subsidised treatment under this treatment phase restriction once during a short-term course of treatment.					
7606	**Administrative Advice:** No increase in the maximum quantity or number of units may be authorised.					
7607	**Administrative Advice:** No increase in the maximum number of repeats may be authorised.					

Section 2: Clinical evidence

2.1 Clinical evidence in the ToR 3 report

This report relied on the clinical evidence summarised in the ToR 3 report, as well as a recently published trial comparing VAR+NRT to VAR (9). The results of this recent RCT (Baker et al. 2021) were published after the ToR 3 report was completed. The RCT included four arms, VAR (12 weeks), VAR (24 weeks), VAR+NRT patch (12 weeks) and VAR+NRT patch (24 weeks). The continuous abstinence (CA) rate at 23 weeks of those with VAR monotherapy and VAR+NRT patch (combining the shorter and extended use arms) was 21.9% and 22.2% respectively. The study also included a longer follow-up and found the CA rate at 52 weeks to be 16.1% and 16.6% respectively. The study found no significant difference in the head-to-head effectiveness of combination use (or extended use) compared to 12 weeks of VAR monotherapy.

Below in Section 3.4, we describe how the ToR 3 report evidence translates into informing the cost-effectiveness of different listing options and the remaining evidence gaps to inform decisions on what to consider listing.

Section 3: Economic evaluation

3.1 Overview and rationale of the economic evaluation

The economic analysis considers the relative cost-effectiveness of the following comparisons of medicines for smoking cessation:

1. VAR versus NRT
2. VAR+NRT versus VAR
3. VAR+NRT versus NRT
4. NRT+NRT versus VAR
5. NRT+NRT versus NRT
6. VAR+NRT and NRT+NRT versus VAR+NRT

And thus, provided evidence on the cost-effectiveness of the potential PBS listing of the following scenarios:

(i) VAR+NRT only
(ii) NRT+NRT only
(iii) both VAR+NRT and NRT+NRT

Specifically, the comparisons considered in the analysis consider both first and subsequent quit attempts. We assume the use of a particular product for the first assisted quit attempt considered in the model (i.e., the first cycle), and then we assumed patients may use (or not use) different products for the subsequent quit attempts depending on what is available. For simplicity, we model subsequent quit attempts as the weighted average (cost and effect) associated with the estimated utilisation of different products. Further detail of the scenarios considered is presented in Section 3.8 below.

Evaluating the cost-effectiveness of smoking cessation products has distinct challenges. There is often a high chance of relapse, even a year after a successful quit attempt, and individuals can have multiple assisted, and unassisted, quit attempts over their lifetime. Thus, estimating the cost-effectiveness of subsidising access to a new cessation product, or combination of products, for both current, and potentially future, quit attempts requires modelling the probable implications of changes in smoking patterns (e.g., multiple quit attempts or changes in smoking intensity) on the risk of future health events.

The SDI model v1.0 was developed to model the cost-effectiveness for a number of Australian NHMRC funded smoking cessation trials. It was designed to consider the dynamic nature of smoking cessation and capture the relationship between smoking duration and intensity (as measured by pack-years) on the risk of key smoking-related health events in the contemporary Australian context. Importantly, this model considered the characteristics of Australian smokers currently looking to quit. This aspect of the model is vital because the population attempting to quit has likely changed over time (e.g. those still smoking are more likely to be poorer and smoking at a higher intensity than those that were smoking 20 years ago) and these characteristics can influence smoking patterns and, in turn, the benefits associated with cessation (10, 11).

The SDI model was created via a collaboration between the CHE at Monash University and smoking cessation experts based at the National Drug and Alcohol Research Centre (NDARC), along with input from other smoking cessation and health economics experts. Below we

summarise existing smoking cessation models before describing Version 1.0 of the SDI model. We then describe how the SDI model is used to estimate the cost-utility of Australian-based listing of VAR+NRT, NRT+NRT, or both based on direct and indirect evidence from randomised trials. It is important to note that an added complexity of evaluating the cost-effectiveness of subsiding smoking cessation products is that the effectiveness estimates from head-to-head comparisons alone is unlikely to fully capture the potential value of subsiding a new cessation product; as subsiding it may also encourage additional, or more frequent, assisted cessation attempts. This may be particularly important when individuals experience side effects from other available products.

Table 11: Key components of the economic evaluation

Component	Description	Justification/comments
Type of analysis	Cost-utility analysis	Smoking cessation reduces the risk of a number of health conditions and therefore improves quality of life and reduces mortality.
Outcomes	Quality-adjusted life years	Smoking cessation reduces the risk of a number of health conditions and therefore improves quality of life and reduces mortality.
Time horizon	50 years (close to a lifetime)	The benefits of smoking cessation are largely experienced between 50-80 years old when the risk of smoking related diseases starts to rise even though the earlier a smoker quits the larger their expected benefits due to the damage related to smoking being highly cumulative in nature.
Discount rate	5%, 3.5%, 0%	Given the large time lag between quitting and experiencing the benefits of quitting, using an accurate discount rate for Australian time preferences is critical to establish its value for money.
Methods used to generate results	Microsimulation	Cessation, relapse, and the risk of future smoking related health events depend on a number of characteristics that change over an individual's lifetime. These are best captured through a microsimulation model.
Health states	Smoking status (smoker or ex-smoker) & health states (no smoking related disease, chronic states for lung cancer and COPD; acute states for AMI, and stroke; dead)	This allows us to fully capture the dynamic nature of smoking and quit attempts and the implications for the future health of these smokers and ex-smokers.
Cycle length	6 months	To match the commonly observed frequency of re-attempts
Transition probabilities	These are specific to each health states and are discussed in more detail in section 3.4.	To capture the rate of transitions into different health states possible in the model.
Software package	TreeAge Pro Suite 2021	Can incorporate the complexity needed to accurately model the implications of providing smoking cessation products but still provides a user-friendly interface

3.2 Structure and computational methods of the economic analysis

Literature review

The SDI model is similar to other smoking models in terms of model structure and smoking-related health events, albeit directly considering the impact of the duration and intensity of smoking via pack-years (as well as other patient demographics such as age, sex, current smoking status, and years abstained from smoking) on the risk of future health events. The

SDI model is also better able to capture the costs and consequences of subsequent quit attempts compared to cohort models, by tracking individual patients over time. This section provides a brief summary of other smoking cessation models in the literature and the model submitted by [redacted] during the PMR.

[redacted]

Figure 5: [redacted]

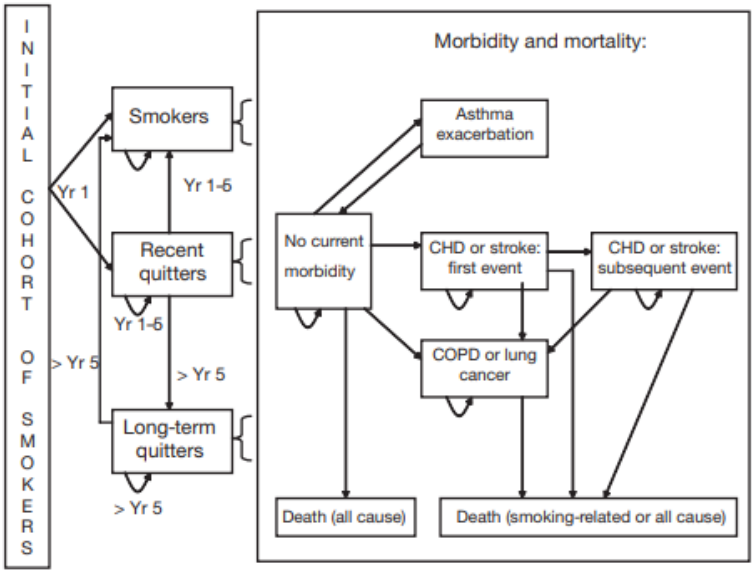
[Figure redacted]

[redacted]

Benefits of Smoking Cessation on Outcomes (BENESCO) model

The Benefits of Smoking Cessation on Outcomes (BENESCO) model is a state transition model designed to estimate the costs and consequences of smoking cessation treatment. The model [redacted] has been used to inform numerous economic evaluations in the literature (although none in an Australian context) (12-16). The model consists of three health states related to smoking status (smoker, recent quitter, and long-term quitter) as well as smoking related-diseases (COPD, lung cancer, chronic heart disease [CHD], stroke, and asthma exacerbation), as summarised in Figure 6.

Figure 6: BENESCO model structure



Source: Hoogendoom et al. 2008 (12)

Patients enter the model in the smoker health state and make a pharmacologically assisted quit attempt in the first cycle. Patients who quit smoking transition to the recent quitter health state (and can relapse) whereas patients who do not quit remain in the smoking health state for the duration of the model (i.e., future quit attempts are not modelled). Conditional on survival and CA, after 5 years, patients in the recent quitter health state transition to the long-term quitter health state. Patients in either the recent or long-term quitter health state can relapse in any cycle and transition back to the smoker health state. Within the smoker and quitter health states, the model distributes the cohort between chronic disease health states (COPD and lung cancer), acute disease health states (CHD event and stroke) and one transient health state (asthma exacerbation). Limitations are that transitions within acute and chronic conditions are not allowed and, therefore, it is not possible for patients to experience a CHD event following a stroke (or vice versa), or both COPD and lung cancer. Transitions from acute disease states to chronic disease states are possible, but not from chronic conditions to acute conditions. Asthma exacerbations can only occur from the no current morbidity health state. This is likely to result in the harms of continuing smoking and the benefits of smoking cessation being underestimated. All individuals are exposed to the same 'all-cause' mortality rates but different mortality rates for smoking-related conditions (but using the same hazard ratios as for the incidence rate of these smoking related conditions). Evidence on the differences in mortality by smoking status once an individual has a condition is limited (discussed further below) and using the same hazard ratio as for the incidence may overestimate the hazards of smoking.

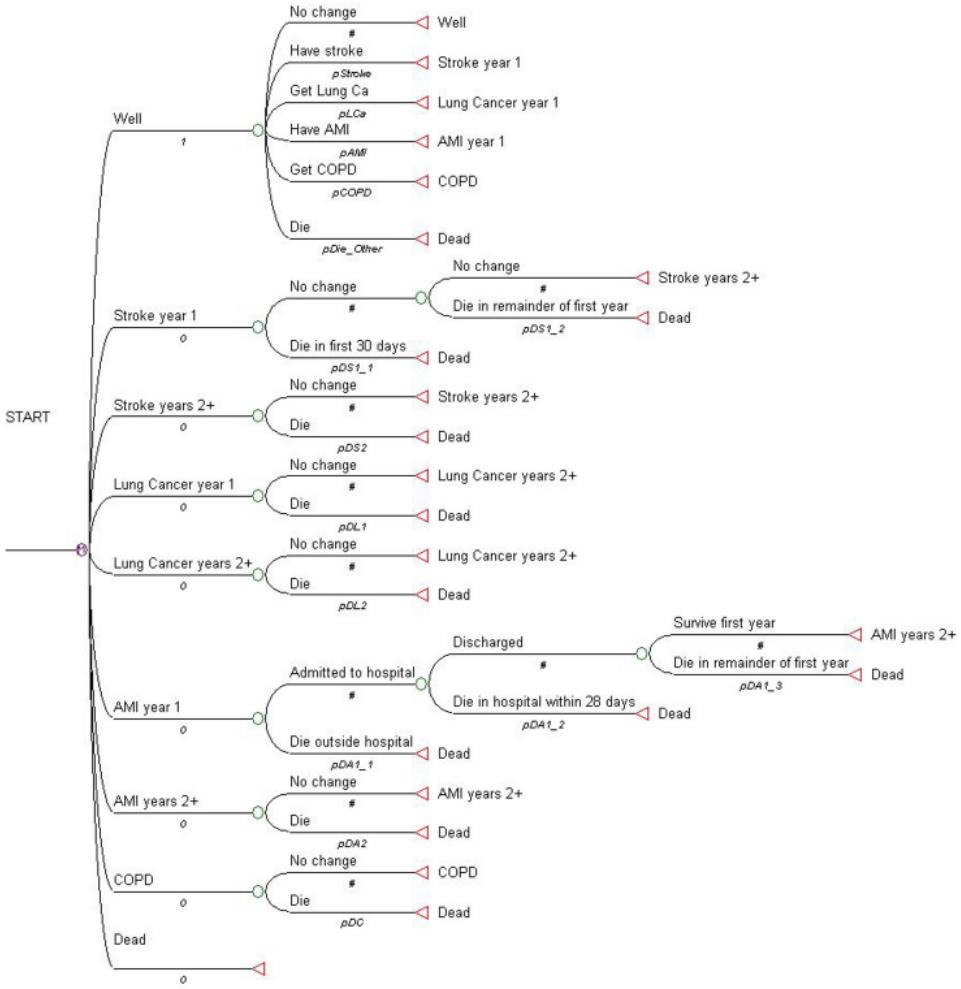
Transitions between the disease states are dependent on smoking status, time since quit ('recent quitters,' 1 to 5 years, versus 'long-term quitters,' more than 5 years), age and sex. However, the model does not consider the long-term benefits from any years of being smoke-free if an individual does at some stage relapse. From this perspective, the likely benefits of additional periods of being smoke-free are underestimated. A key criticism of the model is that it does not consider the costs and benefits of subsequent quit attempts. This is important because the PBS listing or subsidising of an additional cessation option may not only impact

on the current quit attempt but also on what type of cessation aid is used and the success of future quit attempts.

Quit Benefit Model (QBM)

The Quit Benefit Model (QBM) model is a state transition model designed to estimate the costs and consequences of smoking cessation treatment in Australia (17). The model predicts the mean costs and benefits of quitting smoking at different ages by sex. That is, the model predicts outcomes for ex-smokers versus a matched group of smokers (i.e., the counterfactual). Figure 7 presents a summary of the QBM model structure.

Figure 7: QBM model structure



Source: Figure 1, Hurley and Matthews 2007.

Patients (i.e., a cohort of smokers or recent quitters) enter the model in the well health state and each cycle have the chance of developing one of four smoking-related diseases (lung cancer, COPD, stroke, or AMI) or death. The smoking-related health states are mutually exclusive and hence the model only considers patients' first event (however, mortality from other causes would capture deaths from subsequent and other events). The model does not directly consider quit attempts, the effectiveness of different treatments or relapse.

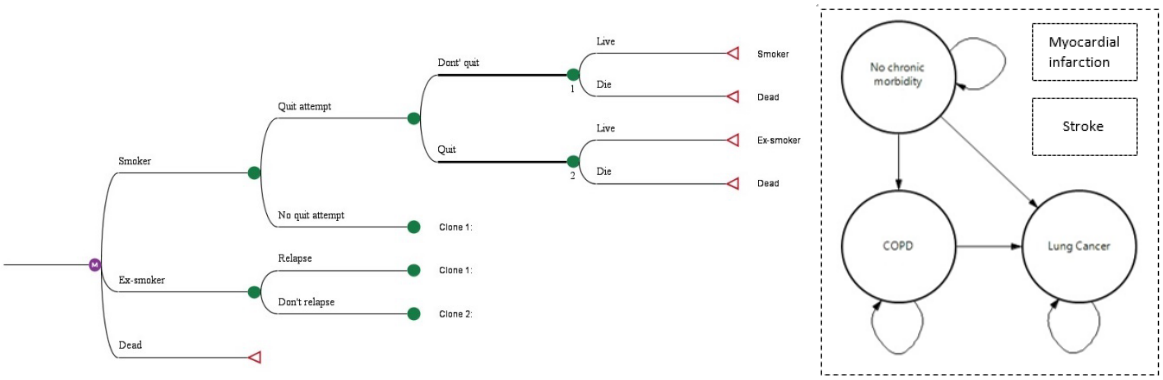
Transitions between disease states are dependent on current smoking status, time since quitting (i.e., recent quitters – within 5 years – versus long-term quitters), age and sex. The risk of developing the four specified smoking-related diseases declines over time for quitters

and increases over time for smokers. The model assumes that following a diagnosis of one of the smoking-related diseases, the probability of death due to the disease is independent of smoking or quitting status, but the risk of death from other causes declines over time for quitters relative to smokers. The model uses a combination of population-level data (Australian national statistics in 2001), literature estimates on smoking prevalence rates and RRs (e.g., CPS-II data from the 1980s), and other assumptions to derive transition probabilities for the smokers and quitters.

Structure of the SDI economic model

The SDI model (Version 1.0) is a state-transition patient simulation model designed to explore the impacts of smoking duration and intensity (in terms of pack-years) on key smoking-related health events, costs, and quality of life. The model consists of health states related to smoking-status (smoker and ex-smoker), as well as smoking-related diseases (COPD, lung cancer, AMI, and stroke). The four smoking-related diseases included in the model are consistent with those considered by other models in the literature, and capture the majority (over 60%) of smoking related mortality (17, 18). Although smoking is considered a risk factor for many other diseases, there is limited data currently available to accurately model the causal impact of these risks. Figure 8 presents a summary of the SDI model structure.

Figure 8: SDI model structure (simplified)



All patients enter the model in the smoker health state and make a pharmacologically assisted quit attempt in the first cycle. Conditional on surviving the cycle, patients who 'quit' smoking (defined as 6 months CA) transition to the ex-smoker health state in the subsequent cycle whereas patients who don't quit remain in the smoker health state. In subsequent cycles, patients in the smoker health state have the chance to make additional quit attempts and quit smoking, and patients in the ex-smoker health state have the chance to relapse and restart smoking.

Smokers may also start the model within a chronic disease health state if for example they have a prior history of COPD or lung cancer. Every cycle, patients without one of these comorbidities ('well') are at risk of developing either COPD or lung cancer, and patients with COPD remain at risk of developing lung cancer. For simplicity, the model does not model COPD diagnosis or progression after a lung cancer diagnosis (this is primarily due to the short overall survival expected with lung cancer and therefore will have little impact). The COPD health state is further divided into mild, moderate, severe, and very severe disease defined by FEV1% predicted, which is strongly correlated with costs and outcomes. After diagnosis, patients have the chance to experience worsening COPD each cycle. In addition, all patients are at risk of having an AMI or stroke each cycle, which are modelled as transient events. The model

tracks prior transient events to account for changes in risks of subsequent events and ongoing impacts on costs and quality of life.

For simplicity, quit attempts and smoking-relapse are assumed to occur at the start of the model cycle, clinical events are assumed to occur in the middle of the cycle and mortality (non-acute and other causes) is assumed to occur at the end of the cycle. A half-cycle correction was not applied given these assumptions and the relatively short cycle length.

Time horizon

The SDI model can model lifetime consequences however for the purposes of the current economic evaluation we applied a time horizon of 50 years given that for a young smoker looking to quit, the majority of the benefits are likely to be experienced many years in the future. Thus, taking this longer time horizon best captures the long-term impacts of smoking and the benefits of smoking cessation on health outcomes and survival. A sensitivity analysis applying a 20-year time horizon is also applied to enable comparison to earlier models (see section 3.9).

Input data

The evidence used to inform the parameters in v1.0 of the SDI model is presented in Table 12 below.

Table 12: Data sources for key input parameters

Data input	Source	Reference
Patient characteristics at baseline		
Age, sex, medical history, smoking-related characteristics	Household, Income and Labour Dynamics in Australia survey	Section 3.3
Transition probabilities		
Quit and relapse rates	Saxby et al. (10)	Section 3.4
Smoking-related diseases	See specific sub-sections	
All-cause age-related mortality	Australian life tables	
Utilities		
Progression free health state	McCaffrey et al. 2016.(19)	Section 3.5
Progressed disease health state – COPD	Fishwick et al. 2015.(20)	
Progressed disease health state – Lung cancer	Sturza et al. 2010.(21)	
Progressed disease health state – stroke	Luengo-Fernadez et al. 2013.(22)	
Progressed disease health state – myocardial infarction	Nikolik et al. 2013. (23)	
Costs		
Lung cancer	Queensland Hospital Admitted Patient Data Collection, Goldsbury et al. 2020 (24), see specific sub-sections.	Section 3.6
COPD		
AMI		
Stroke		

3.3 Population and setting

Demographic and patient characteristics

The population used in the model is a hypothetical sample of smokers with baseline characteristics representative of Australian daily smokers. Specifically, this sample was sourced from the HILDA survey who reported to 'quit' smoking between 2007 and 2019. The HILDA survey is a large household-based panel study, which collects sociodemographic, economic and wellbeing information from more than 17,000 Australians each year (25). We assume that the HILDA quit population, which includes both shorter-term quitters (i.e., last

observed smoking less than one year ago) and longer-term quitters, is a reasonable proxy for Australian smokers looking to quit smoking (see Section 3.4 for further details about the HILDA quit population).

To account for important correlations between key baseline characteristics, we applied different distributions depending on the age of an individual at baseline. For example, younger smokers are more likely to have started smoking during adolescence and smoke less intensively compared to older smokers who have not yet been able to successfully quit. For medical history at baseline, we assume the prevalence of 'bronchitis or emphysema' and CHD in the HILDA quit population as reasonable proxies for COPD and prior AMI, respectively. As expected, the prevalence rates in the HILDA quit population are slightly higher than the prevalence rates in the Australian population (which includes smokers, ex-smokers, and non-smokers). Given limited data on prior stroke or lung cancer in HILDA, we assumed prevalence rates from the Australian population for prior stroke and assumed that no one entering the model initially had lung cancer.

Table 13 summarises the baseline characteristics of the model population, where pack-years at baseline is calculated as a function of age of the smoker, age started smoking, and intensity. For simplicity, we assume that smoking intensity remains constant and hence the accumulation of pack-years is constant over time.

Table 13: Assumed baseline characteristics for hypothetical cohort of Australian quitters

<table>
<tr><th></th><th>Distribution</th><th>Mean</th><th>Source</th></tr>
<tr><td>Age, years</td><td>LogNormal</td><td>42.0 years</td><td>HILDA quit population</td></tr>
<tr><td>Gender, % males</td><td>Table</td><td>51.7% male</td><td>HILDA quit population</td></tr>
<tr><td>Age started smoking, years</td><td>LogNormal (for each of seven age categories)</td><td>Average age started smoking: 17.6 years old (=24.6 years smoking on average)</td><td>HILDA quit population</td></tr>
<tr><td>Smoking intensity, cigs/day</td><td>LogNormal</td><td>Average smoking intensity: 12.2 cigs / day (=15.8 pack-years on average)</td><td>HILDA quit population</td></tr>
<tr><td>Education</td><td>Table</td><td>Average: 26.3%, 45.6% and 28.1% with less than high school, high school, and tertiary degree respectively</td><td>HILDA quit population</td></tr>
<tr><td>Income quartile</td><td>Table</td><td>Average: 27.9%, 26.3%, 25.5% and 20.3% lowest to highest income quartiles respectively</td><td>HILDA quit population</td></tr>
<tr><td>Lung Cancer</td><td>N/A</td><td>To simplify we assume that no one entering the model starts with lung cancer. Given the low rates of lung cancer and high mortality this assumption is likely to have little impact on the overall cost-effectiveness estimates.

Prevalence rates of lung cancer, Australian population
<table>
<tr><td></td><td>40-49</td><td>50-59</td><td>60-69</td><td>70-79</td><td>80+</td></tr>
<tr><td>Male</td><td>0.02%</td><td>0.07%</td><td>0.23%</td><td>0.47%</td><td>0.46%</td></tr>
<tr><td>Female</td><td>0.02%</td><td>0.06%</td><td>0.16%</td><td>0.25%</td><td>0.18%</td></tr>
</table></td><td>Australia population statistics, AIHW</td></tr>
<tr><td>COPD mild %</td><td>Table</td><td>Prevalence rate of chronic bronchitis or emphysema, HILDA quit population
<table>
<tr><td></td><td>40-50</td><td>50-60</td><td>60-70</td><td>70+</td></tr>
<tr><td>Male & Female</td><td>3.7%</td><td>11.7%</td><td>13.4%</td><td>22.8%</td></tr>
</table>
Prevalence rates of COPD, Australian population
<table>
<tr><td></td><td>45-54</td><td>55-64</td><td>65-74</td><td>75+</td></tr>
<tr><td>Male</td><td>2.0%</td><td>3.6%</td><td>7.5%</td><td>7.3%</td></tr>
<tr><td>Female</td><td>2.5%</td><td>6.2%</td><td>6.7%</td><td>5.9%</td></tr>
</table></td><td>HILDA quit population

(Alternative : Australian population statistics, AIHW)</td></tr>
<tr><td>Prior stroke</td><td>Table</td><td>Prevalence rates of stroke, Australian population
<table>
<tr><td></td><td>45-54</td><td>55-64</td><td>65-74</td><td>75-84</td><td>85+</td></tr>
<tr><td>Male</td><td>0.9%</td><td>2.0%</td><td>6.4%</td><td>10.8%</td><td>16.0%</td></tr>
<tr><td>Female</td><td>1.0%</td><td>2.0%</td><td>3.0%</td><td>7.1%</td><td>12.3%</td></tr>
</table></td><td>Australian population statistics, AIHW</td></tr>
<tr><td>Prior AMI</td><td>Table</td><td>Prevalence rate of CHD, HILDA quit population
<table>
<tr><td></td><td>40-50</td><td>50-60</td><td>60-70</td><td>70+</td></tr>
<tr><td>Male & Female</td><td>2.9%</td><td>8.2%</td><td>14.9%</td><td>20.2%</td></tr>
</table>
Prevalence rates of CHD, Australian population
<table>
<tr><td></td><td>45-54</td><td>55-64</td><td>65-74</td><td>75+</td></tr>
<tr><td>Male</td><td>1.6%</td><td>6.1%</td><td>10.5%</td><td>20.7%</td></tr>
<tr><td>Female</td><td>0.7%</td><td>3.6%</td><td>6.0%</td><td>8.1%</td></tr>
</table></td><td>HILDA quit population (Alternative : Australian population statistics, AIHW)</td></tr>
</table>

Assumed based on those recorded as quitting in HILDA 2002-2019.

The model population had a mean age of 42.0 years, with 51.7% being male and more likely having lower levels of education and income compared to non-smokers. In terms of smoking characteristics, patients had smoked for on average 24.6 years with an average smoking intensity of 12.2 cigarettes per day, corresponding to 15.8 pack-years.

Overall, the model population is generally similar to patients accessing smoking cessation treatments on the PBS in terms of age and sex (based on evidence from the ToR 2 report). An analysis presented in ToR 2 found that patients accessing their first smoking cessation treatment on the PBS (between 2010 and 2015) had a mean age of 43 years (SD = 14.6) and

56% were male. In addition, the majority (approx. 72%) of patients were living in regions with higher levels of socio-economic disadvantage.

It should be noted that not all assisted quit attempts in Australia will be observable based on PBS data given that a substantial number of those attempting to quit will be using OTC NRT or quitting unassisted 'cold turkey.' This is particularly important for those without a healthcare card where the savings from having an NRT PBS prescription may not outweigh the out-of-pocket costs and inconvenience of obtaining the scripts from a general practitioner (GP). Therefore, those with a healthcare card are more likely to be using PBS-subsided products and thus more likely to be older and on lower incomes than the general population looking to quit. We also observe in the HILDA data that those quitting are likely to be smoking fewer cigarettes per day compared with those who enrol in smoking cessation trials.

3.4 Transition probabilities and extrapolation

Quit rates

For the economic model, we developed estimates of the absolute quit rates associated with the use of four alternative smoking cessation therapies (NRT, VAR, VAR+NRT, NRT+NRT) as well as the quit rate associated with unassisted quit attempts (i.e., estimated by the placebo arm in the clinical trial evidence). To do this we used the quit rate associated with VAR in Australia as the reference group and applied the RRs for the effectiveness of each alternative.

Treatment effects (relative risks)

We based the estimates of the RRs on the evidence identified in the ToR 3 report as well as a recent RCT that has since been published by Baker et al. 2021 (9). The ToR 3 report identified several published meta-analyses and NMAs for the relevant comparisons, and estimated new meta-analyses (head-to-head comparisons only) using up-to-date evidence for three types of patient:

- 'Treatment-naïve' patients treated with a cessation therapy
- 'Treatment-experienced non-abstainers' re-treated with a cessation therapy
- 'Treatment-experienced abstainers' treated with a cessation therapy for relapse prevention.

Where multiple definitions of abstinence were assessed at multiple time points, the methodology in the ToR 3 report assumed the strictest of these definitions (i.e., continuous/prolonged abstinence over point prevalence abstinence) over the longest follow-up data (24+weeks). See Sections 3.1.10 and 3.1.11 (pages 32-153) of the ToR 3 report.

There are a number of complexities associated with using this evidence in the economic evaluation. These relate to the population, outcome of interest (CA versus point prevalence abstinence), and the time point after treatment when this was assessed (12, 24 or 52 weeks). This is especially important given the high relapse rates immediately following treatment as well as smokers who have an unsuccessful quit attempt making another attempt soon after relapse.

In the economic model, we focused on the evidence identified for the 'treatment-naïve' and 'treatment-experienced non-abstainer' populations, who had both used a cessation therapy for a quit attempt. Although the ToR 3 report differentiated between these two populations, there is not a clear distinction between the two types of trials. For example, most of the trials

classified as 'treatment-naïve' trials in the ToR 3 report actually enrolled patients who had made prior assisted quit attempts with at least one of the study medications. The key difference appears to be that all of the non-abstainer re-treatment trials were placebo-controlled trials where all patients had made a prior quit attempt with the active medicine. In addition, the ToR 3 report only classified 4 RCTs as investigating one of the smoking cessation therapies in treatment-experienced non-abstainers (1 RCT for VAR vs placebo, 2 RCTs for BUP vs placebo, 1 RCT for NRT vs placebo).

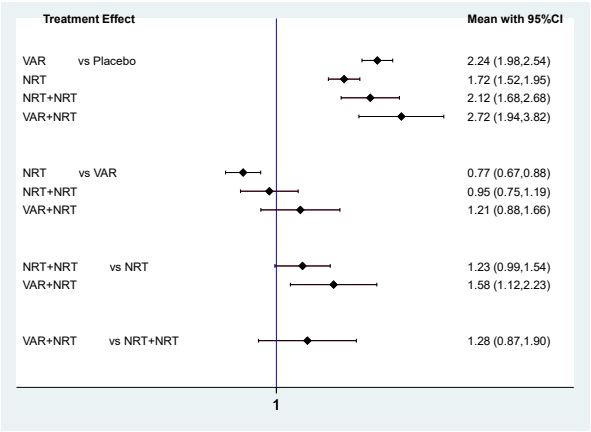
Hence, given the evidence available, we did not estimate different treatment effects for first and subsequent (including re-treatment) quit attempts. We further consider that the key findings in the ToR 3 report, that BUP and NRT may be less effective for re-treatment, should be interpreted with caution. The finding for BUP re-treatment was based on two small RCTs (one by Selby et al. 2003 [26] was an abstract only conference submission), with results that appeared to favour BUP versus placebo in terms of re-treatment (26,27). The finding for NRT was based on one small and dated RCT by Gourlay et al. (1995), which re-randomised moderate to heavy smokers shortly after (17 to 30 weeks) an unsuccessful quit attempt with NRT in another RCT (28). The trial also reported an unusually low proportion of patients with CA at week 26 in both treatment arms (1.6% with NRT and 1.3% with placebo).

In terms of the outcome, we defined a successful quit attempt by CA rather than point-prevalence abstinence. This choice was made given point-prevalence abstinence may include patients making a subsequent quit attempt. The model assumed 6-month cycles to match the majority of the evidence measured at 24 weeks, but we also explored CA at 52 weeks as a sensitivity analysis. The assumed 6-monthly cycle length allowed for patients with an unsuccessful quit attempt to make a subsequent quit attempt in the same year. This assumption is consistent with the advice of smoking experts from the NDARC at the University of New South Wales, as well an analysis of PBS data presented in the ToR 2 report. For VAR, the current PBS restriction (Authority Required – STREAMLINED) states *'the period between commencing varenicline … or a new course of varenicline must be at least 6 months'* and allows for up to 24 weeks of treatment per 12 months. For NRT, the current PBS restriction (Restricted Benefit) allows 12 weeks of treatment (or 24 weeks for Aboriginal and/or Torres Strait Islander patients) per 12 months, but the ToR 2 report found approximately 12% of patients use more than 12 weeks of PBS-subsidised treatment per year. This finding is consistent with some patients making two PBS assisted quit attempts with NRT in the same year. The model did not consider the costs and consequences of allowing for a further 12 weeks of VAR for relapse prevention.

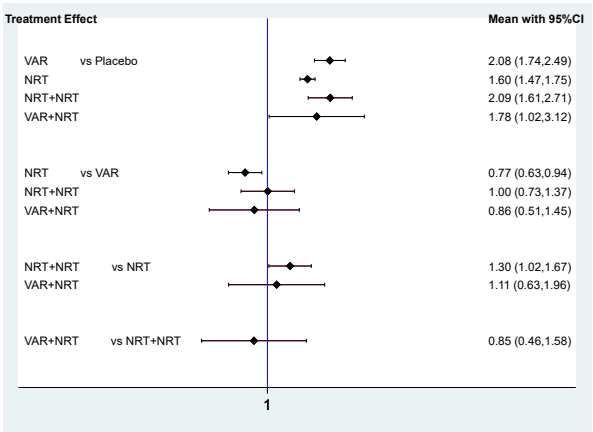
To provide consistent evidence for the economic evaluation across the five treatment options considered, we synthesised this evidence using a NMA. This differed to the approach taken in the ToR 3 report, which focused on meta-analysis of head-to-head evidence between any two of the cessation treatments. The NMA has the added advantage of making the most efficient use of the evidence available through also considering indirect comparisons. The NMA comprised of 53 RCTs with results at week 24 and 80 RCTs with results at week 52. Figure 9 presents the results of the NMA.

Figure 9: Results of the network meta-analysis for smoking cessation therapies

24-week continuous abstinence



52-week continuous abstinence



The results of the NMA showed that all four treatments significantly reduce smoking compared to placebo at 24 and 52 weeks post-treatment, but with a smaller reduction at 52 weeks post-treatment owing to high levels of relapse between 24 and 52 weeks. In terms of the key comparisons versus VAR, the evidence generally supports the conclusion that NRT is less effective than VAR, and both VAR+NRT and NRT+NRT have similar effectiveness compared to VAR (i.e., RR close to 1).

Table 14 provides the results of the NMA for the key parameters used in the model and a comparison to the corresponding estimates presented in the ToR 3 report. The results of the NMA for the effectiveness of placebo and NRT compared to VAR were similar to the results in the ToR 3 report, but the results for combination therapies differ slightly (for reasons discussed below).

Table 14: 24 weeks CA relative risks comparison with the ToR 3 conclusions

Comparisons versus VAR	NMA		Findings in ToR 3.
	24 Weeks	52 Weeks	
Unassisted (placebo)	0.45 (0.39, 0.51)	0.48 (0.40, 0.57)	SIMILAR: RR = 0.46 (0.40, 0.53)^ for continuous abstinence of at least six months, meta-analysis of 32 RCTs using a random effects model (ToR 3 Table 15).
NRT	0.77 (0.67, 0.88)	0.77 (0.63, 0.94)	SIMILAR: RR = 0.83 (0.71, 0.96) for point prevalence abstinence at 24 weeks with a NRT patch, meta-analysis of 9 RCTs using a random effects model (ToR 3 Table 27).
VAR+NRT	1.21 (0.88, 1.66)	0.86 (0.51, 1.45)	SOME DIFFERENCES: RR = 1.42 (1.13, 1.79) * using a fixed effects model or 1.41 (0.98, 2.04) using a random effects model, for the quit rate after 24 weeks or more, based on the meta-analysis of 2 RCTs conducted by Chang et al. 2015 (ToR 3 Table 68). Excludes recent RCT.
NRT+NRT	0.95 (0.75, 1.19)	1.00 (0.73, 1.37)	SOME DIFFERENCES: RR = 0.66 (0.45, 0.96) for 7 day point prevalence at 6 months based on direct evidence in one RCT (ToR 3 Table 64). Alternatively, RR = 0.94 (0.68, 1.33)# for the quit rate after at least six months, based on a NMA by Cahill et al. 2013 (ToR 3, Figure 18).

^ Inverse of the relative risk for VAR versus placebo, RR=2.16 (1.88, 2.48).

* The ToR 3 report presented the odds ratio from Chang et al. 2015 using a fixed effects model (OR = 1.62, 95%CI: 1.18, 2.23); the RR is presented in the table for consistency with other estimates.

Inverse of the relative risk for VAR versus NRT+NRT, RR=1.06 (0.75, 1.48)

For the comparison between VAR+NRT versus VAR, the ToR 3 report concluded results significantly favoured VAR+NRT (RR=1.42, 95%CI: 1.13, 1.79) based on a meta-analysis by Chang et al. 2015 (29). In contrast, we estimated a lower treatment effect in favour of VAR+NRT which did not reach statistical significance (RR=1.21, 95%CI: 0.88, 1.66). The main reason for these differences was due to the inclusion of an additional recent trial by Baker et al. 2021 (9) as well as changing from a fixed effects model as assumed by Chang et al. 2015 (29) to a random effects model as recommended by the PBAC guidelines. The random effects model is more appropriate than the fixed effects model because there is meaningful heterogeneity in the treatment effects across the trials (though not significantly different given the small sample sizes). Table 15 summarises the impact of the different trials and model assumptions on the estimated RR between VAR+NRT and VAR.

Table 15: 24 weeks outcome for VAR+NRT versus VAR under alternative trial and meta-analysis assumptions

	VAR + NRT	VAR	**RR (95%CI)**	
1 – Koegelenberg 2014 (30)	71/222 (32.0%)	42/224 (18.8%)	**1.71 (1.22,2.38)**	
2 – Ramon 2014 (31)	56/170 (32.9%)	48/171 (28.1%)	1.17 (0.85,1.62)	
3 – Baker 2021 (9)	66/314 (21.0%)	72/315 (22.9%)	0.92 (0.68,1.24)	
			Fixed effects	**Random effects**
Meta-analysis, 1+2	127/392 (32.4%)	90/395 (22.8%)	**1.42 (1.13,1.79)**	1.41 (0.98,2.04)
Meta-analysis, 1+2+3	193/706 (27.3%)	162/710 (22.8%)	**1.20 (1.00,1.44)**	1.22 (0.86,1.73)

For the comparison between NRT+NRT versus VAR, the ToR 3 report concluded that the combination of NRT patch + NRT lozenge was inferior to VAR based on 7-day point-prevalence abstinence at 24 weeks in one small RCT by Chen et al. 2020 (RR=0.66, 95%CI: 0.45, 0.96) (32). In contrast, we estimated similar efficacy between NRT+NRT (irrespective of the combination of product types) and VAR (RR=0.95, 95%CI: 0.75, 1.19), which aligned with the estimate from another NMA by Cahill et al. 2013 (RR=0.94, 95%CI: 0.68, 1.33) (33). The ToR 3 report identified the results from Cahill et al. 2013, however preferred the direct evidence from Chen et al. 2020. We note that the indirect evidence used in the NMA is the reasonably large body of evidence which shows the benefit of NRT+NRT compared to NRT (RR = 1.26, 95%CI: 1.11, 1.42; Table 60 of the ToR 3 report) is similar to the benefit of VAR compared to NRT (RR = 1.20, 95%CI: 1.04, 1.41; Table 27 of the ToR 3 report), corresponding to a similar effectiveness between NRT+NRT and VAR. Although direct evidence is generally preferred to indirect evidence, given that these other comparisons are reliable and also highly relevant to the current cost-effectiveness analysis, for consistency we prefer to rely on the indirect estimates from the NMA. In addition, although the statistical inference based on hypothesis testing from the NMA and the Chen study appear to produce conflicting results, the NMA point estimate for NRT+NRT versus VAR (RR=0.95) falls within the 95% confidence interval from the Chen et al. 2020 study (95% CI: 0.45, 0.96). Thus, given the small sample size in the Chen study its result is not necessarily inconsistent with the evidence produced by the NMA (i.e., there is a reasonable chance to get such an extreme point estimate given the small sample involved).

Assumed underlying 6-month success rate

To estimate absolute quit rates with all of the smoking cessation treatments in the model, we applied the estimated RRs from the NMA to an assumed underlying quit rate for the Australian population. It is noted that there are a number of factors independent of treatments associated with the success of a quit attempt, including the level of nicotine dependence (related to heaviness of smoking and time to first cigarette each day).

Importantly, the literature indicates that the level of nicotine dependence is a prognostic factor for the success of a quit attempt, where, for example, patients who smoke more cigarettes per day are less likely to quit smoking from a quit attempt compared to lighter smokers (10). The literature also indicates that the relative effectiveness of smoking cessation treatments themselves is not associated with the level of nicotine dependence and therefore the RRs estimated above can be applied to all patients (i.e. the level of nicotine dependence is not a treatment effect modifier when considering a constant relative effect) (34).

In a recent Australian trial by Courtney et al. 2021, the quit rate (CA at 24 weeks) in the VAR treatment arm was 13.3% for the intention to treat (ITT) population, 8.4% in the subgroup with 'high' nicotine dependency based on the Heaviness of Smoking Index (HSI) and 15.6% in the subgroup with 'low/medium' nicotine dependence (1). For the base case analysis, we assumed that the quit rate observed in this trial is a reasonable proxy for the underlying quit rates in Australia for those using VAR. There are some small differences in baseline characteristics between the trial and HILDA quit populations in terms of cigarettes smoked per day and level of education, but these differences likely work in opposite directions on the quit rate. We further assume that cigarettes per day is a reasonable proxy for nicotine dependence measured by the HSI, which is based on both cigarettes per day and time to first cigarette. That is, we assumed the quit rate for patients with a high nicotine dependence (5-6 on this HSI) is applicable to heavy smokers (≥20 cigarettes per day) in the model, and the quit rate for low/medium nicotine dependence (0-4 on this HSI) is applicable to light/medium smokers (<20 cigarettes per day) in the model. There is generally strong agreement between heavy smoking and high nicotine dependence, but weaker agreement between light/medium smokers and low/medium nicotine dependence (given some light/medium smokers have high nicotine dependence) (35). Hence, this assumption means we likely applied a higher absolute increase in the quit rate with pharmacotherapies for light/medium smokers than otherwise expected.

It is also acknowledged that the quit rate for VAR observed in the ITT population of Courtney et al. 2021 (13.3%) is at least half the average quit rate for VAR across all of the trials included in the NMA (26.6% at Week 24) and the assumed rate in the [redacted] model [redacted]. There are several reasons why these latter estimates may not reflect successful CA in real world smoking attempts. Most of these other trials were not conducted in Australia and instead were conducted in countries with higher rates of smoking. Also, participants in trials are often provided the treatments for free and are closely monitored (for both adherence and safety), which might encourage higher rates of success than in real world attempts. We test the underlying quit rate of VAR assumed in the base case in a sensitivity analysis, by doubling it, resulting in an average quit rate with VAR of approximately 29% across the population.

Table 16 outlines the assumed quit rates for both heavy and light smokers for each of the smoking cessation treatments considered.

Table 16: Successful quit rates at 6 months applied in the model in first and subsequent quit attempts

	Base case		Sensitivity analysis	
Product	Light/Mod Smokers (<20 cigarettes / day)	Heavy smokers (≥20 cigarettes / day)	Light/Mod Smokers (<20 cigarettes / day)	Heavy smokers (≥20 cigarettes / day)
Unassisted (placebo)	6.9%	3.7%	13.8%	7.4%
NRT	12.0%	6.5%	24.1%	13.0%
VAR*	15.6%	8.4%	31.2%	16.8%
VAR+NRT	19.1%	10.3%	38.2%	20.6%
Combination NRT	14.9%	8.0%	29.8%	16.1%

Notes: Assumes an underlying quit rate for VAR of 8.4% for heavy smokers and 15.6% for light/moderate smokers. All other quit rates are estimated based on this and the results of the NMA described above.

Relapse and subsequent quit attempts

Relapse rates for successful quitters and subsequent quit attempts for those still smoking were key inputs for the SDI model. In the model, and as described above, we allowed the success of each quit attempt to vary by whether the individual was a heavy or light/moderate smoker and depending on the product used during the quit attempt. However, we allow the rate of subsequent quit attempts and relapse to vary by age, sex, educational attainment, household income, and smoking intensity (number of cigarettes smoked per day).

To estimate the relapse rate and subsequent quit attempts we obtained contemporary and representative Australian estimates for quit and relapse rates using data from the HILDA survey (working paper by Saxby et al. 2022) (10). The HILDA survey has followed a nationally representative longitudinal cohort of Australian households annually since 2001, making it an ideal source to understand smoking cessation and relapse among Australians. Unfortunately, HILDA does not ask questions about quit attempts and only about smoking status so there is still a need to convert the reported quit rate in HILDA into the likely quit attempts.

Saxby et al. 2022 (10) employ a longitudinal study design and analyse a 19-year analysis period (2001 to 2019), which allows for the dynamic nature of smoking behaviour to be captured. In particular, quit and relapse rates may vary over time for an individual. Factors such as age, sex, educational attainment, household income and smoking intensity may all influence a smoker's propensity to quit or relapse. The authors account for these factors in their logistic model, results reproduced in Table 17 below. On average, using the HILDA data, 14% of smokers quit by the following year and 15% of ex-smokers were found to relapse each year. They find that smoking intensity is highly associated with smoking cessation. For instance, the odds ratio (OR) of reporting quitting from one year to the next is 0.46 [95% CI (0.42,0.51)] for someone who smokes 20 or more cigarettes per day, relative to someone who smokes 10 or fewer cigarettes per day. Similarly, the length of abstinence is significantly associated with smoking relapse, with the OR of relapse for someone who has reported to have abstained for seven or more years 0.04 [95% CI (0.03, 0.05)] relative to someone who has abstained for only one or two years. The HILDA model also estimates the impact of household members smoking status; however, we do not consider household characteristics in our smoking intensity model estimates without these household relationship variables. Saxby et al. 2022 find little evidence that the drivers of quit rates and relapse are significantly changing over their period of analysis.

Table 17: Factors related to reported changes in smoking status

	(1) **Quit**		(2) **Relapse**	
	OR	[95% CI]	OR	[95% CI]
Previous quit recorded	2.24***	[2.08,2.41]	-	-
Years abstained:				
0-1 years abstained (ref)	-	-	1.00	[1.00,1.00]
1-2 years abstained	-	-	0.36***	[0.32,0.40]
2-3 years abstained	-	-	0.21***	[0.18,0.24]
3-6 years abstained	-	-	0.10***	[0.09,0.12]
6 or more years abstained	-	-	0.04***	[0.03,0.05]
Level of smoking:				
10 or fewer cigarettes per day (Ref)	1.00	[1.00,1.00]	1.00	[1.00,1.00]
11-19 cigarettes per day	0.55***	[0.50,0.59]	1.14*	[1.01,1.29]
20 or more cigarettes per day	0.46***	[0.42,0.51]	1.06	[0.92,1.23]
Sex:				
Male	0.99	[0.93,1.07]	1.04	[0.95,1.14]
Age (years):				
Under 30	1.59***	[1.43,1.77]	1.19*	[1.03,1.38]
30-39	1.25***	[1.12,1.40]	1.06	[0.91,1.23]
40-49	0.98	[0.88,1.10]	1.09	[0.93,1.26]
50-59 (Ref)	1.00	[1.00,1.00]	1.00	[1.00,1.00]
60-69	1.33***	[1.16,1.53]	0.70***	[0.58,0.84]
Over 70	1.32**	[1.07,1.63]	0.52***	[0.39,0.69]
Education:				
Less than high school	1.00	[1.00,1.00]	1.00	[1.00,1.00]
High school or equivalent	1.15***	[1.06,1.24]	0.93	[0.83,1.05]
University degree	1.43***	[1.30,1.57]	0.80**	[0.70,0.92]
Equivalised household income:				
First quartile (lowest income)	1.00	[1.00,1.00]	1.00	[1.00,1.00]
Second quartile	1.07	[0.98,1.17]	0.85*	[0.74,0.97]
Third quartile	1.24***	[1.13,1.36]	0.75***	[0.66,0.86]
Fourth quartile (highest income)	1.50***	[1.36,1.65]	0.73***	[0.63,0.83]
Constant	0.10***	[0.09,0.11]	0.70***	[0.60,0.83]
N	*37,096*		*17,478*	
Mean of outcome	*0.14*		*0.15*	

Source: Reproduced from Saxby et al. 2022.

While this data provides detailed information on quitting and relapse behaviour in Australia, since these rates refer to year on year changes in reported smoking status, they are likely to represent both short-term quitters (e.g., those who may have quit within the last month) and long-term successful quitters (e.g., those who have not smoked for 6 months or more). This is compared with our SDI model, which considered 6-month CA as a 'successful' quit attempt. Applying these annual point estimates for smoking status alongside our estimate of the likely success of each quit attempt, we estimated the rate of subsequent quit attempts for the smoking intensity simulation model. To do this calibration we first estimated the likelihood of success for those who attempted to quit. We did this based on the reported use of NRT and a cessation pill (which we assume to be VAR given the low relative use of BUP in Australia during this period) in the 2019 NDSHS versus an unassisted quit attempt (30%, 12% and 58%). We assumed the same use of cessation products for heavy and light or moderate smokers. Based on the quit rates in Table 17 above, this produced a *status quo* quit success rate of 5.1% for heavy smokers and 9.5% for light or moderate smokers. We estimated the 6-monthly quit

attempt rates based on a separate calibration factor for heavy versus light and moderate smokers. To do this we assumed that one third of those who were making a quit attempt would likely have been surveyed during their quit attempt (i.e., they had not yet achieved a 6-month CA).

It should also be noted that the annual relapse rate for the reference group 0-1 years was also considered as relapse for short-term quitters which would potentially overestimate relapse in those who have been smoke-free for 6 months. Thus, we extrapolated the likely relapse rate after 6 months based on the predicted relapse rate for 1-2 years and longer, assuming an exponential decay in the relapse rate over time. Given the follow up data in HILDA for those who quit smoking is limited to ~10 years, we use data from Krall et al. 2002 to inform the probability of relapse after 10 years (0.1% per annum) (36).

Tables 18 and 19 present a summary of the corresponding probability of making a quit attempt and probability of relapse, for patients with characteristics associated with highest and lowest likelihoods of these events by smoking intensity, respectively. This is compared with the NDSHS 2019 which estimated that 45% of all Australian smokers made a quit attempt in the last year (though this included smokers who have never before made a quit attempt and from HILDA we know that those smokers who were observed making a past attempt are much more likely to try again). The BENESCO model assumed that 25% of United States (US) smokers are trying to quit each year (15).

Table 18: Highest and lowest predicted probabilities of making a quit attempt (assisted or unassisted) every 6 months given a prior quit attempt applied in the model

	Light smoker, ≤10 cigs/day	Moderate smoker, >10 to <20 cigs/day	Heavy smoker, ≥20 cigs/day
Base case – underlying quit rate from Courtney et al. 2021			
Highest probabilities in model^	100%	68.2%	68.1%
Lowest probabilities in model*	41.7%	24.9%	24.1%

^ Characteristics associated with highest probability of subsequent quit attempt given prior attempt: female, <30 years, university, and highest income.

* Characteristics associated with lowest probability of subsequent quit attempt given prior attempt: male, 40-49 years, less than high school, lowest income

Table 19: Highest and lowest predicted probabilities of relapse every 6 months applied in the model (note annualised probability presented in the brackets)

Years since successful quit attempt (24 week continuous abstinence)	Light smoker, ≤10 cigs / day	Moderate smoker, >10 to <20 cigs/day	Heavy smoker, ≥20 cigs / day
Highest probabilities in model^			
<1 years (24 to 52 weeks)	20.0% (36.1%)	21.6% (38.6%)	20.7% (37.1%)
≥1 to <2 years	12.9% (24.1%)	14.3% (26.6%)	13.5% (25.1%)
≥2 to <3 years	8.1% (15.5%)	9.1% (17.4%)	8.5% (16.3%)
≥3 to <6 years	4.1% (8.1%)	4.7% (9.1%)	4.3% (8.5%)
≥6 to <10 years	1.6% (3.2%)	1.9% (3.7%)	1.7% (3.4%)
≥10 years	0.05% (0.1%)	0.05% (0.1%)	0.05% (0.1%)
Lowest probabilities in model*			
<1 years (24 to 52 weeks)	6.9% (13.4%)	7.8% (14.9%)	7.3% (14.0%)
≥1 to <2 years	3.6% (13.4%)	4.1% (8.0%)	3.8% (7.4%)
≥2 to <3 years	2.1% (4.2%)	2.4% (4.8%)	2.2% (4.4%)
≥3 to <6 years	1.0% (2.1%)	1.2% (2.3%)	1.1% (2.2%)
≥6 to <10 years	0.4% (0.8%)	0.5% (0.9%)	0.4% (0.8%)
≥10 years	0.05% (0.1%)	0.05% (0.1%)	0.05% (0.1%)

^ Characteristics associated with highest probability of relapse: male, <30 years, less than high school, lowest income.

* Characteristics associated with lowest probability of relapse: female, ≥70 years, university degree, highest income.

To provide external validation for our assumed relapse rates for those studies in the NMA that collected estimates of CA at 6 and 12 months, we pooled the data across all these studies to estimate the relapse rate between 6 and 12 months (i.e., the percentage of those who were recorded as CA at 6 months who were not recorded as CA at 12 months). This provided an estimated relapse rate of 22.7% (452 out of 1,991). This was similar to the estimate derived from the HILDA analysis. Also, worth noting is that we obtained similar estimates for >1 years to <10 years from Hawkins et al. 2010, based on the British Household Panel Survey (37). There is little other published literature to validate our estimated rates of quit attempts, but our assumptions are consistent with the literature on making successful quit attempts. Overall, the assumptions of our model imply that smokers with higher levels of nicotine dependence are less likely to make a quit attempt and also find it more difficult to quit.

Smoking-related disease

Lung cancer

To model the incidence of lung cancer diagnosis as a function of pack-years of smoking, we adjusted the age-based incidence rates in never smokers (European descent population) reported by Thun et al. 2008 using the ORs for current smokers versus never smokers reported by Pesch et al. 2013 (38, 39). We assumed that the ORs are constant across age groups and convert them to RRs, where RR = OR / (1 – baseline risk + (baseline risk * OR)). To account for lower risk in ex-smokers, we assumed a reduction in the RR as a function of years smoke-free, based on an analysis comparing ex-smokers versus never smokers by Pesch et al. 2013 (39). The risk of lung cancer in ex-smokers gradually declines towards the background risk in never smokers the longer patients remain abstinent (5.3% of the elevated risk remains after 35 years of abstinence).

Table 20 summarises the annual probability of developing lung cancer by age and pack-years of smoking for current smokers and relatively recent quitters (note the table does not show results for longer term quitters for brevity purposes). We assumed a linear relationship to predict the elevated risk of lung cancer for pack-years between the mid-point of those ages presented in the table.

Table 20: Model predictions: annual probability of lung cancer diagnosis (results not presented for ex-smoker, ≥7.5 years smoke-free)

Age (yrs)	MALE								FEMALE							
	Pack-years								Pack-years							
	0 (NS)	10	25	35	45	55	65	*BEN*	*0 (NS)*	10	25	35	45	55	65	BEN
Current smoker																
35-39	*0.00%*	0.01%	0.01%	0.02%	0.03%	0.04%	0.04%		*0.00%*	0.00%	0.01%	0.01%	0.01%	0.01%	0.02%	
40-44	*0.00%*	0.01%	0.03%	0.04%	0.05%	0.07%	0.07%		*0.00%*	0.02%	0.03%	0.06%	0.06%	0.08%	0.11%	
45-49	*0.00%*	0.02%	0.04%	0.06%	0.08%	0.12%	0.12%		*0.00%*	0.02%	0.03%	0.06%	0.07%	0.08%	0.12%	
50-54	*0.00%*	0.04%	0.08%	0.12%	0.15%	0.22%	0.22%	*0.1%*	*0.01%*	0.03%	0.06%	0.11%	0.12%	0.15%	0.22%	0.02%
55-59	*0.01%*	0.07%	0.13%	0.19%	0.25%	0.36%	0.37%		*0.01%*	0.04%	0.09%	0.16%	0.17%	0.22%	0.31%	
60-64	*0.01%*	0.13%	0.25%	0.35%	0.46%	0.66%	0.68%		*0.01%*	0.04%	0.09%	0.16%	0.17%	0.22%	0.31%	
65-69	*0.02%*	0.22%	0.42%	0.60%	0.79%	1.13%	1.16%		*0.03%*	0.09%	0.19%	0.34%	0.36%	0.46%	0.66%	
70-74	*0.03%*	0.29%	0.56%	0.80%	1.05%	1.49%	1.54%		*0.04%*	0.14%	0.29%	0.51%	0.56%	0.71%	1.01%	
75-79	*0.04%*	0.39%	0.74%	1.06%	1.38%	1.96%	2.02%	*1%*	*0.04%*	0.14%	0.30%	0.53%	0.57%	0.73%	1.04%	0.44%
80-84	*0.06%*	0.55%	1.05%	1.49%	1.95%	2.76%	2.84%		*0.04%*	0.15%	0.32%	0.56%	0.61%	0.78%	1.11%	
85+	*0.19%*	1.65%	3.10%	4.37%	5.64%	7.78%	7.99%		*0.05%*	0.18%	0.37%	0.64%	0.70%	0.89%	1.27%	
Ex-smoker 2.5 years smoke-free: 76.5% of the elevated risk																
35-39		0.01%	0.01%	0.02%	0.02%	0.03%	0.03%			0.00%	0.00%	0.01%	0.01%	0.01%	0.02%	
40-44		0.01%	0.02%	0.03%	0.04%	0.05%	0.05%			0.01%	0.02%	0.04%	0.05%	0.06%	0.08%	
45-49		0.02%	0.03%	0.05%	0.06%	0.09%	0.09%			0.01%	0.03%	0.05%	0.05%	0.06%	0.09%	
50-54		0.03%	0.06%	0.09%	0.12%	0.17%	0.17%	0.04%		0.02%	0.05%	0.08%	0.09%	0.12%	0.17%	0.03%
55-59		0.05%	0.10%	0.15%	0.19%	0.28%	0.28%			0.03%	0.07%	0.12%	0.13%	0.17%	0.24%	
60-64		0.10%	0.19%	0.27%	0.35%	0.51%	0.52%			0.03%	0.07%	0.12%	0.13%	0.17%	0.24%	
65-69		0.17%	0.32%	0.46%	0.61%	0.87%	0.89%			0.07%	0.15%	0.26%	0.28%	0.36%	0.51%	
70-74		0.22%	0.43%	0.61%	0.81%	1.15%	1.18%			0.11%	0.22%	0.39%	0.43%	0.54%	0.78%	
75-79		0.30%	0.57%	0.81%	1.06%	1.50%	1.55%	0.43%		0.11%	0.23%	0.40%	0.44%	0.56%	0.80%	0.20%
80-84		0.42%	0.80%	1.15%	1.50%	2.12%	2.18%			0.12%	0.25%	0.43%	0.47%	0.60%	0.85%	
85+		1.27%	2.38%	3.37%	4.35%	6.01%	6.17%			0.13%	0.28%	0.49%	0.53%	0.68%	0.97%	
Ex-smoker 7.5 years smoke-free: 43.3% of the elevated risk																
35-39		0.00%	0.01%	0.01%	0.01%	0.02%	0.02%			0.00%	0.00%	0.00%	0.00%	0.01%	0.01%	
40-44		0.01%	0.01%	0.02%	0.02%	0.03%	0.03%			0.01%	0.01%	0.02%	0.03%	0.03%	0.05%	
45-49		0.01%	0.02%	0.03%	0.04%	0.05%	0.05%			0.01%	0.01%	0.03%	0.03%	0.04%	0.05%	
50-54		0.02%	0.03%	0.05%	0.07%	0.09%	0.10%	0.04%		0.01%	0.03%	0.05%	0.05%	0.07%	0.10%	0.03%
55-59		0.03%	0.06%	0.08%	0.11%	0.16%	0.16%			0.02%	0.04%	0.07%	0.07%	0.09%	0.14%	
60-64		0.06%	0.11%	0.15%	0.20%	0.29%	0.30%			0.02%	0.04%	0.07%	0.07%	0.09%	0.14%	
65-69		0.10%	0.18%	0.26%	0.35%	0.49%	0.51%			0.04%	0.08%	0.15%	0.16%	0.20%	0.29%	
70-74		0.13%	0.24%	0.35%	0.46%	0.65%	0.67%			0.06%	0.13%	0.22%	0.24%	0.31%	0.44%	
75-79		0.17%	0.32%	0.46%	0.60%	0.85%	0.88%	0.43%		0.06%	0.13%	0.23%	0.25%	0.32%	0.45%	0.20%
80-84		0.24%	0.45%	0.65%	0.85%	1.21%	1.24%			0.07%	0.14%	0.25%	0.27%	0.34%	0.48%	
85+		0.72%	1.36%	1.92%	2.49%	3.45%	3.55%			0.08%	0.16%	0.28%	0.30%	0.39%	0.55%	

COPD

To model the incidence of COPD as a function of pack-years of smoking, we used the age-based incidence rates in never smokers reported by Afonso et al. 2011 and the predicted increase in COPD prevalence for each additional pack-year (after adjusting for age, race, sex, body-mass-index, scanner type, centre, age of smoking onset, and current smoking status) as estimated by Bhatt et al. 2019 (11, 40). The RR in prevalence provides a close approximation for the RR of incidence by pack-years given the low incidence rate. The corresponding relationship between pack-years and COPD is consistent with other estimates of incidence from the literature, including those by Yannick et al. 2009 (41). We also assumed that the risk of developing COPD decreased in ex-smokers over time as a function of years since cessation, independent of pack-years, based on the relationship reported by Chang et al. 2021 (29). Although found to be statistically significant, the effect of year-since-quit is minor.

Table 21 summarises the annual probability of developing COPD assumed in the model by age and pack-years of smoking for current smokers and relatively recent quitters (note the table does not show results for longer term quitters for brevity purposes). We assumed a linear

relationship to predict the elevated risk of COPD for pack-years between those presented in the table.

Table 21: Model predictions: annual probability of COPD diagnosis (results not presented for ex-smoker, ≥7.5 years smoke-free)

Age (yrs)	MALE								FEMALE							
	Pack-years								Pack-years							
	0 (NS)	5	15	25	35	45	55	BENESCO#	NS	5	15	25	35	45	55	BENESCO#
Current smoker																
40-44	0.02%	0.03%	0.05%	0.06%	0.08%	0.10%	0.12%		0.01%	0.02%	0.03%	0.04%	0.05%	0.06%	0.07%	
45-49	0.02%	0.04%	0.06%	0.08%	0.11%	0.13%	0.15%		0.01%	0.02%	0.03%	0.05%	0.06%	0.07%	0.09%	
50-54	0.02%	0.03%	0.05%	0.07%	0.09%	0.10%	0.12%	0.02%	0.04%	0.06%	0.10%	0.14%	0.18%	0.21%	0.25%	0.02%
55-59	0.06%	0.08%	0.13%	0.19%	0.24%	0.29%	0.35%		0.06%	0.09%	0.15%	0.21%	0.27%	0.33%	0.39%	
60-64	0.16%	0.24%	0.39%	0.55%	0.70%	0.86%	1.01%		0.09%	0.14%	0.23%	0.32%	0.41%	0.50%	0.59%	
65-69	0.32%	0.48%	0.78%	1.08%	1.38%	1.69%	1.99%		0.16%	0.24%	0.39%	0.55%	0.70%	0.86%	1.01%	
70-74	0.41%	0.60%	0.97%	1.35%	1.73%	2.10%	2.48%	0.55%	0.24%	0.35%	0.58%	0.80%	1.03%	1.25%	1.48%	0.44%
75-79	0.60%	0.88%	1.43%	1.98%	2.53%	3.08%	3.63%		0.32%	0.47%	0.77%	1.07%	1.36%	1.66%	1.96%	
80+	0.72%	1.06%	1.73%	2.40%	3.07%	3.73%	4.39%		0.33%	0.49%	0.80%	1.11%	1.42%	1.73%	2.04%	
Ex-smoker 2.5 years smoke-free: 97.5% of the elevated risk																
40-44		0.03%	0.04%	0.06%	0.08%	0.10%	0.11%			0.02%	0.03%	0.04%	0.05%	0.06%	0.07%	
45-49		0.04%	0.06%	0.08%	0.10%	0.13%	0.15%			0.02%	0.03%	0.05%	0.06%	0.07%	0.08%	
50-54		0.03%	0.05%	0.07%	0.08%	0.10%	0.12%	0.02%		0.06%	0.10%	0.13%	0.17%	0.21%	0.25%	0.01%
55-59		0.08%	0.13%	0.18%	0.23%	0.29%	0.34%			0.09%	0.15%	0.21%	0.27%	0.33%	0.38%	
60-64		0.23%	0.38%	0.53%	0.68%	0.83%	0.98%			0.14%	0.22%	0.31%	0.40%	0.48%	0.57%	
65-69		0.46%	0.76%	1.06%	1.35%	1.65%	1.94%			0.23%	0.38%	0.53%	0.68%	0.83%	0.98%	
70-74		0.58%	0.95%	1.32%	1.68%	2.05%	2.42%	0.40%		0.34%	0.56%	0.78%	1.00%	1.22%	1.44%	0.43%
75-79		0.85%	1.40%	1.93%	2.47%	3.01%	3.54%			0.46%	0.75%	1.04%	1.33%	1.62%	1.91%	
80+		1.04%	1.69%	2.34%	2.99%	3.64%	4.28%			0.48%	0.78%	1.08%	1.38%	1.69%	1.99%	
Ex-smoker 7.5 years smoke-free: 92.7% of the elevated risk																
40-44		0.03%	0.04%	0.06%	0.08%	0.09%	0.11%			0.01%	0.02%	0.03%	0.04%	0.05%	0.06%	
45-49		0.03%	0.06%	0.08%	0.10%	0.12%	0.14%			0.02%	0.03%	0.04%	0.06%	0.07%	0.08%	
50-54		0.03%	0.04%	0.06%	0.08%	0.10%	0.11%	0.02%		0.06%	0.09%	0.13%	0.16%	0.20%	0.23%	0.0%
55-59		0.08%	0.13%	0.17%	0.22%	0.27%	0.32%			0.09%	0.14%	0.20%	0.25%	0.31%	0.37%	
60-64		0.22%	0.37%	0.51%	0.65%	0.79%	0.94%			0.13%	0.21%	0.29%	0.38%	0.46%	0.54%	
65-69		0.44%	0.72%	1.00%	1.28%	1.57%	1.85%			0.22%	0.37%	0.51%	0.65%	0.79%	0.94%	
70-74		0.55%	0.90%	1.25%	1.60%	1.95%	2.30%	0.05%		0.33%	0.54%	0.75%	0.95%	1.16%	1.37%	0.04%
75-79		0.81%	1.33%	1.84%	2.35%	2.86%	3.37%			0.44%	0.71%	0.99%	1.27%	1.54%	1.82%	
80+		0.98%	1.61%	2.23%	2.85%	3.47%	4.08%			0.45%	0.74%	1.03%	1.32%	1.61%	1.89%	

Age based probabilities applied in the BENESCO model for a UK population

After COPD diagnosis, the model tracked COPD progression through four severity health states to better account for the impacts of the disease on costs, quality of life and mortality (i.e., small impact for mild disease compared to large impact for severe disease). In accordance with the literature, the model defined COPD severity in terms of FEV1%; mild (FEV1 ≥80% predicted), moderate (50% ≤ FEV1 <80% predicted), severe (30% ≤ FEV1 <50% predicted), very severe (FEV1<30% predicted). At diagnosis, patients started in one of the severity health states based on the proportions reported by Afonso et al. 2011 (79.3% mild, 13.3% moderate and 7.4% severe) (40). Patients then had the chance to progress to the next severity health state in subsequent cycles.

To estimate the probability of COPD progression each cycle, we calculated the average time for an average COPD patient to progress through the health states using a similar methodology as Spencer et al. 2012 (42). Using this method, we first estimated FEV1 predicted using the reference equations reported by Quanjer 1993 and the average FEV1 decline over time for smokers and non-smokers. For smokers, we assumed an excess annual decline in FEV1 of 66.1mL/year for men and 54.2mL/year for women based on Anthonisen et al. 2002 (43, 44). We then calculated the average time to transition between the four severity

health states using the different FEV1% thresholds and convert the average time into a probability, where annual probability = 1 – exp (ln (0.5)/average time). We estimated different probabilities for the first and subsequent transitions because we assumed patients that were diagnosed with an FEV1% predicted at the mid-point of the range (and hence the FEV1% thresholds differ). Table 22 summarises the probability of COPD progression applied in the model for smokers and ex-smokers.

Table 22: Annual probability of worsening COPD in smokers and ex-smokers for the first and subsequent progressions

	Male		Female	
	Smoker	**Ex-smoker**	**Smoker**	**Ex-smoker**
First progression (after diagnosis)				
Mild to moderate (FEV1, 90% to 80%)	12.30%	10.74%	14.52%	13.37%
Moderate to severe (FEV1, 65% to 50%)	7.21%	6.12%	8.48%	7.66%
Severe to very severe (FEV1, 40% to 30%)	9.49%	7.88%	11.04%	9.85%
Subsequent progressions				
Moderate to severe (FEV1, 80% to 50%)	3.67%	3.11%	4.34%	3.91%
Severe to very severe (FEV1, 50% to 30%)	4.86%	4.02%	5.68%	5.05%

Acute Myocardial Infarction

The model assumed that the probability of first-ever myocardial infarction is a function of age and pack-years, and subsequent events are independent (due to a lack of data). To model the incidence of first ever AMI, we adjusted the age-based incidence rates in never smokers reported by Banks et al. 2019 using RRs reported by Lubin et al. 2016 (45, 46). We assumed the same probability for males and females owing to a lack of robust data broken down by sex. As Banks et al. 2019 only reports incidence for individuals over 45 years, we estimated the incidence in patients 40 to 44 years assuming that the incidence rate is proportional to the mortality rate for those 40-45 is the same as those 45-64 using mortality data from 2017. For subsequent myocardial infarctions, we assumed an annual probability of 6.81% for smokers and 5.28% for ex-smokers, based on an analysis by Rea et al. 2002 (47). Finally, we assumed 7.6% of patients died immediately after experiencing an AMI (first-ever and subsequent events) before admission to hospital, based on data reported in Banks et al. 2019 (45). Table 23 presents the annual probability of first-ever and subsequent AMI assumed in the model.

Table 23: Annual probability of acute myocardial infarction, males, and females

First-ever event							
Age	**Pack-years**						
	0 (NS)	**10**	**25**	**35**	**45**	**55**	**BENESCO#**
40-44^	0.02%	0.03%	0.04%	0.04%	0.05%	0.05%	M: 0.05% to 0.10%
45-64	0.11%	0.14%	0.18%	0.20%	0.22%	0.23%	F: 0.01% to 0.05%
65-79	0.32%	0.41%	0.53%	0.60%	0.65%	0.70%	M: 0.68% to 1%
≥80	1.28%	1.66%	2.12%	2.40%	2.61%	2.80%	F: 0.5% to 0.86%
Subsequent events							
Smoker	6.81%						M: 0.19% to 1.74%. F: 0.05% to 1.18%
Ex-smoker	5.28%						M: 0.07% to 1.16% F: 0.02% to 0.69%

^ The incidence for 40-44 years was estimated assuming a mortality rate of 0.219 compared to 45-64 years

Age-based probabilities assumed in the BENESCO model for a UK population. Probabilities differ by smoking status and time since quit.

Stroke

Due to the absence of data on the incidence rate of first ever stroke in never smokers in the literature, we used the total incidence of first ever stroke based on an Australian study by Islam et al. 2008 along with the RRs of stroke for never, ex-smokers and smokers in Banks et al. 2019 and the prevalence of each smoking status in the matching years based on Australian Bureau of Statistics (ABS) estimates, to estimate the incidence rate of first ever stroke in never smokers (45, 48). We then estimated the incidence of first ever stroke as a function of pack-years of smoking using RRs reported by Lubin et al. 2016 (46). For subsequent stroke events, we assumed an annual probability of 3.30% for current smokers and 2.00% for ex-smokers in the first year after the stroke, and 1.91% for current smokers and 1.15% for ex-smokers in subsequent years after their stroke based on data reported in risks estimated from Chen et al. 2019 and Flach et al. 2020 (49, 50). Finally, we assumed 6.4% of patients died immediately after experiencing a stroke (first-ever and subsequent events) before admission to hospital, based on data reported in Banks et al. 2019 (45). Table 24 presents the annual probability of first-ever and subsequent stroke assumed in the model.

Table 24: Annual probability of first-ever stroke (fatal / non-fatal), males and females

First-ever event							
Age	**Pack-years**						
	NS	**10**	**25**	**35**	**45**	**55**	**BENESCO#**
40-44^	0.007%	0.008%	0.010%	0.011%	0.013%	0.015%	M: 0.11 to 0.26% F: 0.05% to 0.2%
45-64	0.02%	0.03%	0.03%	0.04%	0.04%	0.05%	
65-74	0.28%	0.32%	0.42%	0.45%	0.54%	0.62%	
75-84	0.75%	0.85%	1.10%	1.20%	1.42%	1.62%	M: 0.61 to 0.92% F: 0.46% to 0.74%
≥85	1.11%	1.25%	1.62%	1.76%	2.08%	2.38%	
Subsequent events							
Smoker	≤12 months prior event: 3.30%, >12 months prior event: 1.91%						M: 0.35% to 1.55% F: 0.28% to 1.33%
Ex-smoker	≤12 months prior event: 2.00%, >12 months prior event: 1.15%						M: 0.00% to 1.03% F: 0.00% to 1.0%

^ The incidence for 40-44 years was estimated assuming a mortality rate of 0.303 compared to 45-64 years

Age-based probabilities assumed in the BENESCO model for a UK population. Probabilities differ by smoking status and time since quit.

Mortality

Individuals in the SDI model are at risk of death from myocardial infarction, stroke, COPD, lung cancer and other causes. These other cause mortality rates were based on 2017-18 Australian cause elimination mortality rates (where the deaths due to AMI, stroke, COPD and lung cancer are excluded) and are assumed to be the same regardless of pack-years (51). Individuals could also die in the SDI model due to having a fatal myocardial infarction or stroke, or they could die due to excess mortality risk associated with having previously had a non-fatal myocardial infarction, non-fatal stroke, lung cancer or COPD (where the risk of death is also related to their severity of COPD).

As discussed above, the probability of a fatal myocardial infarction or fatal stroke prior to hospital admission is based on the proportion of individuals who had the event listed as their cause of death but had no hospital admission for this event recorded, plus all those who were recorded to have made it to hospital for each event. We thus assumed 7.6% of patients died immediately after experiencing an AMI and 6.4% died immediately after experiencing a stroke (first-ever and subsequent events) before admission to hospital, based on data reported in Banks et al. 2019 (45).

Excess mortality for those who experienced non-fatal AMIs and strokes (i.e., those who made it to hospital) is based on 30-day, and subsequent, survival rates for those hospitalised for the first time in Queensland in 2010 and allowed to vary by age and sex; estimated using a logistic regression for the 30-day mortality and a Gompertz survival model for post 30-day survival (using linked mortality data up until the end of 2015). The 30-day survival for these events is further calibrated to provide a population 30-day post hospitalisation survival rate of 9.2% for AMI and 14.3% for stroke based on 2009-2014 Australian stroke registry data (52) based on the frequency of first hospitalisations for AMI and Stroke in Queensland in 2010 (52). The 30-day and subsequent survival was used to estimate the excess mortality in the first 6 months following the myocardial infarction or stroke and the subsequent survival was used to estimate the excess mortality in all periods after this.

For lung cancer, we converted the Australian 5 year survival rates by age and sex into 6-monthly mortality rates assuming a constant mortality rate over this period and used this to estimate the excess mortality associated with developing lung cancer (53). For COPD we apply RRs for all-cause mortality by COPD severity for males and females (40).

3.5 Health outcomes

To value patient time in the model in terms of QALYs, we estimated disease-based utility weights using a multiplicative approach where baseline utility is multiplied by the proportional impact of each condition or event. We assumed baseline utility for smokers and ex-smokers with no current comorbidity is the same, using the age-based general population utility profile in Australia estimated by McCaffrey et al. 2016 (19). The study estimated health-related quality of life (EQ-5D-5L) for a randomly selected, community sample in South Australia aged 15-75+ years (n = 2,908).

For COPD, we estimated the impact of the decline in FEV1% predicted on quality of life based on a univariate analysis by Fishwick et al. 2015 (20). From this paper, we estimated patients with COPD experience a 5%, 19%, 33% and 47% decrease in utility relative to baseline for mild, moderate, severe, and very severe disease, respectively. For lung cancer, we assumed patients experience a 13% decrement for non-metastatic disease and a 43% decrement for metastatic disease based on a meta-analysis of lung cancer utilities by Sturza et al. 2010 (21). The meta-analysis provides a more reliable estimate for the impact on quality of life than individual trials, given the wide range of utility estimates in the literature. In the model, the utility decrement for metastatic disease is applied once when patients with lung cancer die (all-cause mortality).

For stroke, the model applied a 24.1% decrement in the cycle patients experienced an acute stroke (i.e. within the first 6 months) and a permanent 17.6% decrement in subsequent cycles (i.e. post stroke) based on Luengo-Fernadez et al. 2013 (22). The study compared quality of life as assessed by the EQ-5D in stroke patients (N=748) to matched controls over a five-year follow-up in the United Kingdom. For myocardial infarction, the model assumes a 15%

decrement in the cycle patients experience the event (i.e. within the first 6 months) but no permanent decrement in subsequent cycles[2](23).

Table 25 summarises the utility values applied in the model for each chronic and acute event. The multiplicative utility model means lower utilities are applied for patients with multiple chronic and acute events. The lowest possible utility in any cycle of the model is 0.16, applied to patients over 75 years with very severe COPD, lung cancer, and prior stroke who then experienced an acute stroke and died (all-cause mortality) in the cycle.

Table 25: Utility values applied in the model for chronic and acute events (values for multiple conditions not presented)

Age	No co-morbidity	Mild COPD	Moderate COPD	Severe COPD	V. severe COPD	Lung Ca (m0)	Lung Ca (m1)	Acute MI	Acute stroke	Post-stroke
15-24	0.96	0.91	0.78	0.64	0.51	0.79	0.55	0.82	0.73	0.79
25-34	0.95	0.90	0.77	0.64	0.51	0.78	0.54	0.81	0.72	0.78
34-44	0.92	0.87	0.74	0.62	0.49	0.76	0.53	0.78	0.70	0.76
45-54	0.89	0.84	0.72	0.60	0.48	0.73	0.51	0.76	0.68	0.73
55-64	0.89	0.84	0.72	0.60	0.48	0.73	0.51	0.76	0.68	0.73
65-74	0.87	0.82	0.70	0.58	0.46	0.72	0.50	0.74	0.66	0.72
75+	0.83	0.78	0.67	0.56	0.44	0.68	0.48	0.71	0.63	0.68

3.6 Health care resource use and costs

In the base case analysis, we assumed patients will use the full course of smoking cessation therapy for every quit attempt. For NRT and NRT+NRT, the full course includes one GP consultation with repeat prescriptions provided at this visit. In contrast, the full course of VAR and VAR+NRT included two GP consultations, where the first allows for the VAR initiation pack (and NRT and repeats) and the second for the VAR continuation pack. As the model only considered effectiveness data associated with a 12-week course of VAR, costs associated with the completion pack for relapse prevention (i.e., 12 to 24 weeks) were not included. Other costs associated with a quit attempt (for example, the use of Quitline) were ignored as they were assumed to be consistent across alternatives. Tables 26 and 27 provides the estimated costs for a quit attempt associated with each product.

[2] The PLATO study (Nikolic et al. 2013) used an absolute utility decrement of 0.0627 for those in the first year after a non-fatal myocardial infarction compared to a baseline of 0.8748 for those <69 years old. Concentrating this loss within the first 6 months equates to a 14.3% decrement however, they use a larger percentage decrement for older people in the non-fatal myocardial infarction state due to a smaller baseline utility weight as people age. Therefore, in the SDI model we apply a 15% decrement for all ages in the non-fatal myocardial infarction state. The PLATO study does assume the absolute utility decrement of 0.0627 continues in the post-myocardial infarction state as well but we make no such assumption in the SDI model an instead assume a complete recovery.

Table 26: Health care resource items and unit costs

Resource item	Unit cost	Source
Varenicline Initiation (11x0.5mg tablets and 42x1mg tablets) Continuation (112x1mg tablets)	 $87.24 $193.16	 PBS item 9218K PBS item 9129L
NRT All items (28 patches, 216 lozenges, or 216 pieces of gum)	$49.96	PBS items 3414Q, 5571F, 5572G, 5573H, 5465P, 10076H, 11617K, 11619M, 11612E
GP consultation	$39.10	MBS item 23

Note: as the model only considers effectiveness data associated with a 12-week course of VAR, costs associated with the completion pack (i.e., 12 to 24 weeks) are not included. We assume a fixed unit cost for all NRT even though there is some small variation across products.

Table 27: Assumed costs of quit attempts

Product used	Assumed Cost	
	Base case (full course)	Adherence adjusted*
Unassisted	$0	$0
NRT	$188.98	$139.02
VAR	$358.59	$242.47
VAR+NRT	$508.47	$342.39
Combination NRT	$338.86	$238.94

*The adherence adjusted costs assumes only 2 out of the 3 NRT scripts are filled on average per quit attempt and for VAR it is assumed that only 50% of those making a quit attempt will return to the GP to obtain and fill the continuation pack. These same assumptions are applied for VAR+NRT and combination NRT.

The costs of managing smoking-related diseases in the SDI model were based on recent Australian costs and, where applicable, inflated into 2021 Australian dollars. The model applied both background health-state costs based on prior events as well as transitory costs associated with modelled events. As we assumed modelled events occurred in the middle of the cycle, health-state costs were adjusted to capture increased costs associated with modelled events during the cycle, such as lung cancer diagnosis, COPD diagnosis, or COPD progression. The model also applied a separate transitory cost for lung cancer diagnosis (above background costs), AMI, acute stroke, and death. For patients who died in the same cycle as a lung cancer diagnosis, the model only applied a cost of death (rather than both diagnosis and death costs) as these patients are assumed to be palliative. The cost of death is also dependent on prior and current events. No death cost was applied to patients who died in the same cycle as an acute event (i.e., costs were likely to be minimal given they did not make it to hospital), and patients who died with lung cancer were assumed to have higher end-of-life costs than non-cancer patients.

The model assigned costs to patients in the lung cancer health-state based on a recent analysis of Australian cost data reported by Goldsbury et al. 2020 (24). For all patients in the lung-cancer health state, the model applies an average annual excess cost of $7,797 to capture the relatively stable costs associated with 'continuing care' (i.e., excluding initial and terminal costs). In the cycle of diagnosis, the model assigned an additional cost (in excess of the cost for continuing care) of $23,154 to capture the increased costs within the first 6 months of diagnosis. Similarly, to account for increased terminal costs in the last 6 months of life, the model assigned an additional cost of $33,601 in the cycle patients die (all cause) with lung cancer. For patients who died in the same cycle as diagnosis, the model only applied the terminal cost. For non-cancer deaths, we assume an end of life cost of $19,696 for the last 6 months of life based on data reported by Reeve et al. 2018 (54).

In the absence of Australian specific utilisation data, we estimated the annual cost of COPD by FEV1% health state based on the average resource use in Canada reported by Oostenbrink

et al. 2005, multiplied by Australian unit costs (see tables below) (55). Given the Canadian data does not capture recent changes to inhaler treatments, we assumed patients with mild COPD used a long-acting muscarinic antagonist (LAMA) inhaler, patients with moderate COPD used a LAMA + long-acting beta-agonist (LABA) inhaler and patients with severe or very severe COPD used a LAMA + LABA + inhaled corticosteroid (ICS) inhaler. Data from a recent PMR of COPD medicines in Australia does not report the utilisation of services by FEV1%. As the COPD health states in the model include exacerbations, we estimated an additional annual cost for managing exacerbations based on exacerbation rates reported by Hurst et al. 2010 and Kim et al. 2016 (56,57). Overall, we calculated annual costs for mild COPD, moderate COPD, severe COPD, and very severe COPD of $829, $1,888, $3,200, and $5,661, respectively.

Table 28: Cost for maintenance treatment of COPD

Resource item	Cost per unit of resource			Annual resource use by FEV1%			
	Natural unit	Unit cost	Source	MILD*	MOD	SEV	V.SEV
Specialist	Visit	$90.35	MBS 104	0	0	0.8	2.8
GP	Visit	$39.10	MBS 23	1	1	1.2	1.2
Spirometry	Test	$21.40	MBS 11506	1	1	1	1
Oxygen	Days	$12.11	DOH report#	0	2.96	27.21	67.31
LAMA	Scripts	$60.41	PBS 10187E	12	0	0	0
LAMA+LABA	Scripts	$89.47	PBS 10188F	0	12	0	0
LAMA+LABA+ICS	Scripts	$94.63	PBS 11379X	0	0	12	12
Total annual maintenance cost				**$785**	**$1,170**	**$1,606**	**$2,272**

* Assumed resource use for mild COPD

Department of Health Aged Care Subsidies and Supplements, Daily Payments from 20 September 2021.

Table 29: Cost for treatments for exacerbations of COPD

Resource item	Cost per unit of resource			Resource use by exacerbation severity	
	Natural unit	Unit cost	Source	Moderate	Severe
Hospital admission	Visit	$6317.00	DRG E68B E65A^	0	0.95*
ED administration only	Visit	$579	URG non-admitted^	0	0.05*
Specialist	Visit	$90.35	MBS 104	0.14	0.05
GP	Visit	$39.10	MBS 23	0.88	0.12
Other health professional	Visit	$64.80	MBS 10960	0.02	0.18
Antibiotics	Days	$1.77	PBS 11933C	5.84	4.86
Systemic steroids	Days	$0.55	PBS 1916W	3.40	5.18
Oxygen	Days	$12.11	DOH report#	0.17	3.62
Total cost per exacerbation				**$63**	**$6,106**

* Adjusted to remove double counting

Department of Health Aged Care Subsidies and Supplements, Daily Payments from 20 September 2021.

^ National Hospital Cost Data Collection Report, Round 23 (Financial year 2018-2019).

Table 30: Cost for maintenance treatment of COPD

	MILD	MOD	SEV	V.SEV
Annual rate of moderate exacerbations	0.69	0.74	1.09	1.46
Annual rate of severe exacerbations	0	0.11	0.25	0.54
Total annual cost for managing exacerbations	**$43**	**$718**	**$1,595**	**$3,389**

For non-fatal myocardial infarctions and strokes (i.e., those who make it to hospital), we estimated the hospital costs by using the average length of hospital stay in the 6 months after the event for those hospitalised for these events in Queensland in 2010, using the Queensland Hospital Admitted Patient Data Collection.

Table 31: Average costs for myocardial infarction and stroke within the first 6 months of an event and every 6 months thereafter

	First 6 months (acute costs)	After 6 months (chronic costs)
Myocardial infarction		
Total Government costs	$23,243.92	$364.20
Hospital	($22,500.30)	-
Out-of-hospital	($375.33)	($162.52)
Prescriptions	($368.29)	($201.69)
Stroke		
Total Government costs	$25,704.48	$324.10
Hospital	($25,246.80)	-
Out-of-hospital	($285.21)	($163.07)
Prescriptions	($172.47)	($161.03)

All costs are inflated to 2021 dollars based on the consumer price index and monthly costs are converted to 6-monthly costs. Costs are based on a 50-year-old male.

3.7 Model validation

There are a number of limitations with v1.0 of the SDI model. Firstly, while the smoking related diseases modelled are the four leading causes of smoking related mortality, and were estimated to make up over 60% of the smoking attributable mortality in the US between 2005-2009, they are unlikely to fully capture all the harms of smoking and benefits of smoking cessation (18). Thus, assuming other cause mortality is the same for smokers regardless of pack-years likely underestimates the benefits of smoking cessation. However, given that COPD is likely correlated with smoking, and that smoking also increases the risk of mortality from other diseases, the RRs used in the model may overestimate the additional risk related to COPD itself (for example, they also include the additional risk of lung cancer mortality). This approach may therefore slightly overestimate the benefits of smoking cessation. Where possible, we have used RRs associated with pack-years where other potential confounding factors (e.g., education, income, alcohol consumption) have been controlled for, but there remains a possibility that some confounding still exists.

In addition, in v1.0 of the SDI model, we have assumed that in the short-term, smoking cessation has no benefit on morbidity other than preventing or delaying these diseases, most of which occurs later life. While there is evidence that current smokers are less healthy than never or former smokers there is still considerable uncertainty around the size of any short-term benefits of smoking cessation. Estimating the benefits is also challenging given that many smokers attempt to quit due to poor health or a health shock. A US Department of Health and Human Services report highlighted that understanding the short-term benefits on morbidity of healthy smokers quitting is an important avenue for future research (18). In addition, in v1.0 of the SDI model, we have not accounted for any morbidity associated with making a quit attempt in terms of withdrawal symptoms (which may be more acute when an unassisted attempt is made), or side effects associated with the products used in a cessation attempt. In general, there is limited evidence available in the literature on this quality of life impact.

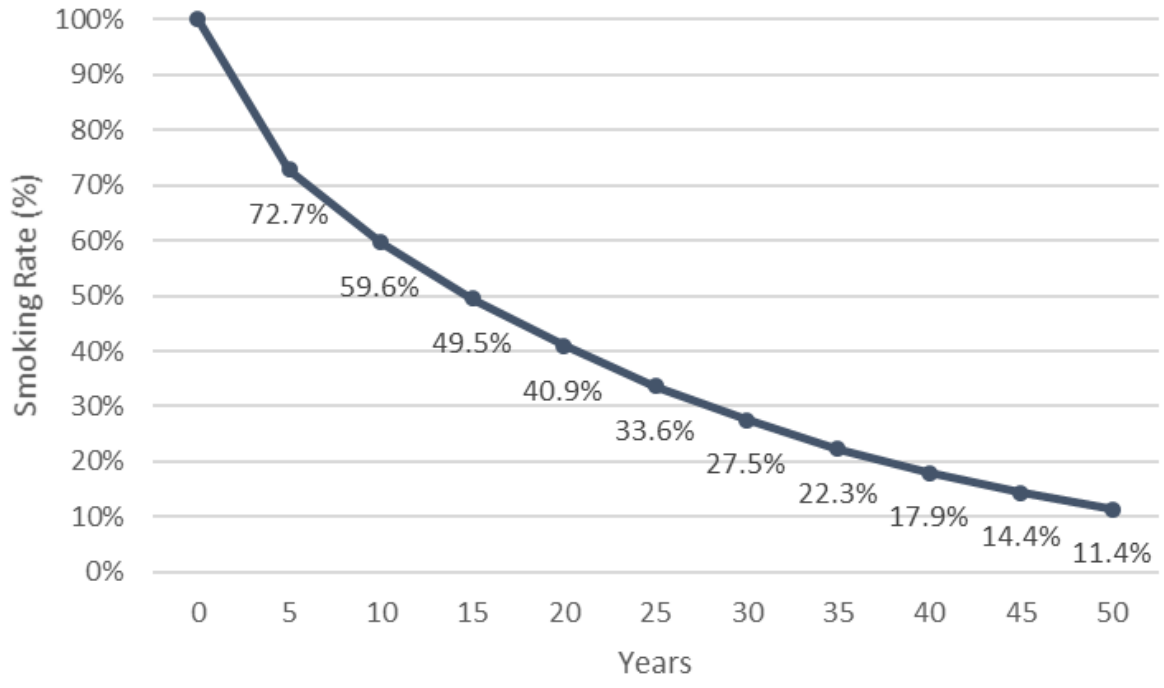
In order to validate the results of v1.0 of the SDI model we compared the outcomes for a simulated population of Australian smokers making a quit attempt with current smoking cessation therapies against other estimates available in the literature. Where possible these were Australian-based estimates.

Long-term trends in smoking behaviour of those attempting to quit

Given the lack of longitudinal population data on quit attempts and the numbers of those who have been smoke-free for 6 months, it is difficult to compare the results observed in the SDI model with other published estimates. Instead, we calculate long term quit rates using data from the HILDA survey to see how this compared to what is predicted by the SDI model's integrated set of equations for quit attempts, cessation products used and successful 6-month CA. There were 2,901 smokers in wave 2 of the HILDA survey (2002) of which 13.7% responded as a non-smoker by the following year. To calculate long term quit rates we consider a 'quit' to be two consecutive responses as a non-smoker. The 5, 10 and 15-year quit rates were 20.2%, 35.4% and 46.7% respectively. However, it should be noted that this will include smokers who have not previously attempted to quit. Thus, using a sample of 476 smokers in wave 9 (2009) who have previously quit, the 1, 5 and 10-year quit rates were 24.3%, 37.9% and 49.9% respectively. The long term quit rates are higher for this group, as expected, indicating that those who have previously quit are more likely to make subsequent quit attempts.

The long term quit rates from the SDI model are displayed in Figure 10 below. The SDI model yields 5, 10 and 15-year quit rates of 27.3%, 40.4% and 50.5% respectively. These all broadly align with the quit rates observed in HILDA. The higher initial quit rate in the SDI model may be attributable to the fact that the modelled population are assumed to all be making a quit attempt in the first period.

Figure 10: Simulated long-term smoking rate (SDI v1.0)



Acute myocardial infarction and stroke

In a prospective study of 188,167 individuals aged 45 and over from the Australian population, with 8% reporting being current smokers and 34% former smokers, Banks et al. 2019 investigate the impact of current and past smoking on the prevalence of cardiovascular and cerebrovascular disease. They find that AMI occurs in current smokers at a rate of 6.20 per

1,000-person years, age-sex standardised to the New South Wales (NSW) 2006 population 45 and over. Past smokers and never smokers suffer AMI at a lower rate of 3.22 and 2.84 per 1000-person years respectively. Current smokers also suffer a higher prevalence of stroke than never smokers – 3.53 versus 1.57 per 1,000-person years respectively. [3]

We compare these rates with the simulated outcomes from the SDI model for those aged over 45 years. 100,000 individuals over 80 years (by 6-month intervals) are simulated in the SDI model. The simulated population start as current smokers making a quit attempt with demographic and smoking intensity characteristics aligned to the distribution of smokers in HILDA.

We find that the rates of AMI and stroke for current smokers in the SDI model aligns very closely to the rates reported by Banks et al. 2019. While the model is calibrated to the incidence of AMI in never smokers reported in Banks, we combine this with the RRs associated with pack-years in a separate study. Therefore, these results suggest that the implied pack-years based on the cigarettes smoked in HILDA and the RRs from Lubin et al. 2016 combine to provide an accurate estimate of these diseases in current and former smokers in Australia (46). It should be noted that former smokers in Banks are likely to include more former smokers that had quit at younger ages (i.e., had accumulated fewer pack-years) while the former smokers in the SDI simulation include those that are currently smoking but who are expected to quit in the future. In addition, in the Banks et al. 2019 study current smokers may also include former smokers that have recently quit given that smoking status is not observed over time like in the SDI model.

Table 32: Standardised rates of AMI and stroke per 1000-person years

	SDI v1.0	Banks et al.
Myocardial infarction		
Current Smokers	6.20	6.20
Former Smokers	4.46	3.22
Never Smokers	NA	2.84
Stroke		
Current Smokers	3.51	3.53
Former Smokers	2.61	-
Never Smokers	NA	1.57

Note: Standardised rates to the NSW population 45 years and older based on ABS population estimates. We define stroke using the following ICD10 codes - I61, I63 and I64.

COPD

The Burden of Obstructive Lung Disease (BOLD) Australia study provides estimated rates for COPD by age and gender (58) however, it only reports the proportion of each group that ever smoked and does not report the COPD rates by smoking status. The international BOLD study however, which includes some participants from Sydney, provides the prevalence of Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage II or higher COPD reported by gender and pack-year categories:

- never smoked: men 4.3% women 4.9%; and

[3] Stroke is defined using the following three International Classification of Diseases (ICD-10) codes: I61 "Nontraumatic intracerebral haemorrhage," I63 "Cerebral infarction" and I64 "Stroke, not specified as haemorrhage or infarction."

- 20+ pack-years: men 21.7% women 23.8% (59).

The prevalence of COPD age-standardised to the US 2000 population in those aged ≥18 years was found to be 15.2% among current cigarette smokers, 7.6% among former smokers, and 2.8% among adults who had never smoked (Wheaton et al. 2019). However, the SDI model output only suggests a prevalence of 4.1% for current smokers and 2.2% for former smokers standardised to the US 20+ population. While the absolute numbers differ, both imply current smokers have around twice the prevalence of COPD as former smokers.

These differences may be due to the significant numbers of those with COPD who are undiagnosed in the population. A confirmed COPD diagnosis requires spirometry and many younger individuals with mild COPD may find that it has little impact on their quality of life. In the BOLD Australia study, it was found that under one quarter of those who likely had COPD had previously been diagnosed (60). In the SDI model the initial incidence of COPD is based on a reported diagnosis and therefore many smokers many have had undiagnosed COPD at this stage. As such the SDI model may underestimate the benefit of smoking cessation due to the reduction in the incidence and progression of COPD. Another possible explanation for the lower prevalence of COPD in the SDI model may be that mortality from COPD is overestimated.

Lung cancer

Bruder et al. 2018 estimated the 10-year risk of lung cancer using a sample from Switzerland (61). The output from the SDI model yields similar 10-year risk estimates, potentially overestimating at the oldest ages.

Table 33: 10-year and lifetime rates of Lung Cancer used in the SDI model versus Bruder

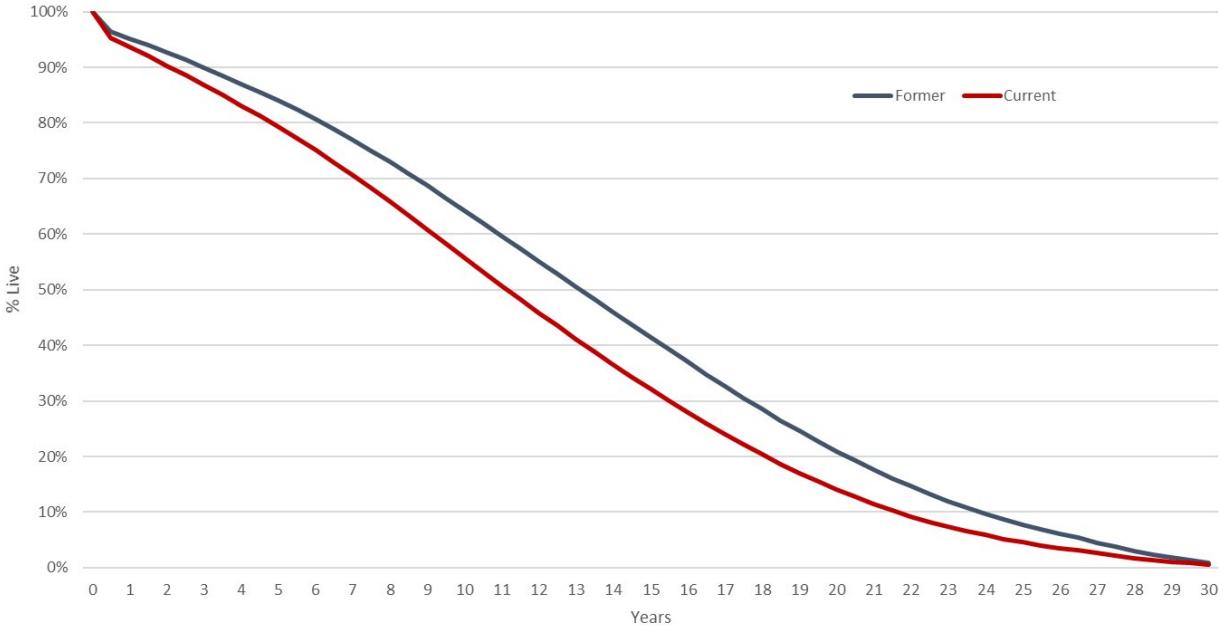
	Former		Current	
	10 year		10 year	
Age Group	SDI	Bruder^	SDI	Bruder^
40-44	0.1%	0.1%	0.4%	0.2%
45-59	0.2%		0.7%	
50-54	0.3%	0.8%	1.4%	1.3%
55-59	0.6%		2.5%	
60-64	1.0%	1.5%	4.1%	3.3%
65-69	1.3%		6.0%	
70-74	1.5%	2.1%	7.7%	4.3%
75-79	1.8%		9.8%	
80-84	2.2%	1.8%	12.2%	0.5%
85+	2.3%		14.3%	

*Rates were standardised to the European population to compare with Bruder et al.
^Average of male and female rates

Life expectancy

Based on data from the Australian Longitudinal Study of Ageing which followed up older people living in Australia from 1992-93 until the majority had died, the estimated remaining life expectancy in males aged 70 years with no respiratory symptoms was 16.6 years (95%CI: 14.8-17.7) for never smokers, 16.3 years (95%CI: 15.5-17.2) for former smokers and 13.6 years (95%CI: 11.6-15.3) for current smokers (Petrie et al. 2020) (62). The SDI model finds that the remaining life expectancy for males aged 70 and without COPD was 15.2 years for former smokers and 13.2 years for current smokers. The survival rate from the SDI model of former and current smokers aged 70-74 years old is shown below in Figure 11.

Figure 11: Survival rate SDIv1.0 (70-74 years old)



Model traces

To highlight the key drivers of the model, the figures below present the model traces for one of the comparisons included in the analysis i.e., the listing of VAR+NRT (VAR+NRT on the first attempt and also some substitution with subsequent attempts) versus VAR (VAR on the first attempt and the current market split of VAR and NRT for subsequent attempts).

Figure 12 illustrates how the proportion of patients smoking changes over time depending on the smoking cessation treatment used. Whilst quit rates are higher with VAR+NRT compared to VAR, the model assumes that smokers who have an unsuccessful quit attempt rapidly make a subsequent attempt. As a result, the implication of using a less effective smoking cessation treatment is largely a delay in quitting rather than long-term differences in the proportion of people continuing to smoke. The expected delay in quitting can be estimated by the horizontal distance between the smoker curves.

Figure 13 illustrates that the proportion of patients making quit attempts with VAR+NRT in subsequent years is lower than the proportion using VAR. This results in a reduction of downstream costs associated with these future quit attempts.

Figure 14 shows that a lower proportion of smokers translates to fewer accumulated pack-years which ultimately results in a lower prevalence of COPD and lung cancer (as well as a lower incidence of myocardial infarction and stroke) (Figure 15 and 16). Because the risk of these events are often many years in the future, the health benefits in the model are not realised for a number of years.

Figure 12: Proportion of patients smoking, conditional on survival

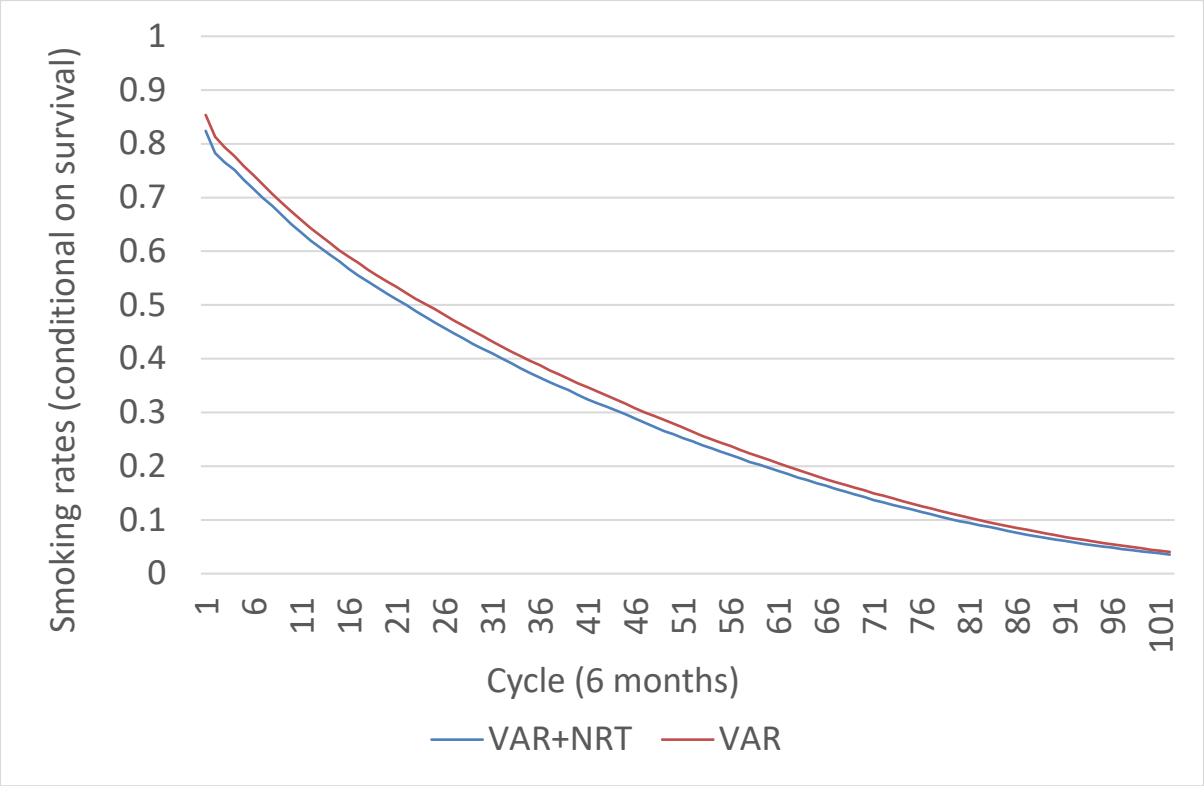


Figure 13: Proportion of patients making quit attempts, conditional on survival

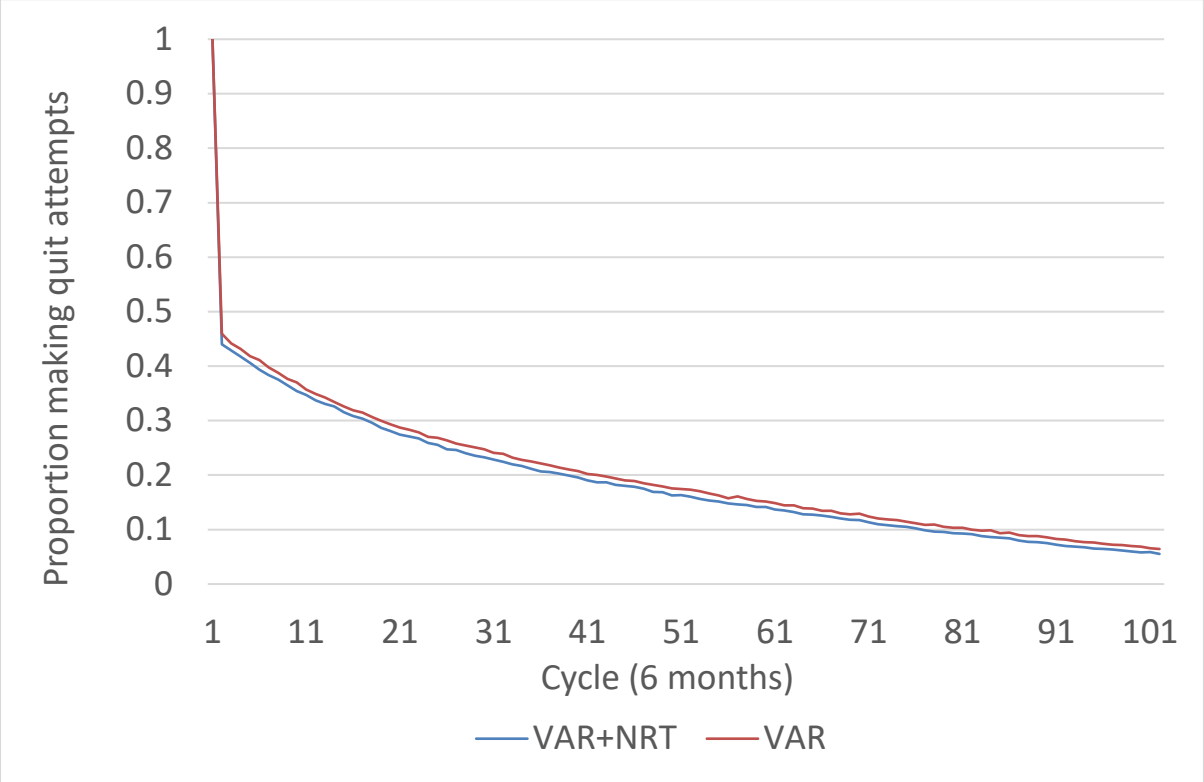


Figure 14: Average pack-years, conditional on survival

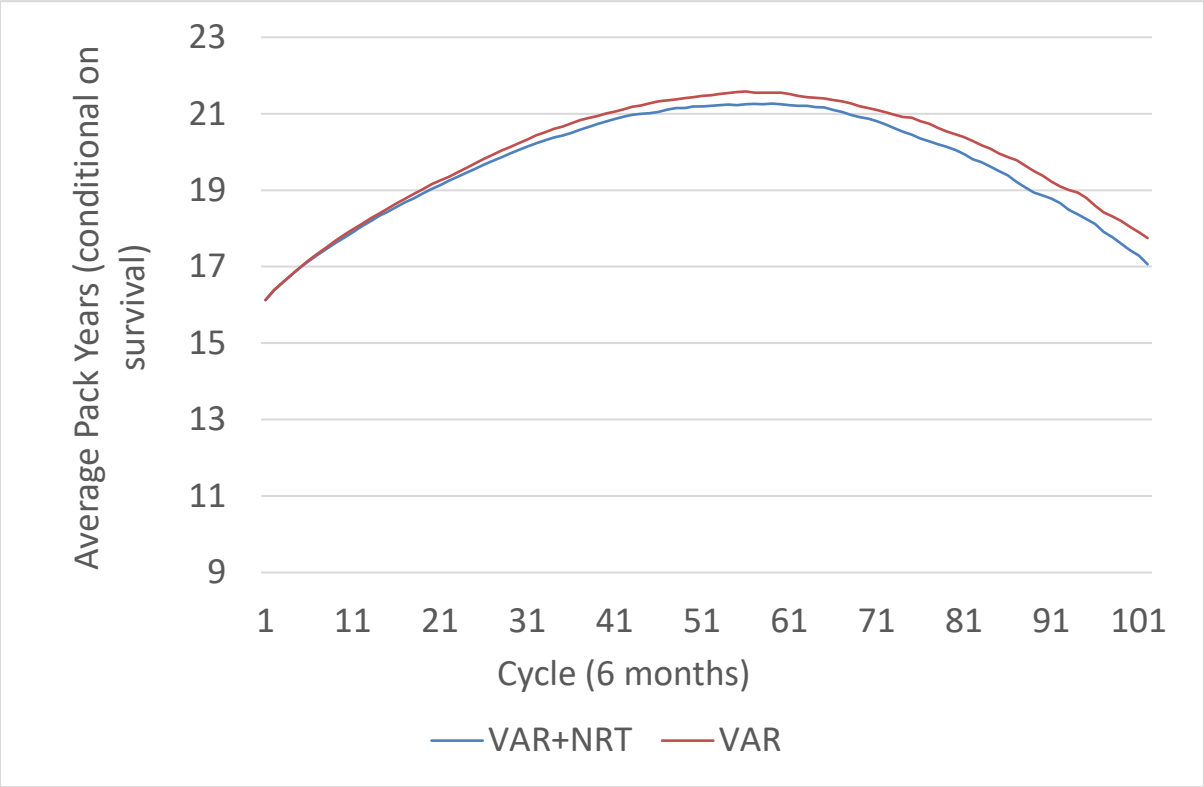


Figure 15: COPD prevalence, conditional on survival

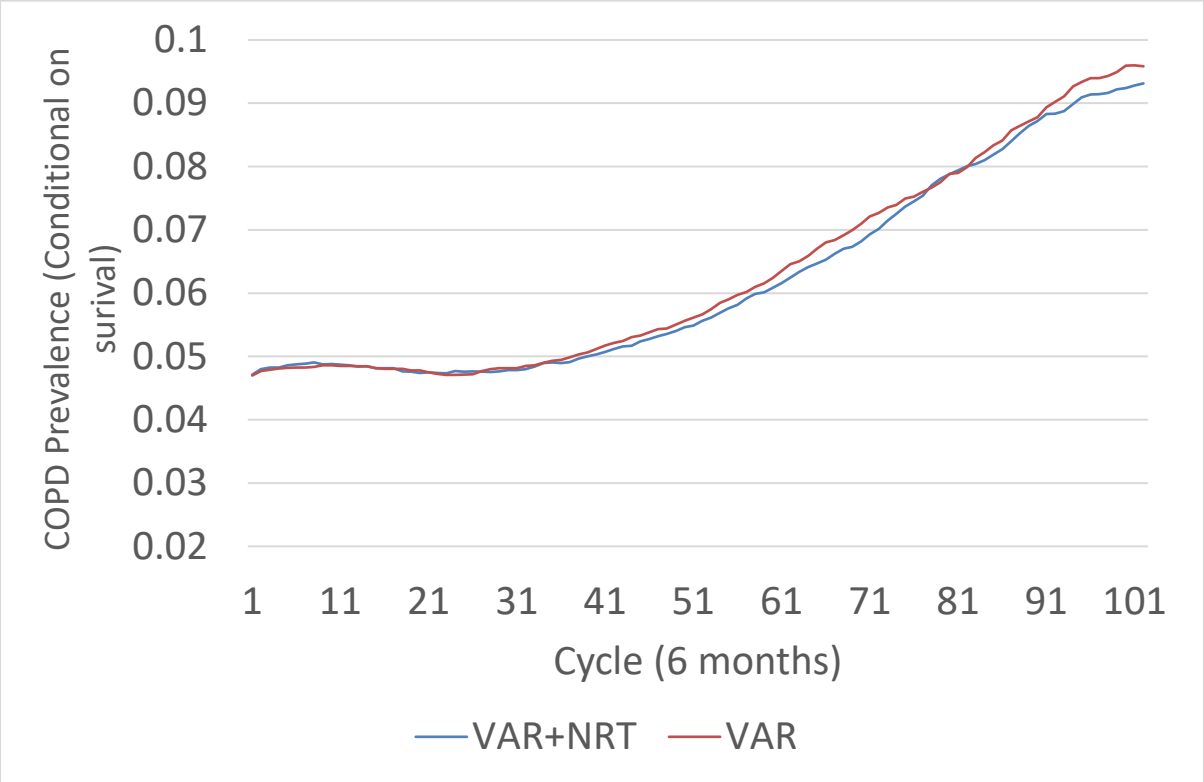
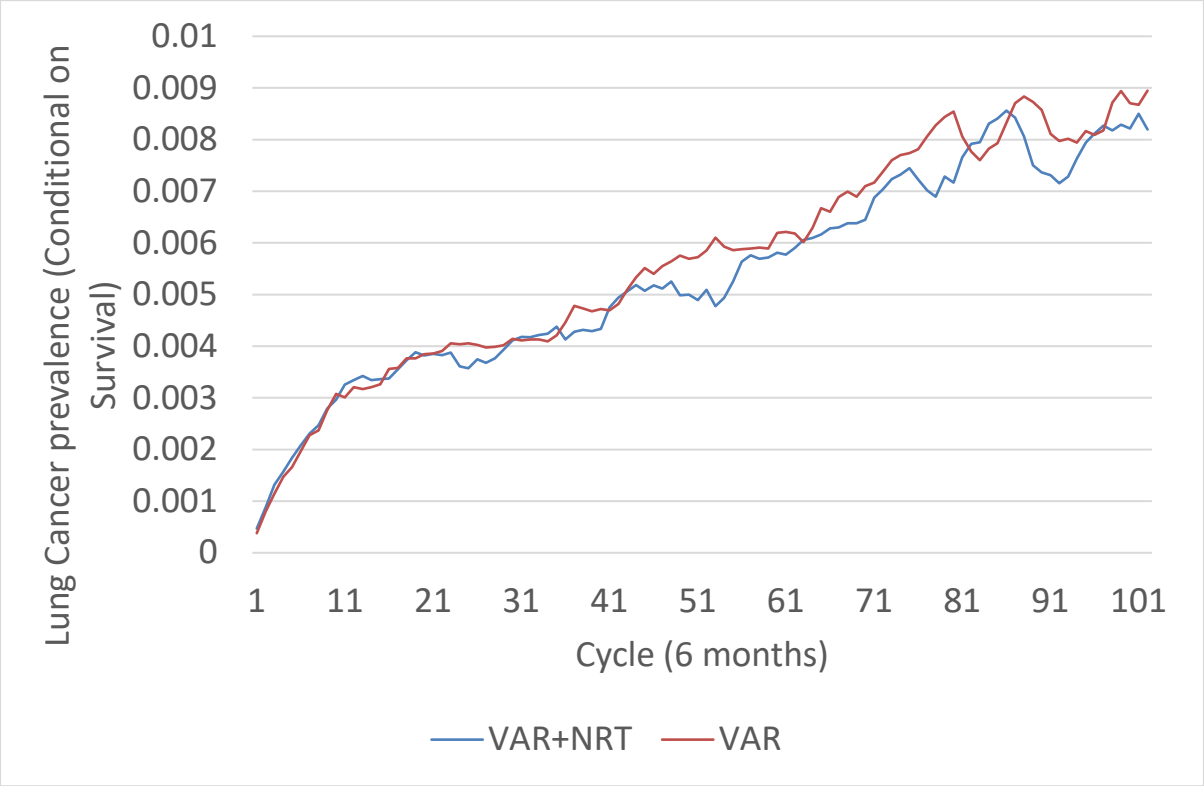


Figure 16: Lung cancer prevalence, conditional on survival



3.8 Results of the economic evaluation

Modelled scenarios - treatments used in the first and subsequent cycles

The SDI model included several treatment arms corresponding to the treatment received by a patient in the first 6-month cycle. The model then allowed patients to use the same treatment, or switch to a different treatment in subsequent cycles. The proportion of use per treatment in subsequent cycles was based on the displacement rates applied in the final year of the financial estimates model (see Table 41, Section 4.1 below) and the use of current treatments reported in the NDSHS[4] (58% unassisted, 30% NRT and 12% VAR[5]). The assumed proportion of treatment use per quit attempt applied in the first and subsequent cycles of the base case analysis is presented in Table 34 below.

[4] Data in the NDSHS captures use of both PBS and non-PBS NRT. Therefore, some reported NRT use will be accessed OTC and not incur costs to the PBS.

[5] This includes a very small proportion of patients using bupropion.

Table 34: Proportion of use per treatment applied in the first and subsequent cycles of the SDI model

Treatment arm	First quit attempt	Treatment used for subsequent quit attempts				
		Unassisted	NRT	VAR	VAR+NRT	NRT+NRT
VAR	VAR: 100%	58.0%	30.0%	12.0%	0%	0%
NRT	NRT: 100%	58.0%	30.0%	12.0%	0%	0%
VAR+NRT	VAR+NRT: 100%	58.0%	21.0%	8.4%	12.6%	0.0%
NRT+NRT	NRT+NRT: 100%	58.0%	15.0%	9.6%	0.0%	17.4%
VAR+NRT & NRT+NRT	VAR+NRT: 40.7%, NRT+NRT: 59.3%	58.0%	9.0%	7.2%	10.5%	15.3%

In the base case analysis, it was assumed that there will be no additional quit attempts as a result of the proposed listings for combination treatment and that uptake of combination treatment will be driven entirely by substitution away from monotherapy to dual therapy. However, the scenario of an increase in assisted quit attempts as a result of the PBS listing of combination treatments was tested in a sensitivity analysis. Table 35 shows the proportion of treatment use per quit attempt applied in subsequent cycles of the SDI model assuming funding leads to an increase in assisted quit attempts.

Table 35: Proportion of use per treatment applied in subsequent cycles of the SDI model assuming funding leads to an increase in assisted quit attempts (considered in a sensitivity analysis)

Treatment arm	Treatment used for subsequent quit attempts				
	Unassisted	NRT	VAR	VAR+NRT	NRT+NRT
VAR+NRT	57.0%	21.0%	8.4%	13.6%	0.0%
NRT+NRT	56.0%	15.0%	9.6%	0.0%	19.4%
VAR+NRT & NRT+NRT	55.75%	9.0%	7.2%	11.25%	16.8%

Results of the economic analysis

Table 36 presents the results of the economic evaluation for the five comparisons, with a discount rate of 5%. Because most of the benefits of smoking cessation occur many years in the future (especially for younger smokers who quit) the results are highly sensitive to the discount rate. Therefore, alternative discount rates (0% and 3.5%) are tested in a sensitivity analysis.

The first comparison evaluates the cost-effectiveness of VAR versus NRT (as the treatment used in the first cycle of the model) and provides a benchmark for the remaining comparisons. Those who do not quit, or those who relapse, with VAR or NRT may then go on to make further quit attempts. The assumed proportion of smokers making subsequent assisted quit attempts with VAR or NRT is based on the proportions reported in the 2019 NDSHS. Treatment in the VAR arm of the model has a higher overall cost than the NRT arm due to the higher cost of VAR in the initial cycle however, some of these costs are offset by fewer subsequent quit attempts in future cycles due to VAR's higher level of effectiveness. In addition, there are minor cost offsets due to less smoking related disease in the VAR arm in the future. The higher quit rate for VAR versus NRT, leads to earlier quitting for some smokers however, many of these smokers would still have quit, only later. Overall, the VAR arm results in the accumulation of fewer pack-years of smoking which in turn leads to a lower incidence of morbidity and mortality. There is a small incremental cost ($136 on average) and benefit (0.009 QALYs on average) with VAR as the first-line treatment compared to NRT, resulting in an ICER between $55,000 to < $75,000/QALY.

The second and third comparisons consider the value for money of the use of VAR+NRT in the first cycle versus VAR and NRT respectively. Substitution to VAR+NRT from other treatments (NRT and VAR) is assumed for subsequent quit attempts based on expected changes from that reported in the NDSHS. The VAR+NRT arm produces higher costs due to the higher cost in the first cycle and the higher average costs in subsequent cycles for those who were unsuccessful at quitting or who relapse (and may also use VAR+NRT in subsequent attempts). These costs are partially offset due to fewer smokers making fewer future quit attempts resulting in a reduction in healthcare costs. VAR+NRT treatment causes smokers to quit earlier and thus accrue fewer pack-years resulting in more QALYs gained. The VAR+NRT arm provides ICERs of between $35,000 to < $45,000 versus both VAR and NRT.

The third and fourth comparisons consider the value for money of the use of NRT+NRT in the first cycle versus VAR and NRT respectively. Substitution to NRT+NRT from other products is assumed for subsequent quit attempts based on expected changes to that reported in the NDSHS. The estimated ICERs for NRT+NRT versus VAR and NRT were within the range of $15,000 to < $25,000 and $25,000 to < $35,000 respectively.

The final comparison considers the value for money of listing NRT+NRT assuming VAR+NRT has already been listed. It is assumed that 40.7% of patients in the VAR+NRT and NRT+NRT arm use VAR+NRT for their first attempt and 59.3% use NRT+NRT. Substitution to NRT+NRT and VAR+NRT from VAR and NRT is assumed for subsequent quit attempts. The VAR+NRT and NRT+NRT arm is dominated (I.e., is both costlier and less effective) versus NRT.

Table 36: Results of the economic evaluation (considering only substitution between treatments)

Comparison	Costs ($AU)			Health outcomes (QALYs)			ICER range ($ per QALY)
	Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
(VAR) vs (NRT) [a]							
(VAR+NRT) [b] vs (VAR)							
(VAR+NRT) [b] vs (NRT)							
(NRT+NRT) [b] vs (VAR)							
(NRT+NRT) [b] vs (NRT)							
(VAR+NRT & NRT+NRT) [b] vs (VAR+NRT) [b]							

[a] This only considered the use of NRT versus VAR on the first attempt. The assumed use of NRT and VAR for subsequent attempts was assumed to be the same in both cases.

[b] Assumptions were also made about how the listing of these new combinations would also impact on the use of products in subsequent quit attempts. These results were produced by simulating 600,000 patients through each possible scenario for 50 years. 600,000 patients were used to minimise the Monte Carlo error.

The cost-effectiveness of VAR+NRT as a first line treatment, versus as a second line treatment following initial treatment with VAR, was also explored and the results are presented in Table 37 below. Whilst VAR is less costly than VAR+NRT, first line use of VAR may delay quitting for some smokers. The results below show that providing VAR+NRT first line, as opposed to

second line, generates an ICER between $45,000 to < $55,000/QALY. This relatively high ICER is due to the higher upfront costs associated with VAR+NRT generating a relatively small QALY gain. When compared to VAR, VAR+NRT is slightly more cost-effective as a second line treatment ($15,000 to < $25,000/QALY) compared to as a first-line treatment ($35,000 to < $45,000/QALY).

Table 37: Immediate versus delayed access to VAR+NRT

Comparison	Dis rate (%)	Costs ($AU)			Health outcomes (QALYs)			ICER ($ per QALY)
		Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
(VAR+NRT) vs (VAR+NRT available only for second line treatment)	5							

3.9 Sensitivity analysis

A number of assumptions were made in the economic analysis due to the lack of evidence to inform certain model parameters. Therefore, a sensitivity analysis was conducted to ascertain how the base case results vary in response to a change in these parameters. For example, in the base case analysis it was assumed that the listing of VAR+NRT and/or NRT+NRT would only lead to substitution away from currently listed smoking cessation medicines. This assumption is relaxed in a sensitivity analysis to consider the impact of an increase in assisted quit attempts as a result of the PBS listing of combination treatments (see Table 38).

Table 38: Proportion of use per treatment assumed in subsequent cycles assuming funding leads to an increase in assisted quit attempts

Treatment arm	Treatment used for subsequent quit attempts				
	Unassisted	NRT	VAR	VAR+NRT	NRT+NRT
VAR+NRT	57.0%	21.0%	8.4%	13.6%	0.0%
NRT+NRT	56.0%	15.0%	9.6%	0.0%	19.4%
VAR+NRT & NRT+NRT	55.75%	9.0%	7.2%	11.25%	16.8%

In addition, due to the low success rates associated with any one quit attempt, the high frequency with which smokers make quit attempts and the multiple treatments available to assist in these attempts the modelled ICERs will be highly sensitive to the assumptions applied in the base case analysis. Table 39 below shows how the ICERs for the various treatments respond to a change in these assumptions.

The results are highly sensitive to the discount rate and time horizon used given the majority of the health benefits from quitting smoking included in the model accrue many years in the future, especially for younger smokers (e.g., at a 5% discount rate little value is placed on encouraging a 20-year-old smoker to quit and preventing them developing lung cancer at age 65). The higher the discount rate, the less importance is given to future health gains and the savings from a reduction in future healthcare costs. The impact of discounting on the costs associated with future quit attempts is more complex however, overall, the impact of discounting on incremental costs is small. In general, more effective treatments become more cost effective when a lower discount rate or longer time horizon is applied. In both the VAR+NRT and NRT+NRT scenarios considered in Table 39 when a 20-year, as opposed to a 50-year, time horizon is used the incremental QALYs nearly halve which leads to a near doubling of the ICER for both comparisons. Such sensitivity highlights the substantial time lag between

quitting smoking and the gain in health benefits, which is especially acute for younger smokers.

Table 39 shows that changing the assumed underlying quit rates, even by a substantial margin, has little impact on the ICER results. Doubling all the quit rates to align them more closely with the overseas trials only slightly increases the ICERs. This is because while doubling the quit rates results in an increase in the absolute numbers of smokers quitting (i.e. the vertical gap in smokers increases), the cost of not quitting in the current cycle significantly decreases because those who are still smoking after the first cycle are now also more likely to quit in future cycles (i.e. the delay in quitting substantially reduces and thus the horizontal gap decreases by more than the vertical gap given the frequent attempts made by those who are trying to quit). As a result, the difference in pack-years (area between the smoker curves in each scenario) decrease. Because pack-years are the main driver of the difference in future health outcomes, these also reduce. However, there is now a larger reduction in future assisted quit attempts from the use of more effective treatments which reduces the incremental costs. The net effect of this results in a minimal impact on the final ICER.

Whilst the assumed costs used for the various treatments assume complete adherence, this is unlikely the case in practice. Therefore, the impact of lower adherence rates and thus lower costs were explored, though we did not assume any change in effectiveness. Persons with low adherence are likely to be those who were unsuccessful at quitting early in their quit attempt. The costs associated with lower adherence match those considered in the budget impact section and reflect adherence estimates from ToR 2. In general, lower costs increase the cost-effectiveness of the more intensive options.

We also considered the impact if the price of VAR reduced by 25% due to potential future price decreases associated with the entry of generic brands to the market. In terms of relative cost-effectiveness, this has little impact. We also considered the consequences if the 52-week CA follow-up evidence from the RCTs was used for the RRs instead of the 24-week follow-up evidence. Given this suggests VAR+NRT is less effective, VAR+NRT becomes less cost-effective.

The implications if the split of treatments used more closely matched the split seen in PBS data (higher rates of VAR compared to NRT) as opposed to that reported in population surveys (i.e., NDSHS 2019) was also investigated. We find that applying the PBS spilt has very little impact on either incremental costs or QALYs and thus little impact on the ICERs (except for when both VAR+NRT and NRT+NRT is listed).

Table 39: Exploring the implications of alternative assumptions

Comparison	Costs ($AU)			Health outcomes (QALYs)			ICER ($ per QALY)
	Proposed treatment	Comparator treatment	Diff.	Proposed treatment	Comparator treatment	Diff.	
(VAR+NRT) vs VAR							
Base case							
0% discount rate							
3.5% discount rate							
Double quit rate							
Lower Adherence (Cost)							
20-year time horizon							
PBS rather than 2019 NDSHS use of products for subsequent attempts*							
VAR 25% price reduction							
52 Week CA relative risk							
Small reduction in unassisted quit attempts							
(NRT+NRT) versus NRT							
Base case							
0% discount rate							
3.5% discount rate							
Double quit rate							
Lower Adherence (Cost)							
20-year time horizon							
PBS rather than 2019 NDSHS use of products for subsequent attempts*							
VAR 25% price reduction							
52 Week CA relative risk							
Small reduction in unassisted quit attempts							
(VAR+NRT & NRT+NRT) vs (VAR+NRT)							
Base case							
0% discount rate							
3.5% discount rate							
Double quit rate							
Lower Adherence (Cost)							
20-year time horizon							
PBS rather than 2019 NDSHS use of products for subsequent attempts*							
VAR 25% price reduction							
52 Week CA relative risk							
Small reduction in unassisted quit attempts							

*Assumes 18.48% NRT & 23.52% VAR on subsequent attempts without funding changes; 1.34% NRT 14.28% VAR 16.38% VAR+NRT (when VAR+NRT is listed); 7.14% 0.14.7% VAR 20.16% NRT+NRT (when NRT+NRT is listed); 4.2% NRT 10.5% VAR 10.08% VAR+NRT 17.22% NRT+NRT (when both are listed).

Section 4: Predicted use and budget impact analysis

The financial implications estimated below are based on a mix of both epidemiological and market share approaches. PBS utilisation statistics reported in the ToR 2 report inform a number of key model parameters including the number of quit attempts per financial year and the current market shares of smoking cessation treatments. We then consider the financial implications associated with additional utilisation of smoking cessation therapies under three listing scenarios:

Scenario 1: VAR+NRT listed on the PBS
Scenario 2: NRT+NRT listed on the PBS
Scenario 3: Both VAR+NRT and NRT+NRT listed on the PBS

For the base case analysis, our estimates extrapolate trends in the utilisation of smoking cessation products on the PBS for the five-year period to the 2019-2020 financial year. This provides an initial estimate but since this time, there have been two noticeable shocks to the market which need to be acknowledged. First, the data does not include the impacts of the COVID-19 epidemic on the propensity of smokers to make quit attempts (either pent up demand for access to smoking cessation products or potentially changed behaviours due to lockdown and increased episodes of smoking). Second, VAR was removed from the market in 2021 with expected return in October 2023. This has caused a major disruption to the market with likely substitution to BUP, PBS-listed NRT and OTC NRT but also potential discouraged assisted quit attempts. We consider the impact of this second market shock in a sensitivity analysis.

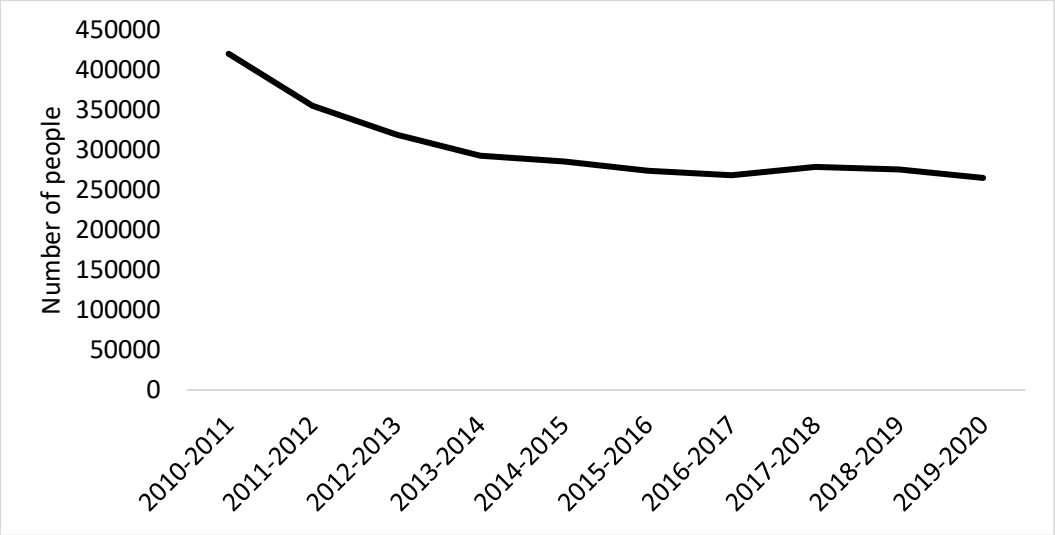
4.1 Justification of the selection of data sources

Market size: pharmacological assisted quit attempts

The financial model predicts the number of PBS pharmacological assisted quit attempts as a reasonable basis to estimate the budget impact of the three proposed scenarios (VAR+NRT listed; NRT+NRT listed; both listed). This approach avoids the unnecessary complexities associated with modelling a dynamic smoking population (where the eligible population is related to smoking-related behaviours as well as treatments).

Figure 17 shows the number of people using at least one smoking cessation treatment on the PBS/RPBS each financial year in the past decade, as cited in the ToR 2 report. The figure shows there has been gradual decline in the number of patients using treatment over time, with numbers generally plateauing in the past five years. The small increase in the number of patients in the 2017-2018 financial year may be due to the revised listing of VAR effective 2018 which permitted patients who started VAR in hospital to continue VAR in the community on the PBS. Given the current market is relatively stable, the projected number of patients in future years was estimated based on the last five years of data using a simple power function.

Figure 17: People prevalent to PBS-subsidised smoking cessation medicines



Source: Figure 11, ToR 2 report

To estimate the number of unique quit attempts each year (i.e., incidence) from the prevalent number of people using smoking cessation medicines, adjustment is required to account for i) double counting of patients when the same quit attempt spans two financial years and ii) people making more than one quit attempt in the same year either with the same or alternative products. Based on a mean duration of treatment of two months per quit attempt, observed as one month between scripts in the data used to generate the figure above, the incident number of patients using a smoking cessation treatment is 8% less than the prevalent number of patients. It was then estimated that approximately 15% of people overall would make two pharmacological-assisted quit attempts in the same year based on predictions for the average patient in the economic model.

Table 40 presents the projected number of patients using smoking cessation treatments and corresponding number of quit attempts per financial year, assuming no change to the PBS listing of smoking cessation treatments.

Table 40: Estimated number of pharmacological assisted quit attempts using a PBS-listed therapy

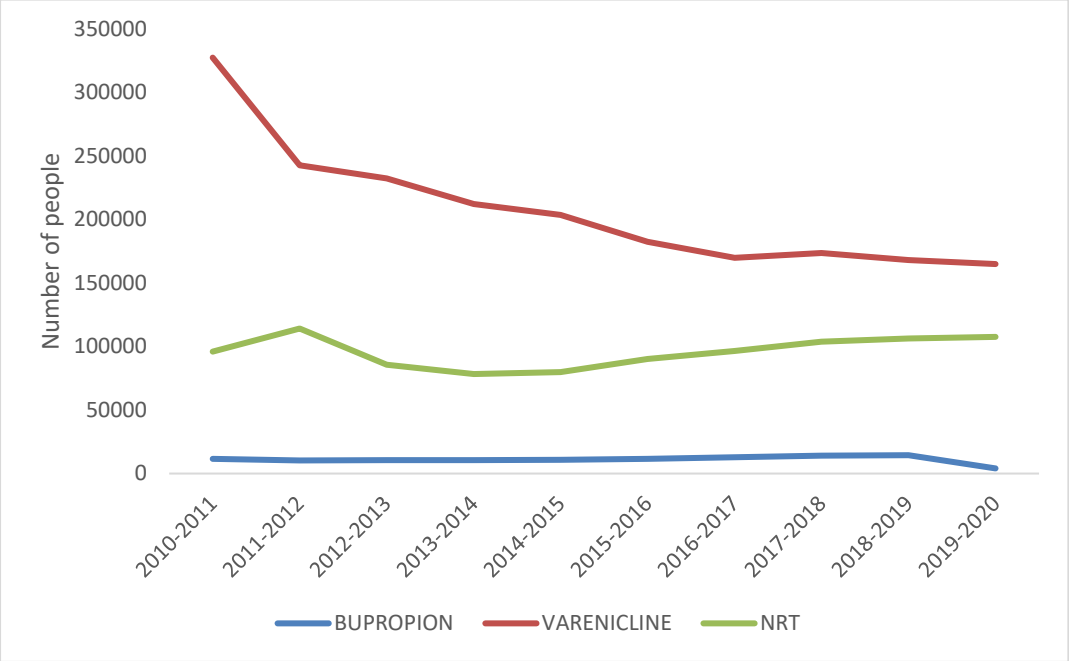
	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Patients using PBS smoking cessation treatments	270,818	270,595	270,395	270,215	270,051
Pharmacological assisted quit attempts using PBS-listed therapy	287,484	287,247	287,035	286,844	286,669

Market share: treatment choice for quit attempts

Figure 18 shows the number of prevalent people using smoking cessation treatments each financial year by type of therapy, as cited in the ToR 2 report. As the majority of patients did not use combination treatment of PBS-listed medicines, the proportional use of therapy reported in the figure is a reasonable proxy for the market shares for treatments used for each quit attempt. The graph shows VAR and NRT make up the majority of the market, with the use of VAR gradually declining and the use of NRT gradually increasing over the past five years. The uptick in use of NRT in 2011 was likely due to the extended listing to all Australians (having previously been restricted to Aboriginal and Torres Strait Islanders) in February 2011,

but shocks on the type of NRT available appear to have little impact on overall market share given NRT products are substitutes (e.g., GlaxoSmithKline recalled OTC lozenges in 2014, gum and lozenges listed in February 2019). Similar to quit attempts, the model used a simple power function fit to the most recent data (four years prior to 2019-2020[6]) to predict the therapies used for future quit attempts, assuming no change to the PBS listing of smoking cessation treatments.

Figure 18: Number of patients using smoking cessation therapy, by type of therapy



Source: Figure 12, ToR 2 report

The base case analysis assumes that the uptake of combination therapy (i.e., VAR+NRT and NRT+NRT) would replace monotherapy of VAR or NRT, and for simplicity, will not substitute for BUP given utilisation of BUP is historically very low. For example, a proportion of patients who would otherwise be treated with VAR or NRT monotherapy will receive either VAR+NRT or NRT+NRT depending on the listing scenario (i.e., the availability of combination treatment). However, given the recent short-term withdrawal of VAR from the market, we model a scenario analysis assuming much higher utilisation of BUP (instead of VAR) and substitution of NRT+NRT for BUP.

Overall, expert advice from smoking cessation experts based at the NDARC considered it would be reasonable to assume that combination therapy would replace monotherapy for at least 30% of the total pharmacologically assisted quit attempts. This estimate accounts for the current uncertainty around the effectiveness of combination therapy and uncertainty around future recommendations for its use (for example, combination therapy might be preferred after an unsuccessful quit attempt with monotherapy). The expert advice also considered that a similar proportion of patients would switch from VAR to VAR+NRT as NRT

[6] The analysis excluded data from 2019-2020 because recent PBS utilisation data showed use of BUP increased in line with the long-term trend in prior to 2019-2020. A sensitivity analysis including data from 2019-2020 predicts virtually no use of BUP over time.

to VAR+NRT but patients would be more likely to switch from NRT to NRT+NRT than VAR to NRT+NRT. The decision to prescribe VAR+NRT instead of VAR or NRT involves adding one additional therapy. The decision to prescribe NRT+NRT instead of NRT similarly involves adding a therapy but when it replaces VAR the decision is different as it involves replacing one therapy with two others. The advice considered the latter substitution was still likely due to the inferior safety profile of VAR (particularly in patients who may have had adverse events from prior use of VAR).

Table 41 shows the estimated market share of monotherapies used per quit attempt assuming no change to the PBS listing of smoking cessations treatments, and the assumed displacement rates for combination therapy under the different listing scenarios.

Table 41: Estimated market shares and displacement rates

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Current listing scenario: market share of monotherapy chosen per PBS pharmacological assisted quit attempts					
VAR	55.1%	54.5%	54.1%	53.6%	53.3%
NRT	39.4%	39.8%	40.2%	40.5%	40.8%
BUP	5.6%	5.7%	5.8%	5.8%	5.9%
Scenario 1 (VAR + NRT listed): displacement of monotherapy for combination therapy					
VAR to VAR + NRT	20%	25%	30%	30%	30%
NRT to VAR + NRT	20%	25%	30%	30%	30%
Scenario 2 (NRT + NRT listed): displacement of monotherapy for combination therapy					
NRT to NRT+NRT	40%	45%	50%	50%	50%
VAR to NRT + NRT	10%	15%	20%	20%	20%
Scenario 3 (VAR+NRT & NRT+NRT listed): displacement of monotherapy for combination therapy					
VAR to Dual Therapy	20%	30%	40%	40%	40%
VAR to VAR + NRT	15%	20%	25%	25%	25%
VAR to NRT + NRT	5%	10%	15%	15%	15%
NRT to Dual Therapy	50%	60%	70%	70%	70%
NRT to VAR + NRT	15%	20%	25%	25%	25%
NRT to NRT+NRT	35%	40%	45%	45%	45%

Market growth: change in quit attempts

In the base case analysis, we assume the proposed listing scenarios will not impact on the propensity of patients to make a quit attempt with a smoking cessation therapy (including both PBS-listed and non-PBS therapy). We also assume no change in compliance with treatments per quit attempt. There might be increased compliance if patients are more successful at quitting but there might also be lower compliance from using two treatments instead of one.

In contrast, we do assume that the proposed listings will impact on the total number of quit attempts with PBS-listed therapies. There is likely a financial incentive for some patients to switch from non-PBS NRT (i.e., patients who only use OTC treatments or supplement PBS funded treatment with concurrent OTC NRT use) to PBS-listed NRT+NRT as well as VAR+NRT, as the cost of treatment on the PBS for general patients is slightly lower than OTC prices. However, we also assume that the proposed listing of more effective therapies will lead to a reduction in future quit attempts based on estimates from the economic model on the reduction in future quit attempts. Hence, the size of market growth is governed by the relationship between these two effects.

A key variable to consider here is the number of quit attempts made using non-PBS NRT not captured by the PBS data. The ToR 2 report (page 17) estimated that the PBS-listed NRT represented only 7.1% of the overall NRT market in terms of cost for 2019. However, there is

likely a poor relationship between total sales and quit attempts made solely using non-PBS NRT, as the corresponding number of additional quit attempts is implausibly high. This is likely due to a large proportion of patients using non-PBS NRT to supplement quit attempts using PBS listed products, those using more than one non-PBS NRT product and those using non-PBS NRT products for other reasons (i.e., occasional replacement or non-cessation purposes). Instead, we used data from the NDSHS to estimate the number of additional quit attempts made using non-PBS NRT. Based on this data, we estimated that the number of additional quit attempts made using non-PBS NRT is approximately 2.8 times the number of quit attempts using PBS-listed NRT (implying that PBS data captures less than half of the total assisted quit attempts made in Australia per year).

Table 42 presents the estimated number of quit attempts using non-PBS NRT products per financial year and the assumed displacement rates from the non-PBS market to PBS-listed cessation products under the different listing scenarios. We assume that the displacement rates from the non-PBS market will be relatively low given the current market prices but note that there would likely be substantially higher substitution should fixed-dose combination products become available on the PBS given patients would only face one co-payment rather than two.

Table 42: Estimated number of quit attempts using non-PBS NRT and assumed displacement rates

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Pharmacological assisted quit attempts using non-PBS NRT	322,730	318,119	313,999	310,277	306,883
Scenario 1 (VAR + NRT listed)					
Non-PBS NRT to VAR+NRT	10%	10%	10%	10%	10%
Scenario 2 (NRT + NRT listed)					
Non-PBS NRT to NRT+NRT	20%	20%	20%	20%	20%
Scenario 3 (VAR+NRT & NRT+NRT listed)					
Non-PBS NRT to PBS therapy	23%	23%	23%	23%	23%
Non-PBS NRT to VAR+NRT	5%	5%	5%	5%	5%
Non-PBS NRT to NRT+NRT	18%	18%	18%	18%	18%

The second key variable to consider here is the impact of more effective combination therapies on the number of subsequent quit attempts. To do this, we apply the proportional impact on quit attempts each year in the economic model (assuming new entrants - new quitters - each year) to the total quit attempts estimated in the financial estimates. Table 43 presents the estimates applied in the base case analysis. These estimates represent the relative impact on quit attempts each year and are a function of the assumed displacement rates in the previous year.

Table 43: Estimated relative reduction in quit attempts due to displacement of less effective therapies with more effective therapies

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Scenario 1 (VAR + NRT listed)					
	3.3%	4.2%	5.0%	5.0%	5.0%
Scenario 2 (NRT + NRT listed)					
	2.2%	2.5%	2.7%	2.7%	2.7%
Scenario 3 (VAR+NRT & NRT+NRT listed)					
	4.4%	5.5%	6.6%	6.6%	6.6%

Duration of treatment: scripts per quit attempt

The average number of scripts per quit attempt by treatment type was estimated from the average duration of treatment for patients using their first-ever PBS-subsidised smoking cessation treatment in 2018-2019, reported in ToR 2 of the PMR (Tables 9, 10, and 11, pages 43-45). The average script for NRT provides approximately 4 weeks of treatment, corresponding to an average of 1.986 scripts per quit attempt.

For VAR and BUP, the average number of scripts was calculated based on the most likely combination of script types for the corresponding duration of treatment. A key finding from this analysis was that not all quit attempts used an initiation pack for VAR or BUP. This is potentially due to the amended listing of VAR in 2017, which allows patients who initiate VAR in hospital (i.e., non-PBS) to access the PBS-listed continuation pack in the community. There may also be behavioural effects of patients wanting the larger continuation packs dispensed first given the co-payment is the same for both. To account for potential differences between first and subsequent attempts, the estimates for continuation and completion scripts were then calibrated using overall utilisation data in 2020-2021.

Table 44 shows the average scripts per quit attempt used in the financial estimates model.

Table 44: Estimated average PBS scripts per quit attempt, by treatment and script type

	Description	Average scripts per quit attempt
VAR		
Initiation pack (9128K)	4 weeks / script, 0 repeats	0.906
Continuation pack (9129L)	8 weeks / script, 0 repeats	0.397
Completion pack (5469W)	4 weeks / script, 2 repeats	0.485
NRT		
All items# (patch, gum, lozenge)	4 weeks / script, 2 repeats	1.986
BUP		
Initiation pack (8465M)	~2 weeks / script, 0 repeats	0.814
Completion pack (8710K)	~6 weeks / script, 0 repeats	0.690

no adjustment for item 11612E (provides larger quantity), which accounted for less than 5% of total NRT scripts in 2020/2021.

Treatment costs and co-payments

Tables 45 and 46 present the published dispensed price for maximum quantities (DPMQs) used to cost the estimated number of PBS scripts and the estimated average co-payment amounts for each treatment, respectively. We assume a cost of $49.96 applies to all NRT scripts, given this represents the DPMQ corresponding to the vast majority of NRT scripts dispensed.

Table 45: DPMQs applied in the financial estimates, by treatment and script type

Resource item	DPMQ	Source
NRT		
All items (28 patches, 216 lozenges, or 216 pieces of gum)	$49.96^	PBS items 3414Q, 5571F, 5572G, 5573H, 5465P, 10076H, 11617K, 11619M, 11612E
VAR		
Initiation pack (9128K)	$87.24	PBS item 9218K
Continuation pack (9129L)	$193.16	PBS item 9129L
Completion pack (5469W)	$100.69	PBS item 5469W
BUP		
Initiation pack (8465M)	$63.52	PBS item 8465M
Completion pack (8710K)	$169.11	PBS item 8710K

^ A different DPMQ applies to items 4573Q ($58.68), 4572P ($55.72), 4571N ($52.56), 11618L ($68.90) but these represented less than 1% of total NRT scripts on PBS/RPBS in 2020-2021 financial year.

Table 46: Estimated average co-payment by treatment, based on services in the 2020/2021 financial year

	PBS				RPBS	
	General Ordinary	General Safety Net	Concessional Ordinary	Concessional Safety Net	RPBS Ordinary	RPBS Safety Net
Co-payment	$41.30	$6.60	$6.60	$0.00	$6.60	$0.00
Split of services, by treatment						
NRT (all items#)	54.3%	0.4%	38.8%	5.6%	0.7%	0.2%
VAR (9128K, 9129L, 5469W)	18.0%	0.5%	64.4%	15.9%	0.9%	0.3%
BUP (8465M, 8710K)	48.2%	0.4%	42.5%	5.1%	2.9%	0.8%
Average co-payment, by treatment						
NRT	$25.06					
VAR	$11.76					
BUP	$22.94					

^ Items: 3414Q, 5571F, 5572G, 5573H, 5465P, 10076H, 4573Q, 4572P, 4571N, 11617K, 11619M, 11618L, 11612E

Impacts on other healthcare services

The financial estimates include the short-term impact on medical consultations associated with the prescribing decisions rather than the long-term impact on healthcare services associated with smoking related diseases. In the economic model, the majority of smoking related health events avoided occurred after the short time horizon assumed in the financial estimates. For the base case analysis, we assumed patients required one medical consultation with a GP for each script of VAR (initiation, continuation, and completion) and BUP (initiation and completion), and one medical consultation for a course of NRT (with all repeats provided at the first consultation). For combination therapies, we assume the highest number of consultations associated with the individual products.

Table 47 presents the average number of medical consultations associated with each quit attempt using the different smoking cessation therapies, and the unit cost applied for consultation (MBS item 23).

Table 47: Estimated utilisation and costs of MBS services

MBS service	MBS services / quit attempt					Unit cost
	NRT	VAR	BUP	VAR+NRT	NRT+NRT	
GP consultation	1.0	1.8	1.5	1.8	1.0	$39.10

4.2 Estimation of financial impact of the proposed listing scenarios

Tables 48 to 51 present the total costs to the PBS/RPBS for the base case analysis under the current listing scenario (i.e., no change to listings) and the three new listing scenarios, respectively. The financial estimates model predicts a total annual cost to the PBS/RPBS of $30 million to < $40 million in 2022-2023 for all PBS listed smoking cessation products under the current listing scenario, which is consistent with the current costs reported in the ToR 2 report ($35.6m in the 2019-2020 financial year, page 14). The proportional costs for each treatment predicted in the model is also consistent with the ToR 2 report.

Table 48: Estimated utilisation of smoking cessation products under the current listing scenario

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
PBS assisted quit attempts	**287,484**	**287,247**	**287,035**	**286,844**	**286,669**
VAR	158,329	156,688	155,219	153,890	152,677
NRT	113,137	114,285	115,311	116,238	117,083
BUP	16,018	16,274	16,505	16,716	16,910
VAR+NRT	-	-	-	-	-
NRT+NRT	-	-	-	-	-
Scripts	**531,859**	**531,590**	**531,348**	**531,130**	**530,930**
VAR	283,082	280,147	277,521	275,145	272,976
NRT	224,690	226,971	229,008	230,848	232,526
BUP	24,086	24,472	24,820	25,137	25,428
PBS/RPBS cost					
VAR					
NRT					
BUP					
PBS/RPBS cost (less co-pay)					
VAR					
NRT					
BUP					

Table 49: Estimated utilisation of smoking cessation products under the proposed listing scenario 1 (VAR+NRT listed on the PBS)

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
PBS assisted quit attempts	**319,757**	**308,414**	**305,601**	**302,611**	**302,247**
VAR	126,663	113,161	103,795	101,992	101,240
NRT	90,510	82,538	77,109	77,038	77,638
BUP	16,018	15,671	15,767	15,827	16,018
VAR+NRT	86,566	97,045	108,930	107,755	107,350
NRT+NRT	-	-	-	-	-
Scripts	**756,999**	**756,049**	**773,522**	**765,811**	**764,420**
VAR	381,240	375,834	380,339	375,014	372,946
NRT	351,673	356,650	369,473	366,998	367,386
BUP	24,086	23,565	23,710	23,799	24,087
PBS/RPBS cost					
VAR					
NRT					
BUP					
PBS/RPBS cost (less co-pay)					
VAR					
NRT					
BUP					

Table 50: Estimated utilisation of smoking cessation products under the proposed listing scenario 2 (NRT+NRT listed on the PBS)

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
PBS assisted quit attempts	**352,030**	**343,108**	**341,393**	**339,628**	**338,823**
VAR	142,496	129,585	120,523	119,133	118,212
NRT	67,882	61,158	55,960	56,240	56,658
BUP	16,018	15,834	16,020	16,176	16,366
VAR+NRT	-	-	-	-	-
NRT+NRT	125,634	136,530	148,890	148,079	147,587
Scripts	**912,691**	**919,258**	**942,106**	**937,190**	**934,705**
VAR	254,774	231,690	215,487	213,002	211,355
NRT	633,831	663,758	702,529	699,864	698,740
BUP	24,086	23,811	24,090	24,324	24,610
PBS/RPBS cost					
VAR					
NRT					
BUP					
PBS/RPBS cost (less co-pay)					
VAR					
NRT					
BUP					

Table 51: Estimated utilisation of smoking cessation products under the proposed listing scenario 3 (both VAR+NRT and NRT+NRT listed on the PBS)

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
PBS assisted quit attempts	**361,712**	**344,377**	**340,256**	**335,751**	**335,093**
VAR	126,663	103,558	86,967	85,105	84,525
NRT	56,569	43,162	32,304	32,141	32,410
BUP	16,018	15,365	15,413	15,407	15,602
VAR + NRT	56,856	67,075	78,856	77,759	77,571
NRT + NRT	105,606	115,217	126,717	125,338	124,985
Scripts	**996,936**	**1,004,757**	**1,043,739**	**1,030,463**	**1,028,139**
VAR	328,121	305,079	296,480	291,190	289,817
NRT	644,728	676,572	724,082	716,104	714,861
BUP	24,086	23,106	23,177	23,169	23,462
PBS/RPBS cost					
VAR					
NRT					
BUP					
PBS/RPBS cost (less co-pay)					
VAR					
NRT					
BUP					

4.3 Estimated financial implications for the PBS/RPBS

Table 52 presents the incremental cost to the PBS in the base case analysis for the three proposed listing scenarios. Under these assumptions, the incremental cost to the PBS over the first five-years of listing is $60 million to < $70 million for scenario 1 (VAR+NRT listed), $60 million to < $70 million for scenario 2 (NRT+NRT listed) and $90 million to < $100 million for scenario 3 (VAR+NRT and NRT+NRT listed).

Table 52: Estimated incremental net cost to the PBS/RPBS (less co-payment) under the proposed listing scenarios relative to the current listing scenario

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Scenario 1 (VAR+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay) VAR NRT BUP					
Scenario 2 (NRT+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay) VAR NRT BUP					
Scenario 3 (both VAR+NRT and NRT+NRT listed on the PBS)					
PBS/RPBS net cost (less co-pay) VAR NRT BUP					

4.4 Estimated financial implications for the health budget

Table 53 presents the incremental cost to the MBS and government health budget in the base case analysis for the three proposed listing scenarios. There is an increase in the number of GP consultations for combination therapies driven mostly by patients switching from non-PBS NRT to PBS-listed therapies, which requires at least one GP consultation.

Table 53: Estimated incremental net cost to the MBS and government health budget under the proposed listing scenarios relative to the current listing scenario

	2022-2023	2023-2024	2024-2025	2025-2026	2026-2027
Scenario 1 (VAR+NRT listed on the PBS)					
Additional GP consultations MBS net cost Health budget net cost					
Scenario 2 (NRT+NRT listed on the PBS)					
Additional GP consultations MBS net cost Health budget net cost					
Scenario 3 (both VAR+NRT and NRT+NRT listed on the PBS)					
Additional GP consultations MBS net cost Health budget net cost					

4.5 Identification, estimation, and reduction of uncertainty

We consider the uncertainty of key parameters related to the number of assisted quit attempts with non-PBS therapies, assumed substitution rates and the propensity of smokers to make additional quit attempts with new treatment options available. For the substitution rates within the current PBS market, we assume up to double the rates assumed in the base case given the potential that combination therapy could replace monotherapy for the majority of pharmacological assisted quit attempts. We also investigate the impact of doubling the assumed substitution from non-PBS NRT to PBS-subsidised combination therapy, given we assumed relatively low rates in the base case (10% to 23% depending on the scenario). Table 54 summarises the impact of one-way variation around these parameters on the total cost to the PBS/RPBS over the first five years following listing.

Table 54: Sensitivity analyses of the incremental cost to the PBS/RPBS (less co-payment) for the first five years of the proposed listing scenarios

	Scenario 1 (VAR+NRT listed)	Scenario 2 (NRT+NRT listed)	Scenario 3 (VAR+NRT & NRT+NRT listed)
Base case	[redacted]	[redacted]	[redacted]
Number of quit attempts using non-PBS NRT			
+10% relative increase	[redacted] (+5%)	[redacted] (+8%)	[redacted] (+6%)
+20% relative increase	[redacted] (+10%)	[redacted] (+15%)	[redacted] (+12%)
Substitution rates from current PBS therapies			
+50% relative increase	[redacted] (+22%)	[redacted] (+11%)	[redacted] (+17%)
+100% relative increase	[redacted] (+43%)	[redacted] (+22%)	[redacted] (+33%)
Substitution rates from current non-PBS NRT			
No substitution from non-PBS market	[redacted] (-52%)	[redacted] (-75%)	[redacted] (-59%)
+50% relative increase	[redacted] (+26%)	[redacted] (+38%)	[redacted] (+30%)
+100% relative increase	[redacted] (+52%)	[redacted] (+75%)	[redacted] (+59%)
Propensity to make an assisted quit attempt			
+5% relative increase (≈58% to 56% unassisted)	[redacted] (+45%)	[redacted] (+32%)	[redacted] (+22%)
+10% relative increase (≈58% to 54% unassisted)	[redacted] (+89%)	[redacted] (+64%)	[redacted] (+43%)

The results of the univariate sensitivity analysis demonstrate that the estimated budget impact is sensitive to the assumed substitution rates between current PBS monotherapies, the extent to which patients would switch from using non-PBS NRT to PBS-subsidised combination therapy and the propensity of smokers to make an additional assisted quit attempt (i.e., switch from an unassisted to assisted quit attempt). Although not explicitly tested, we might expect higher substitution from non-PBS NRT to PBS combination therapies should combination packs become available in the future (as this would dramatically reduce the out-of-pocket costs).

We also consider a sensitivity analysis to account for the recent withdrawal of VAR from the market, which is not captured in the historical data, and the anticipated re-introduction of VAR to the market at the end of 2023. For this analysis, we assume this market shock impacts on the entire 2022-2023 financial year and half of the 2023-2024 financial year. Given uncertainty around the extent that other alternatives (BUP, NRT, unassisted) would substitute for VAR in the absence of combination therapy, we model two different sensitivities. In the first, we assume moderate substitution from VAR to BUP (40% BUP, 5% NRT and 55% unassisted) and in the second we assume high substitution from VAR to BUP (80% BUP, 5% NRT, 15% unassisted). For the listing scenarios, where combination therapy becomes available, we assume half of the patients who would otherwise switch to BUP or unassisted would now switch to NRT+NRT (where VAR+NRT remains unavailable).

Table 55: Sensitivity analyses on the incremental cost to the PBS/RPBS (less co-payment) accounting for the temporary withdrawal of VAR from the market in the 2022-2023 and 2023-2024 financial years

	2022-2023	2023-2024
Scenario 1		
Base case	[redacted]	[redacted]
Sensitivity 1 – no VAR with moderate substitution to BUP		
Sensitivity 2 – no VAR with high substitution to BUP		
Scenario 2		
Base case	[redacted]	[redacted]
Sensitivity 1 – no VAR with moderate substitution to BUP		
Sensitivity 2 – no VAR with high substitution to BUP		
Scenario 3		
Base case	[redacted]	[redacted]
Sensitivity 1 – no VAR with moderate substitution to BUP		
Sensitivity 2 – no VAR with high substitution to BUP		

The total cost to the PBS/RPBS for smoking cessation treatments is reduced when VAR is unavailable (results not presented), but overall, the results show the temporary withdrawal of VAR would not have a large impact on the incremental cost to the PBS/RPBS under the different listing scenarios. As expected, the incremental cost of listing scenario 1 is zero when VAR is unavailable because there would be no change to the available pharmacotherapies. Under scenarios 2 and 3, the incremental cost of listing NRT+NRT is higher when VAR is unavailable because more patients would make an assisted quit attempt compared to the new counterfactual (where only BUP and NRT would be available). The results demonstrate that the incremental cost is a function of the extent to which patients otherwise treated with VAR would switch to BUP, NRT and no treatment.

References

1. Courtney RJ, McRobbie H, Tutka P, Weaver NA, Petrie D, Mendelsohn CP, et al. Effect of cytisine vs varenicline on smoking cessation: A randomized clinical trial. Jama. 2021;326(1):56-64.
2. McDonough M. Update on medicines for smoking cessation. Australian prescriber. 2015;38(4):106.
3. Australian Institute of Health and Welfare. Burden of tobacco use in Australia: Australian Burden of Disease Study 2015. Available from: https://www.aihw.gov.au/getmedia/953dcb20-b369-4c6b-b20f-526bdead14cb/aihwbod-20.pdf.aspx?inline=true.
4. Whetton S, Robert T, Scollo M, Banks E, Chapman J, Dey T, et al. Identifying the social costs of tobacco use to Australia in 2015/16 2019. Available from: https://ndri.curtin.edu.au/ndri/media/documents/publications/T273.pdf.
5. Therapeutic Guidelines 2021. Available from: http://online.tg.org.au/complete/.
6. Varenicline (Champix) Product Information. Available from: https://www.ebs.tga.gov.au.
7. Bupropion (Zyban) Product Information. Available from: https://www.ebs.tga.gov.au.
8. Therapeutic Goods Administration (TGA) - Australian Register of Therapeutic Goods (ARTG). Available from: https://www.tga.gov.au/ (Accessed 28 October 2021).
9. Baker TB, Piper ME, Smith SS, Bolt DM, Stein JH, Fiore MC. Effects of Combined Varenicline With Nicotine Patch and of Extended Treatment Duration on Smoking Cessation: A Randomized Clinical Trial. JAMA. 2021;326(15):1485-93.
10. Saxby K, Ireland A, Ghijben P, Sweeney R, Sia K-L, Chen E, et al. Household composition, smoking cessation and relapse: results from a prospective longitudinal Australian cohort. medRxiv. 2022:2022.01.03.22268695.
11. Bhatt SP, Kim Y-i, Harrington KF, Hokanson JE, Lutz SM, Cho MH, et al. Smoking duration alone provides stronger risk estimates of chronic obstructive pulmonary disease than pack-years. Thorax. 2018;73(5):414-21.
12. Hoogendoorn M, Welsing P, Rutten-van Mölken MP. Cost-effectiveness of varenicline compared with bupropion, NRT, and nortriptyline for smoking cessation in the Netherlands. Current medical research and opinion. 2008;24(1):51-61.
13. Linden K, Jormanainen V, Linna M, Sintonen H, Wilson K, Kotomäki T. Cost effectiveness of varenicline versus bupropion and unaided cessation for smoking cessation in a cohort of Finnish adult smokers. Current medical research and opinion. 2010;26(3):549-60.
14. Bolin K, Mörk A-C, Willers S, Lindgren B. Varenicline as compared to bupropion in smoking-cessation therapy—Cost–utility results for Sweden 2003. Respiratory medicine. 2008;102(5):699-710.
15. Howard P, Knight C, Boler A, Baker C. Cost-utility analysis of varenicline versus existing smoking cessation strategies using the BENESCO simulation model. Pharmacoeconomics. 2008;26(6):497-511.
16. Knight C, Howard P, Baker CL, Marton JP. The cost-effectiveness of an extended course (12+ 12 weeks) of varenicline compared with other available smoking

cessation strategies in the United States: an extension and update to the BENESCO model. Value in Health. 2010;13(2):209-14.
17. Hurley SF, Matthews JP. The Quit Benefits Model: a Markov model for assessing the health benefits and health care cost savings of quitting smoking. Cost-effectiveness and resource allocation. 2007;5(1):1-20.
18. Health UDo, Services H. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease …; 2014.
19. McCaffrey N, Kaambwa B, Currow DC, Ratcliffe J. Health-related quality of life measured using the EQ-5D–5L: South Australian population norms. Health and quality of life outcomes. 2016;14(1):1-12.
20. Fishwick D, Lewis L, Darby A, Young C, Wiggans R, Waterhouse J, et al. Determinants of health-related quality of life among residents with and without COPD in a historically industrialised area. International archives of occupational and environmental health. 2015;88(6):799-805.
21. Sturza J. A review and meta-analysis of utility values for lung cancer. Medical Decision Making. 2010;30(6):685-93.
22. Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. Neurology. 2013;81(18):1588-95.
23. Nikolic E, Janzon M, Hauch O, Wallentin L, Henriksson M, Group PHES. Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study. European heart journal. 2013;34(3):220-8.
24. Goldsbury DE, Weber MF, Yap S, Rankin NM, Ngo P, Veerman L, et al. Health services costs for lung cancer care in Australia: Estimates from the 45 and Up Study. PloS one. 2020;15(8):e0238018.
25. Wooden M, Watson N. The HILDA survey and its contribution to economic and social research (so far). Economic record. 2007;83(261):208-31.
26. Selby P, Ainslie M, Stepner N, Roberts J. Sustained‐release bupropion (Zybanr) is effective in the re‐treatment of relapsed adult smokers. Am J Respir Crit Care Med. 2003;167(7):A47.
27. Gonzales DH, Nides MA, Ferry LH, Kustra RP, Jamerson BD, Segall N, et al. Bupropion SR as an aid to smoking cessation in smokers treated previously with bupropion: a randomized placebo‐controlled study. Clinical Pharmacology & Therapeutics. 2001;69(6):438-44.
28. Gourlay SG, Forbes A, Marriner T, Pethica D, McNeil JJ. Double blind trial of repeated treatment with transdermal nicotine for relapsed smokers. Bmj. 1995;311(7001):363-6.
29. Chang JT, Meza R, Levy DT, Arenberg D, Jeon J. Prediction of COPD risk accounting for time-varying smoking exposures. PloS one. 2021;16(3):e0248535.
30. Koegelenberg CF, Noor F, Bateman ED, van Zyl-Smit RN, Bruning A, O'Brien JA, et al. Efficacy of varenicline combined with nicotine replacement therapy vs varenicline alone for smoking cessation: a randomized clinical trial. Jama. 2014;312(2):155-61.
31. Ramon JM, Morchon S, Baena A, Masuet-Aumatell C. Combining varenicline and nicotine patches: a randomized controlled trial study in smoking cessation. BMC medicine. 2014;12(1):1-9.

32. Chen LS, Baker TB, Miller JP, Bray M, Smock N, Chen J, et al. Genetic Variant in CHRNA5 and Response to Varenicline and Combination Nicotine Replacement in a randomized placebo‐controlled trial. Clinical Pharmacology & Therapeutics. 2020;108(6):1315-25.
33. Cahill K, Stevens S, Perera R, Lancaster T. Pharmacological interventions for smoking cessation: an overview and network meta‐analysis. Cochrane database of systematic reviews. 2013(5).
34. Vangeli E, Stapleton J, Smit ES, Borland R, West R. Predictors of attempts to stop smoking and their success in adult general population samples: a systematic review. Addiction. 2011;106(12):2110-21.
35. de Leon J, Diaz FJ, Becoña E, Gurpegui M, Jurado D, Gonzalez-Pinto A. Exploring brief measures of nicotine dependence for epidemiological surveys. Addictive Behaviors. 2003;28(8):1481-6.
36. Krall EA, Garvey AJ, Garcia RI. Smoking relapse after 2 years of abstinence: findings from the VA Normative Aging Study. Nicotine & Tobacco Research. 2002;4(1):95-100.
37. Hawkins J, Hollingworth W, Campbell R. Long-term smoking relapse: a study using the british household panel survey. Nicotine & tobacco research. 2010;12(12):1228-35.
38. Thun MJ, Hannan LM, Adams-Campbell LL, Boffetta P, Buring JE, Feskanich D, et al. Lung cancer occurrence in never-smokers: an analysis of 13 cohorts and 22 cancer registry studies. PLoS medicine. 2008;5(9):e185.
39. Pesch B, Kendzia B, Gustavsson P, Jöckel KH, Johnen G, Pohlabeln H, et al. Cigarette smoking and lung cancer—relative risk estimates for the major histological types from a pooled analysis of case–control studies. International journal of cancer. 2012;131(5):1210-9.
40. Afonso AS, Verhamme KM, Sturkenboom MC, Brusselle GG. COPD in the general population: prevalence, incidence and survival. Respiratory medicine. 2011;105(12):1872-84.
41. van Durme YM, Verhamme KM, Stijnen T, van Rooij FJ, Van Pottelberge GR, Hofman A, et al. Prevalence, incidence, and lifetime risk for the development of COPD in the elderly: the Rotterdam study. Chest. 2009;135(2):368-77.
42. Spencer M, Briggs AH, Grossman RF, Rance L. Development of an economic model to assess the cost-effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics. 2005;23(6):619-37.
43. Quanjer PH, Tammeling G, Cotes J, Pedersen O, Peslin R, Yernault J. Lung volumes and forced ventilatory flows. European Respiratory Journal. 1993;6(Suppl 16):5-40.
44. Anthonisen NR, Connett JE, Murray RP. Smoking and lung function of Lung Health Study participants after 11 years. American journal of respiratory and critical care medicine. 2002;166(5):675-9.
45. Banks E, Joshy G, Korda RJ, Stavreski B, Soga K, Egger S, et al. Tobacco smoking and risk of 36 cardiovascular disease subtypes: fatal and non-fatal outcomes in a large prospective Australian study. BMC medicine. 2019;17(1):1-18.
46. Lubin JH, Couper D, Lutsey PL, Woodward M, Yatsuya H, Huxley RR. Risk of cardiovascular disease from cumulative cigarette use and the impact of smoking intensity. Epidemiology (Cambridge, Mass). 2016;27(3):395.

47. Rea TD, Heckbert SR, Kaplan RC, Smith NL, Lemaitre RN, Psaty BM. Smoking status and risk for recurrent coronary events after myocardial infarction. Annals of Internal Medicine. 2002;137(6):494-500.
48. Islam MS, Anderson CS, Hankey GJ, Hardie K, Carter K, Broadhurst R, et al. Trends in incidence and outcome of stroke in Perth, Western Australia during 1989 to 2001: the Perth Community Stroke Study. Stroke. 2008;39(3):776-82.
49. Flach C, Muruet W, Wolfe CD, Bhalla A, Douiri A. Risk and secondary prevention of stroke recurrence: A Population-Base Cohort Study. Stroke. 2020;51(8):2435-44.
50. Chen J, Li S, Zheng K, Wang H, Xie Y, Xu P, et al. Impact of smoking status on stroke recurrence. Journal of the American Heart Association. 2019;8(8):e011696.
51. AIHW. Australian Institute of Health and Welfare. General Record of Incidence of Mortality 2019. 2019. Available from: https://www.aihw.gov.au/reports/life-expectancy-deaths/grim-books/contents/grim-excel-workbooks (accessed December 2020).
52. Cadilhac DA, Kilkenny MF, Levi CR, Lannin NA, Thrift AG, Kim J, et al. Risk‐adjusted hospital mortality rates for stroke: evidence from the Australian Stroke Clinical Registry (AuSCR). Medical Journal of Australia. 2017;206(8):345-50.
53. Australian Institute of Health and Welfare. Cancer in Australia 2019. Available from: https://www.aihw.gov.au/getmedia/8c9fcf52-0055-41a0-96d9-f81b0feb98cf/aihw-can-123.pdf.aspx?inline=true.
54. Reeve R, Srasuebkul P, Langton JM, Haas M, Viney R, Pearson S-A. Health care use and costs at the end of life: a comparison of elderly Australian decedents with and without a cancer history. BMC Palliative Care. 2018;17(1):1-10.
55. Oostenbrink JB, Rutten‐van Mölken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost‐effectiveness of bronchodilator therapy in COPD patients in different countries. Value in health. 2005;8(1):32-46.
56. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. New England Journal of Medicine. 2010;363(12):1128-38.
57. Kim JK, Lee SH, Lee BH, Lee CY, Kim DJ, Min KH, et al. Factors associated with exacerbation in mild-to-moderate COPD patients. International journal of chronic obstructive pulmonary disease. 2016;11:1327.
58. Toelle BG, Xuan W, Bird TE, Abramson MJ, Atkinson DN, Burton DL, et al. Respiratory symptoms and illness in older Australians: the Burden of Obstructive Lung Disease (BOLD) study. Medical Journal of Australia. 2013;198(3):144-8.
59. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. The Lancet. 2007;370(9589):741-50.
60. Petrie K, Toelle BG, Wood-Baker R, Maguire GP, James AL, Hunter M, et al. Undiagnosed and Misdiagnosed Chronic Obstructive Pulmonary Disease: Data from the BOLD Australia Study. International journal of chronic obstructive pulmonary disease. 2021;16:467.
61. Bruder C, Bulliard J-L, Germann S, Konzelmann I, Bochud M, Leyvraz M, et al. Estimating lifetime and 10-year risk of lung cancer. Preventive medicine reports. 2018;11:125-30.

62. Petrie K, Abramson MJ, Cross AJ, George J. Predicting life expectancy of older people using respiratory symptoms and smoking status: data from the Australian longitudinal study of ageing. Respirology. 2020;25(3):267-74.