

Smoking Cessation Treatment and Outcomes Patterns Simulation: A New Framework for Evaluating the Potential Health and Economic Impact of Smoking Cessation Interventions

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Abstract

Background Most existing models of smoking cessation treatments have considered a single quit attempt when modelling long-term outcomes.

Objective To develop a model to simulate smokers over their lifetimes accounting for multiple quit attempts and relapses which will allow for prediction of the long-term health and economic impact of smoking cessation strategies.

Methods A discrete event simulation (DES) that models individuals' life course of smoking behaviours, attempts to quit, and the cumulative impact on health and economic outcomes was developed. Each individual is assigned one of the available strategies used to support each quit attempt; the outcome of each attempt, time to relapses if abstinence is achieved, and time between quit attempts is tracked. Based on each individual's smoking or abstinence patterns, the risk of developing diseases associated with smoking (chronic obstructive pulmonary disease, lung cancer, myocardial infarction and stroke) is determined and the corresponding costs, changes to mortality, and quality of life assigned. Direct costs are assessed from the perspective of a comprehensive US healthcare payer (\$US, 2012 values). Quit

attempt strategies that can be evaluated in the current simulation include unassisted quit attempts, brief counselling, behavioural modification therapy, nicotine replacement therapy, bupropion, and varenicline, with the selection of strategies and time between quit attempts based on equations derived from survey data. Equations predicting the success of quit attempts as well as the short-term probability of relapse were derived from five varenicline clinical trials.

Results Concordance between the five trials and predictions from the simulation on abstinence at 12 months was high, indicating that the equations predicting success and relapse in the first year following a quit attempt were reliable. Predictions allowing for only a single quit attempt versus unrestricted attempts demonstrate important differences, with the single quit attempt simulation predicting 19 % more smoking-related diseases and 10 % higher costs associated with smoking-related diseases. Differences are most prominent in predictions of the time that individuals abstain from smoking: 13.2 years on average over a lifetime allowing for multiple quit attempts, versus only 1.2 years with single quit attempts. Differences in abstinence time estimates become substantial only 5 years into the simulation. In the multiple quit attempt simulations, younger individuals survived longer, yet had lower lifetime smoking-related disease and total costs, while the opposite was true for those with high levels of nicotine dependence.

Conclusion By allowing for multiple quit attempts over the course of individuals' lives, the simulation can provide more reliable estimates on the health and economic impact of interventions designed to increase abstinence from smoking. Furthermore, the individual nature of the simulation allows for evaluation of outcomes in populations with different baseline profiles. DES provides a framework for comprehensive and appropriate predictions when applied to smoking cessation over smoker lifetimes.

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Key Points for Decision Makers

- Future economic evaluations of smoking cessation will be enhanced by the application of discrete event simulation techniques.
- The model described in this paper makes predictions for treatment success and smoking outcomes based on individual smoker profiles, sequences of smoking cessation strategies, time interval between quit attempts, and relapse.
- Analyses conducted to confirm clinical trial replication validate the model's prediction of treatment success.
- Allowing smokers to experience multiple quit attempts shows substantial differences in population health outcomes and costs, compared to a single quit attempt.

1 Background

Smoking is the leading cause of preventable death in the US and results in many serious smoking-related diseases, including lung cancer, coronary heart disease, stroke and chronic respiratory disease [1, 2]. While smoking prevalence in the US has recently declined, 19 % of US adults currently smoke [3]. While many smokers are motivated to attempt to quit, few find they are able to do so easily and many subsequently relapse [4–6]. Tobacco dependence can be viewed as a chronic disease [7] and often requires multiple attempts to quit. For example, in one study, approximately one in four individuals who made a quit attempt reported they had still stopped smoking 8–10 months later [5].

Unassisted quit attempts are common; however, the use of smoking cessation medications has been increasing and in several recent surveys, 40 % or more are using medications to support an attempt [8–10]. The US Public Health Service recommends the use of nicotine replacement therapy (NRT), bupropion, or varenicline (Chantix[®]) [7]. While smoking cessation medications have been shown to increase success rates, sustaining abstinence is difficult, since many relapse and return to smoking until they are motivated to make another attempt to stop [11, 12].

To date, many economic models evaluating the impact of smoking cessation interventions have evaluated the impact of a single quit attempt on long-term health and economic outcomes, and have often assumed that smokers who fail in their quit attempt or who succeed, but later relapse, remain smokers for the remainder of their life [13]. This simplifying assumption is clearly not reflective of the actual patterns of smoking cessation attempts, successes

and failures, and could potentially lead to biased predictions of the long-term effectiveness and cost effectiveness of smoking cessation aids or strategies. While a few models have looked at multiple attempts, they have required major simplifying assumptions such as assuming a 'natural' quit rate [14] or a background quit attempt rate [15].

The discrete event simulation (DES) described here builds upon an earlier DES model which evaluated the impact of treatments over a 1-year time period. [16] The initial 1-year model used subject-level predictions for the success of quit attempts and relapse over a 52-week period. The current model also incorporates sequences of smoking cessation strategies, intervals between quit attempts, short- and long-term relapse risk and, depending on risk exposure, predicts incidence of smoking-related diseases, and consequent mortality and costs. Furthermore, whereas the initial model [16] predicted success and relapse based on two pivotal varenicline clinical trials, the current predictions are based on a broader pool of trial data. The objective of this study was to simulate the multiple quit attempts and relapses of individuals and to provide a realistic representation of smoking cessation behaviour over a lifetime. The model was developed from a comprehensive US healthcare payer perspective.

2 Methods

2.1 Model Overview

This study is based on a simulation of individuals' lifetime smoking behaviours, attempts to quit, and the impact on health outcomes. Based on each individual's smoking or abstinence patterns, the risks of developing smoking-related diseases (chronic obstructive pulmonary disease [COPD], lung cancer, myocardial infarction [MI] and stroke) are determined and the corresponding costs and changes in mortality and quality of life are estimated. The Smoking Cessation Treatment and Outcomes Patterns (STOP) simulation was programmed in ARENA v12 (Rockwell Software, Inc., Warrendale, PA, USA). Fig. 1 provides the conceptual framework for the model, while Fig. 2 is a representation of the model flow. At the beginning of the simulation, a cohort of smokers is created by sampling from subject-level data with individual patient characteristics collected at baseline of five varenicline trials [17–21]. Individuals then start the simulation by either immediately making a quit attempt or being assigned a time for their next quit attempt.

Based on the individual patient's characteristics and assigned quitting method, the outcome of the initial quit attempt is predicted. If the quit attempt is a failure (i.e., the individual fails to achieve abstinence at the end of the

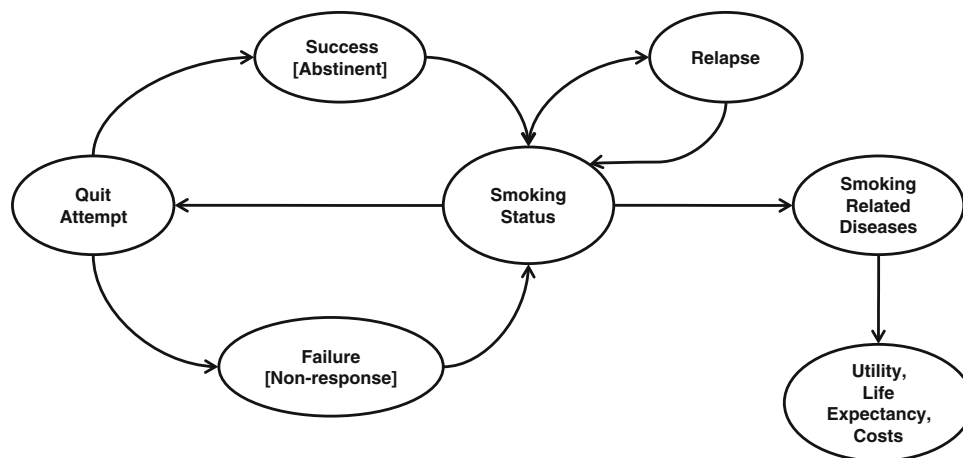


Fig. 1 Influence diagram

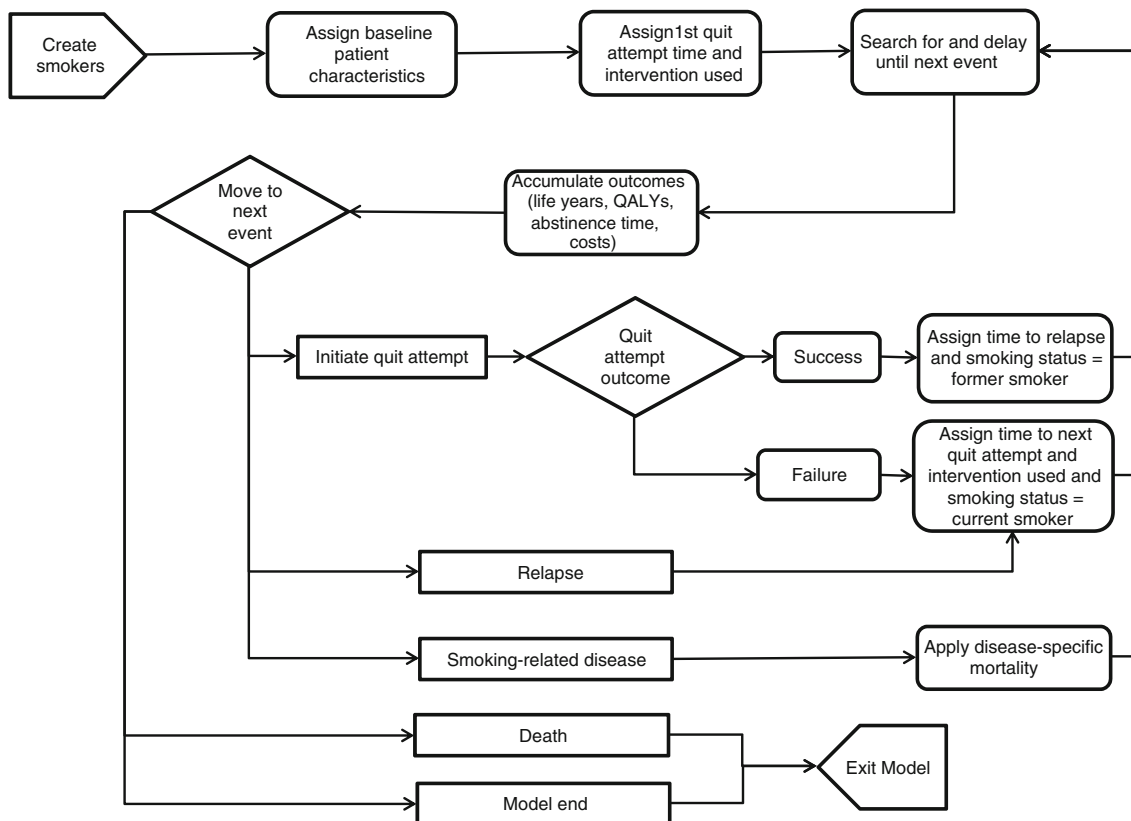


Fig. 2 Schematic representation of the STOP model flow

12-week quit attempt), the time to next attempt and the cessation strategy to support the subsequent attempt are assigned. If successful (i.e., the individual achieves abstinence at the end of the 12-week quit attempt), individuals are at risk of relapsing, and a time to relapse is assigned. Upon relapse, individuals are assigned a time to next quit attempt.

Individualized predictions for treatment success, sequences of smoking cessation strategies, intervals between quit attempts, and relapse are applied throughout the simulation with outcomes being based on the current value of the subject's pertinent characteristics (e.g., age, smoking history). That is, during the simulation, depending on patient characteristics, smoking history, prior quitting

behaviour and medical history, each individual carries risks of events which are calculated as a unique time for each possible event (e.g., smoking-related disease, quitting, relapse, quit attempt, death) based on random sampling from appropriate probability distributions. These risks and the accrual of costs and quality-adjusted life years (QALYs) are updated over time as the individual passes through the model and their characteristics (e.g., smoking status) get modified.

2.2 Data Sources/Population

Each simulated individual has a profile that includes age, sex, race, medical history (history of COPD or cardiovascular disease [CVD]), smoking history (years smoked, age started, reported average number of cigarettes per day in the past month, reported average number of cigarettes per day since start of smoking), Fagerström Test for Nicotine Dependence (FTND) score, and whether each subject has frequent contact with a smoker. In addition, each profile includes details of their prior quit attempts comprising the longest period of abstinence in the past year, number of previous quit attempts and the smoking cessation strategy used in each attempt. Table 1 contains baseline characteristics of the patients from the clinical trial according to medical history (i.e., COPD history alone, CVD history alone, COPD and CVD history, no history of COPD or CVD). Strategies that can be assessed in the simulation are unassisted quit attempts, brief counselling alone, behaviour modification therapy (BMT), NRT, bupropion and varenicline.

STOP creates individual smokers for the simulation by sampling from patient-level data from five 52-week varenicline clinical trials [17–21]:

- Two double-blind trials comparing varenicline with placebo and bupropion [17, 18].
- A randomized, open-label trial comparing varenicline with NRT [19].

- A double-blind trial comparing varenicline with placebo in smokers with stable cardiovascular disease [20].
- A double-blind trial comparing varenicline with placebo in patients with mild to moderate COPD [21].

All interventions in each of the trials were accompanied by brief counselling.

Each of the clinical trials comprised a 12-week treatment period and a subsequent 40-week non-treatment follow-up period. A quit attempt was considered to be successful if the subject was abstinent during weeks 9–12 of the treatment period.

In order to reflect the distribution of smokers with a history of COPD and CVD in the US, sampling weights were assigned to each individual in the simulation according to estimated age and sex-specific prevalence of these diseases in US smokers [22–26]. For males and females respectively, the proportion of the simulated population with a history of COPD alone was 5.0 % and 1.7 %, for CVD alone 28.5 % and 24.8 %, and for both diseases, 1.5 % and 0.4 %.

The clinical trials contained some information on the nature of previous quit attempts (prior unassisted, prior non-medically assisted, and prior medical quit attempts), but did not have information on the actual strategy employed in the five most recent quit attempts, a significant variable in the predictive equation for the assignment of interventions to be used in subsequent quit attempts (described later). This information had to be imputed from another source. A US-based web survey of current and former smokers containing this information was utilized [10]; random sampling from these patient profiles was conducted while ensuring that the quit attempt classification matched that of the clinical trials. For example, if an individual had only a prior unassisted quit attempt according to the clinical trial profile, random sampling from the survey profiles is restricted to those profiles that match this quit attempt history.

Table 1 Baseline profiles of patients from the clinical trials used to create the simulated population [17–21]

	Population			
	No COPD/CVD	CVD only	COPD only	COPD and CVD
<i>N</i> in trial populations	2,375	1,004	349	250
Age, years [mean (SD)]	41.5 (11.0)	53.9 (9.9)	55.2 (9.2)	60.0 (7.9)
Male, %	54.0	70.0	59.6	68.8
Non-white, %	15.5	19.3	15.8	14.4
Years smoked [mean (SD)]	24.0 (11.1)	36.2 (11.2)	38.8 (9.4)	43.6 (8.6)
FTND score [mean (SD)]	5.3 (2.1)	5.5 (2.1)	6.1 (2.1)	6.0 (2.1)
Number of prior quit attempts [mean (SD)]	3.8 (6.9)	4.7 (12.7)	4.3 (8.4)	4.6 (9.2)

COPD chronic obstructive pulmonary disease, CVD cardiovascular disease, FTND Fagerström test for nicotine dependence

2.3 Smoking Cessation Patterns

2.3.1 Smoking Cessation Strategies

Smokers can initiate a quit attempt with one of six cessation strategies: unassisted, brief counselling alone, BMT, NRT, bupropion, or varenicline. In the analyses presented here, the first quit attempt intervention is assigned using data from a 2010 US market survey [9]: unassisted quit attempts (46 %), NRT (27.6 %), BMT alone (9.9 %), varenicline (9.5 %), or bupropion (7 %).

Brief counselling, which best represents the placebo arm in the head-to-head comparisons of the clinical trials, was not included as a category in the market survey, and is therefore not included in these analyses except for the purposes of validation (see Sect. 3 for a description of the validation analyses).

The interventions used for subsequent quit attempts are predicted by a multinomial logistic regression developed by analysis of data collected from the US-based web survey [10]. The regression includes terms for interventions used in the five most recent quit attempts, as well as the number of previous quit attempts, and race (white vs. other) (parameter estimates are provided in Supplement Table S1 [see electronic supplementary material (ESM)]). Individuals were more likely to use pharmacological interventions if they had used them in the past; also, the greater the number of previous quit attempts, the more likely it was that individuals would use pharmacological interventions. The simulation also allows for assignment of interventions based on user-defined probability distributions for subsequent quit attempts. If this option is selected, quit attempt interventions are still assigned probabilistically, but subject characteristics are no longer considered when making the assignment.

2.3.2 Quit Attempt Outcome

Individualized probabilities (i.e., probabilities that account for patient characteristics) of abstinence are applied to determine the outcome of each quit attempt using a logistic regression (Table 2) derived from the varenicline clinical trials [17–21]. The probability of success is a function of the cessation aid being utilized, nicotine dependence, demographics, smoking history and medical history. Because the NRT trial [19] was designed as an open-label trial, the regression included a dummy variable for open-label versus double-blind study design. In the equation shown in Table 2, this term is absorbed into the intercept.

The logistic regression results indicate that subjects on varenicline have the highest success rates. While age is associated with a higher probability of success, this is partially counteracted by the lower success associated with

Table 2 Parameter estimates for logistic regression^c predicting abstinence (success) at 12 weeks following quit attempt initiation^a

Parameter	Estimate β	95 % CI
Intercept β_0	-1.007	-1.549 to -0.466
NRT	0.921	0.556 to 1.286
Varenicline	1.520	1.305 to 1.734
Bupropion	0.891	0.643 to 1.139
Age (years)	0.033	0.019 to 0.048
Race		
Asian	-0.210	-0.649 to 0.229
Black	-0.588	-0.916 to -0.261
Other	-0.107	-0.394 to 0.179
Female	-0.121	-0.269 to 0.027
Number of years smoked	-0.014	-0.028 to -0.000
Cigarettes per day in past month	-0.017	-0.026 to -0.007
Frequent contact with another smoker (yes/no)	-0.151	-0.304 to 0.003
Prior quit attempt (yes/no)	-0.399	-0.633 to -0.166
Prior medical ^b quit attempt (yes/no)	-0.170	-0.326 to -0.013
FTND score	-0.104	-0.147 to -0.061
Number of lifetime quit attempts in excess of 4	-0.008	-0.017 to 0.001
COPD (yes/no)	-1.498	-2.218 to -0.779
COPD (yes/no) × FTND score	0.159	0.059 to 0.258
COPD × active treatment ^b (yes/no)	0.237	-0.243 to 0.718
Double-blind study (yes/no)	-0.575	-0.823 to -0.328

AIC 4553.856

^a Note that this equation can be used to directly estimate the probability of success with brief counselling (i.e., placebo with brief counselling in the clinical trials), varenicline, bupropion, and NRT. Behavioural modification therapy and unassisted quit attempt probabilities have an additional odds ratio term applied to modify the prediction from the logistic regression

^b Varenicline, bupropion, or NRT

COPD chronic obstructive pulmonary disease, FTND Fagerström test for nicotine dependence, NRT nicotine replacement therapy

^c The functional form for the logistic regression to predict the probability of success for an individual (P_i) at 12 weeks following initiation of a quit attempt is given by: $P_i = \frac{e^{\beta_0 + \sum_{j=1} \beta_j x_{j,i}}}{1 + e^{\beta_0 + \sum_{j=1} \beta_j x_{j,i}}}$, where β_0 is the intercept, β_j is the vector of regression coefficients and $x_{j,i}$ is the associated vector of patient characteristics

number of years smoked. Greater nicotine dependence, frequent previous quit attempts, and female sex were associated with lower success rates. Success rates were also influenced by race. Somewhat surprisingly, individuals with COPD were also less likely to successfully quit, especially if attempting without the assistance of pharmacologic therapies.

As no data from the trials were available for unassisted quit attempts and BMT, odds ratios from the literature were

used to modify the logistic regression results for quit attempt success using these strategies. For unassisted quit attempts, an odds ratio of 0.097 versus varenicline was derived based on a study which provided a success rate of 10.9 % at 12 weeks with unassisted quit attempts. [4, 19] For BMT, an odds ratio of 1.524 versus brief counselling was derived using information from each of the trials included in a meta-analysis that assessed quit attempt success with individual behavioural counselling versus minimal contact (i.e., up to 10 min of advice, with or without the provision of self-help materials) [27].

2.3.3 Relapse

For those individuals who make a successful quit attempt (i.e., remain abstinent after 12 weeks), the individualized risk of relapse within the first year is estimated using data from the five varenicline trials [17–21]. Parametric distributions failed to capture the observed distributions of abstinence duration. Thus, a series of interconnecting segments of Kaplan–Meier curves were fitted, with distinct segments specified for weeks 0–13 and weeks 14 or later. The following equation for the underlying risk of relapse was fitted:

$$\ln S_t = \beta_1 t_1 + \beta_2 t_2$$

where the time variables and coefficients were defined as follows:

$$t_1 = \min(t, 13)$$

$$t_2 = \max(0, t - 13)$$

$$\beta_1 = -0.03507, \quad \beta_2 = -0.00984,$$

where t represents time after a successful quit attempt. The observed probability of relapse across the five trials for weeks 0–13 and weeks 14 or later after a successful quit attempt is 36.6 % and 23.3 %, respectively.

A Cox proportional hazards model was then fit to factor in the predictors of risk of relapse (Table 3). Significant predictors included age, measures of smoking history (e.g., number of years smoked), frequent contact with smokers, and a history of COPD (Table 3). Older individuals were at lower risk of relapse, although individuals who started smoking at an older age were more likely to relapse, as were those who had smoked longer and at a higher frequency. Again, subjects with COPD were more likely to relapse. Treatment was not a significant predictor for the risk of relapse. The annual probability of relapse following the first year from the start of a successful quit attempt was derived from a published study that examined sustained abstinence among former smokers [28], with the annual probability of relapsing assigned as follows:

Table 3 Parameter estimates for the Cox proportional hazards model for relapse^b

Parameter	Estimate β	Standard error
Age (years)	−0.055	0.016
Age started smoking (years)	0.039	0.018
Number of years smoked	0.044	0.016
Cigarettes per day since start of smoking	0.010	0.005
Longest number of days of abstinence in the past year	0.003	0.001
Frequent contact with another smoker (yes/no)	0.220	0.084
Number of quit attempts ^a	0.111	0.053
COPD (yes/no)	0.208	0.121

AIC 9373.732

^a Logarithm of the number of quit attempts Winsorized to 20

COPD chronic obstructive pulmonary disease

^b The hazard ratio (HR) to individualize the prediction of relapse is calculated using the following equation: $HR = e^{\sum \beta_j (x_{j,i} - \bar{x}_{j,i})}$, where β_j is the vector of coefficients, $x_{j,i}$ is the associated vector of characteristics and $\bar{x}_{j,i}$ is the mean value of the coefficient j in the population. The HR obtained from this equation is applied to the underlying survival function, which is explained in the Relapse section

- year 1–2: 14.5 %
- years 2–5: 2.8 %
- >5 years: 2.1 %

2.3.4 Time Until Next Quit Attempt

The time from relapse to the initiation of a subsequent quit attempt is estimated from the US-based web survey [10]. The prediction, which assumes an exponential distribution for time to next quit attempt, is individualized by incorporating an individual smoker's number of previous quit attempts, sex, and race (parameter estimates are provided in Supplement Table S2 [see ESM]).

2.4 Smoking-Related Diseases

STOP captures the impact of smoking cessation on the incidence of four smoking-related diseases (COPD, lung cancer, MI, stroke) as a function of age and also the duration of abstinence. Each simulated individual is categorized as either a current smoker or abstinent (considered as a former smoker) throughout their lifetime.

The annual probability (p) of an individual developing each of the smoking-related diseases (COPD, lung cancer, MI and stroke) is determined assuming an exponential distribution:

$$p = 1 - e^{-\lambda t}$$

This equation provides the probability of developing a smoking-related disease in a given year ($t = 1$) for an individual with annual hazard equal to λ , which is assigned conditional on their current smoking status.

The hazards for developing these four smoking-related diseases for current and former smokers (λ_{current} and λ_{former}) are determined as follows:

$$\lambda_{\text{current}} = \lambda_{\text{never}} \times \text{RR}_{\text{current}}$$

$$\lambda_{\text{former}} = \lambda_{\text{never}} \times \text{RR}_{\text{former}}$$

where, λ_{never} is the hazard among never smokers, $\text{RR}_{\text{current}}$ is the relative risk among current smokers, $\text{RR}_{\text{former}}$ is the relative risk among former smokers.

$\text{RR}_{\text{former}}$ during the simulation are determined for each of the four smoking-related diseases as a function of the individual's age and duration of abstinence using the model published by Hoogenveen et al. [29] (disease-specific coefficient estimates are provided in Supplement Table S3 [see ESM]). The derived relative risk estimates for former smokers decrease with longer abstinence, thereby allowing the simulation to appropriately capture the cumulative benefits of sustained abstinence.

Age- and gender-stratified relative risks for current versus non-smokers were derived for each of the four smoking-related diseases from the event rates observed in the Cancer Protection Study (CPS) II [22]. Age- and gender-specific λ_{never} estimates were derived by combining the relative risks calculated from CPS II, with data on the incidence of lung cancer, COPD, MI and stroke obtained from published sources [23, 24, 26, 30–33]. Estimates of the population size and age- and sex-dependent smoking prevalence statistics were obtained from the US census [25]. Specifically, the overall incidence (i_{overall}), of smoking-related diseases (for any sex and age category) can be decomposed as follows:

$$i_{\text{overall}} = i_{\text{never_smoker}} \times P_{\text{never_smoker}} + i_{\text{former_smoker}} \times P_{\text{former_smoker}} + i_{\text{current_smoker}} \times P_{\text{current_smoker}}$$

where P refers to the proportion of individuals in each smoking category. This equation can be further broken down to incorporate the relative risks, as follows:

$$i_{\text{overall}} = i_{\text{never_smoker}} \times P_{\text{never_smoker}} + i_{\text{never_smoker}} \times \text{RR}_{\text{former_vs_never}} \times P_{\text{former_smoker}} + i_{\text{never_smoker}} \times \text{RR}_{\text{current_vs_never}} \times P_{\text{current_smoker}}$$

This equation can be manipulated algebraically to yield the age- and sex-specific annual incidence in never-smokers (i.e., λ_{never}).

Patients without a history of COPD or CVD at baseline can experience each of the smoking-related diseases once

during the simulation. Patients that enter the model with COPD or CVD (MI, stroke, or both) history will not be subject to the risk of developing the particular smoking-related disease over the course of the simulation.

2.4.1 Mortality

For individuals without a history of COPD, lung cancer, stroke or MI, a time of death is assigned at the start of the simulation as a function of each individual's age and gender and is modelled using Gompertz functions derived from US life tables (parameter estimates are provided in Supplement Table S4 [see ESM]) [34]. Individuals entering the simulation with a history of smoking-related disease are assigned a time to death based on disease-specific mortality functions. When a smoking-related disease develops during the simulation, the time of death is updated with the minimum of the previously estimated time of death and the new predicted time.

Post-MI exponential survival functions were fitted to published Kaplan–Meier curves [35]. The probability of death at the time of the event was obtained from the same publication (44 % for males and 45 % for females). The case fatality rate applied in the model is independent of all other patient characteristics.

Parametric survival distributions failed to capture the observed distributions in published Kaplan–Meier curves for COPD [36], lung cancer [37] and stroke [38]. Linear models were fit to log-log survival versus log-time. For COPD and stroke, a series of interconnecting segments of the Kaplan–Meier curves were fitted. Additional details on the equations used to predict time to death are provided in the supplement along with the coefficient estimates for each of the models (Supplement Table S5 [see ESM]).

2.5 Health Utilities

During the simulation, an individual's utility is set to the minimum of the individual's age-dependent utility, and the utility associated with any of the smoking-related diseases that the individual has experienced up to that point in time. This ensures that the model has accounted for the impact of aging and all smoking-related diseases on the individual's utility. Age-dependent health utility values were assigned using the following equation based on reported European Quality of Life-5 Dimensions (EQ-5D) index scores of a nationally representative sample of US adults participating in the 2000–2002 Medical Expenditure Panel Survey [39].

The equation used in the simulation was:

$$\text{Utility} = -0.00002 \times \text{age}^2 - 0.0007 \times \text{age} + 0.9497$$

The values associated with smoking-related diseases were consistent with an existing cost-effectiveness model

of smoking cessation, with the values for coronary heart disease used as estimates for MI [40]. These were 0.76 for COPD [41, 42], 0.61 for the first year following lung cancer [43] and 0.50 in subsequent years, 0.76 for MI [44, 45], and 0.74 for stroke [46, 47].

2.6 Costs

Direct medical costs were assessed from the perspective of a comprehensive US healthcare payer (i.e., all direct medical costs considered), and reported in \$US, 2012 values. All reported costs were inflated to 2012 values using the medical care component of the US consumer price index [48]. The following costs were used in the STOP simulation: MI (acute \$US37,591, annual year 1 \$US24,538, subsequent \$US10,630) [49], COPD (annual \$US4,385) [50], stroke (acute \$US16,217, annual year 1 \$US11,628, subsequent \$US1,324) [49], and lung cancer (annual year 1 \$US67,701, subsequent \$US8,192) [51]. Acute costs are applied immediately at the time of onset of the smoking-associated disease, while annual costs accrue continuously.

The cost of a quit attempt with varenicline (\$US569) or bupropion sustained release (\$US304) consists of the cost of a single physician visit (\$US70.00) [52] plus the cost of the medication based on average wholesale price (AWP) required to cover the 12-week quit attempt [53]. The cost of a quit attempt with NRT (\$US226) is a weighted average of the cost of the available formulations according to the distribution observed in the US-based web survey (51.4 % patch, 34.9 % gum and 13.8 % lozenges) [10]. Medication costs for NRT were derived from AWP [53] and recommendations for use for each presentation [54–57]. The cost per BMT quit attempt (\$US82) was derived from the 2012 Medicare coverage fees for smoking cessation counselling; each attempt is assumed to comprise a maximum of four intermediate or intensive counselling sessions [52, 58].

3 Analyses

Several sets of analyses were conducted to confirm that the simulation accurately replicates the results of the clinical trials. Specifically, the analyses were structured to analyze the proportion of the simulated population that was abstinent at 12 months for individuals initiating a single quit attempt using varenicline, bupropion, NRT, or brief counselling versus the proportions observed in the clinical trials.

We then evaluated outcomes when patients are limited to a single quit attempt versus being allowed to initiate multiple quit attempts over a lifetime time horizon.

Additionally, in order to evaluate how results change in different populations, subgroup analyses were run allowing for multiple quit attempts for the following populations: individuals 45 years of age or younger, individuals with a high degree of nicotine dependence (FTND >5), 100 % males, and 100 % females.

For each analysis, 500,000 subjects were run through the simulation. Probabilistic sensitivity analyses were not conducted as the focus was on assessing the impact of varying individual drivers of outcomes, although a series of one-way sensitivity analyses were performed to establish the importance of key variables on predicted outcomes. QALYs and cost outcomes are discounted at 3 % per annum.

3.1 Results

One-year abstinence rates for the first quit attempt were compared with the five clinical trials individually for each of the trials' treatment arms (Table 4) and generally showed strong concordance with the observed trial results. The one exception was in the trial evaluating varenicline in individuals with stable CVD, where the simulation predicted a higher abstinence rate for individuals on varenicline and placebo. Given that almost 50 % of all patients with a history of CVD were participants in other trials (i.e., not the trial conducted in patients with a history of CVD

Table 4 Predicted vs. observed abstinence at 52 weeks

Trial	Intervention	Trial value (%)	Predicted (%)
Gonzales et al. 2006 [17] and Jorenby et al. 2006 [18]	Varenicline	22	20
	Bupropion	15	14
	Placebo	9	8
Tashkin et al. 2011 [21] (COPD population)	Varenicline	19	18
	Placebo	6	6
Rigotti et al. 2010 [20] (CVD population)	Varenicline	19	24
	Placebo	7	10
Aubin et al. 2008 ^a [19]	Varenicline	26	26
	NRT	20	19

^a Simulation under open-label conditions

COPD chronic obstructive pulmonary disease, CVD cardiovascular disease, NRT nicotine replacement therapy

only), analyses were run on all the subjects with a history of CVD regardless of trial. In these analyses, there was closer alignment between simulated and observed abstinence rates—23.0 % of subjects assigned to varenicline were abstinent at 52 weeks, compared with the observed 21.5 %. For placebo, estimates were 9.2 % and 8.2 % for the simulated and observed subjects, respectively.

The reference analysis comparing predicted outcomes allowing for single versus multiple quit attempts showed a dramatic difference in predictions over a lifetime time horizon. Fig. 3 shows the proportion of patients abstinent over time under both scenarios. Whereas STOP predicts a steady increase in the proportion abstinent, growing from 15 % after 1 year to 68 % by the end of the simulation, the single quit attempt scenario showed a steady decrease, with only 5 % abstinent at the end of the simulation. The divergence occurs even within the first year of the simulation and becomes dramatic by year 5 (30 % abstinence versus 8 %). On average, subjects in the multiple quit attempt scenario made just over nine quit attempts over the course of the simulation with only 9 % of subjects making only one attempt, and 16 % making over 15 attempts.

When looking at cumulative abstinence time at the individual level (Fig. 4), mean cumulative abstinence time in the single quit attempt scenario parallels the course of the bottom quartile of subjects' accumulation of abstinence time in the multiple quit attempt scenario. Fig. 4, which is based on a simulated population of 5,000 subjects, also shows the substantial spread in outcomes across individuals, with the bottom quartile accumulating less than 1 year of abstinence time over their lifetimes, and the top quartile almost 22 years (mean of 13.3 years).

The impact of single versus multiple quit attempts on other outcomes is less dramatic, but nevertheless substantial (Table 5). The predicted number of smoking-related diseases begins to diverge after 5 years, and results in a 19 % difference by the end of the simulation. Similarly, there is a 7 % difference in mortality predictions by year 20, and total discounted QALYs over the course of the simulation differ by 0.6 per patient. Not surprisingly, the costs associated with smoking-related diseases are higher in the single quit attempt scenario, while the costs associated with smoking cessation aids and related monitoring are lower.

3.2 Sensitivity and Scenario Analyses

Outcomes are sensitive to variations in initial treatment response, relapse risk, and the interval between quit attempts (Table 6). Even when reference case parameters were varied by 25 % or even 50 % in a negative direction, estimated QALYs and time spent abstinent were well above predictions with the single quit attempt scenario. Abstinence times were most sensitive to changes in inputs, whereas QALYs and costs showed much less variance. Of note, analyses on time to next quit attempt showed almost no variation in predicted total costs. This is because, as the frequency of quit attempts increases, abstinence time, and hence the cost of smoking-related diseases decreases, whereas the cost of smoking-related interventions increases. The opposite, of course, is true when the frequency of quit attempts is reduced: smoking-related diseases and their associated costs increase, but this is offset by a decrease in intervention costs.

The most striking subgroup analysis results were those run on younger patients (i.e., 45 years of age or younger).

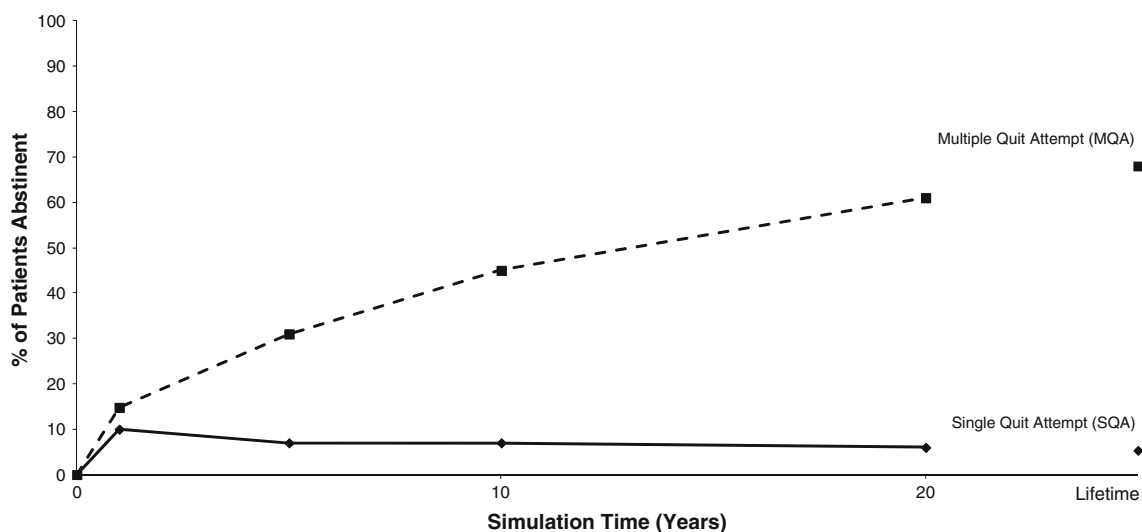


Fig. 3 Proportion of population abstinent over time— single quit attempt versus multiple quit attempts

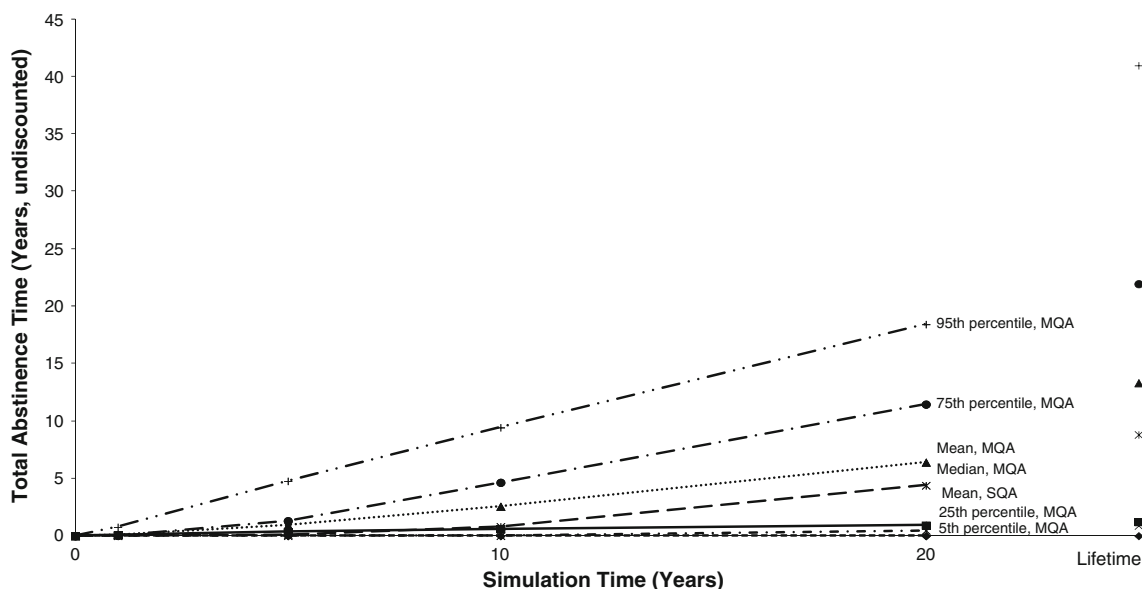


Fig. 4 Average cumulative years abstinent for a sample of 5,000. *MQA* multiple quit attempts, *SQA* single quit attempt

Table 5 Outcomes for base case with a single quit attempt and multiple quit attempts per 1,000 patients

Outcome	Year 1		Year 5		Year 10		Year 20		Lifetime	
	SQA	MQA	SQA	MQA	SQA	MQA	SQA	MQA	SQA	MQA
Incidence of smoking-related diseases										
COPD	21	21	99	97	189	177	341	293	518	424
Lung cancer	2	2	9	9	19	18	41	35	85	62
MI	8	8	40	39	78	74	141	126	210	191
Stroke	9	9	43	42	86	80	166	140	282	247
Number of deaths	22	22	123	122	259	253	523	488	1,000	1,000
Discounted QALYs	839	840	3,744	3,745	6,476	6,488	9,718	9,838	11,817	12,439
Discounted costs (*000 US dollars)										
Quit attempt intervention and monitoring	\$156	\$257	\$156	\$774	\$156	\$1,270	\$156	\$1,850	\$156	\$2,163
Smoking-related diseases	\$1,591	\$1,591	\$8,102	\$8,062	\$15,343	\$14,948	\$26,200	\$24,471	\$36,811	\$33,483
Total	\$1,747	\$1,848	\$8,258	\$8,836	\$15,499	\$16,218	\$26,356	\$26,321	\$36,967	\$35,646

COPD chronic obstructive pulmonary disease, *MI* myocardial infarction, *MQA* multiple quit attempts, *QALY* quality-adjusted life years, *SQA* single quit attempt

Not surprisingly, given the younger age of the population, abstinence times and QALYs were higher in the younger population. What is striking is that total costs are substantially lower in the subgroup despite the longer time they have over which to accumulate costs. This is a direct result of the lower frequency of smoking-related diseases in this population, where the reduction in the incidence of smoking-related diseases can be as much as 19 % compared with the base case considering the overall population. Results in more nicotine-dependent populations (i.e., FTND scores above 5) were, not surprisingly, less favourable, with less time spent abstinent, lower QALYs, and higher total costs. Results in males are also worse, as

this population is older (mean age of 48.8 years at baseline versus 45.2 years in females), has higher nicotine dependence (mean FTND scores of 5.6 and 5.3 in males and females, respectively), and has a higher prevalence of smoking-related diseases at baseline.

4 Discussion

Models assessing the impact of smoking cessation interventions that limit the analytic framework to a single quit attempt lead to substantial mischaracterization of health and economic outcomes in smokers, and may be producing

Table 6 Lifetime outcomes for scenarios and sensitivity analyses (multiple quit attempts, per 1,000 patients)

Scenario	Abstinence time (months)	Discounted QALYs	Discounted costs ('000 US dollars)
Reference case	161,710	12,439	\$35,646
Probability of quit attempt success at week 12			
Decrease 25 %	143,819	12,356	\$36,770
Decrease 50 %	107,773	12,176	\$38,804
Short-term (within first year of quit attempt) risk of relapse			
Decrease 25 %	174,633	12,521	\$35,026
Increase 25 %	149,195	12,364	\$36,467
Long-term (>1 year following quit attempt) risk of relapse			
Decrease 50 %	178,250	12,551	\$34,777
Increase 50 %	134,466	12,268	\$37,263
Time to next quit attempt			
Decrease 25 %	176,950	12,529	\$35,525
Increase 25 %	141,761	12,349	\$35,837
Subjects <45 years of age	232,430	16,309	\$28,306
Subjects with Fagerström score >5	144,731	12,130	\$37,008
Female subjects	179,986	13,819	\$32,035
Male subjects	143,576	11,080	\$39,390

QALY Quality-adjusted life years

biased estimates of the cost effectiveness of smoking cessation strategies. The analyses presented in this paper demonstrate that differences in predicted time spent abstinent are large, even only 5 years into the modelling time horizon, and the consequences of these differences become apparent early on, and are dramatic over a lifetime horizon.

The STOP model we have described not only represents an effort to overcome some of the limitations of previous decision tree and Markov cohort models of smoking cessation by simulating at the individual level, it also enables meaningful analyses of outcomes in population subgroups. For instance, the benefits of initiating quit attempts at earlier ages can be more accurately captured. By accounting for subject characteristics when predicting quit attempt success, relapse, the timing of future quit attempts and the selection of smoking cessation aids, if any, the simulation provides a powerful tool to evaluate the health and economic impact of alternative strategies for improving quit rates, and reducing the risk of relapse. Although the current analyses focus on how predictions of health and economic outcomes change with the adoption of a multiple quit attempt framework, and not on how cost-effectiveness estimates might be modified under alternative cessation strategies, the multiple quit attempt framework should provide a more reliable basis for these estimates.

One of the most widely cited economic models in this area, the BENESCO (Benefits of Smoking Cessation on Outcomes) model [13], adopts a single quit attempt framework. BENESCO also adopts a Markov cohort modelling framework, rather than individual level

modelling. While comparisons of predictions between our model and BENESCO are difficult given differences in model inputs and assumptions, a recent application of the model in the US [40] does provide some basis for comparison of outcomes over time. For example, while our model predicts higher overall mortality (49 % over 20 years when all individuals are initially assigned to varenicline, versus 36 % in the BENESCO model varenicline arm), the differential in mortality projections over time narrows substantially, with a 65 % difference in year 5, dropping to a 35 % difference in year 20. This narrowing is explained by the lower long-term abstinence rates one would expect in the BENESCO model given that subjects who relapse are assumed to remain smokers for life. Other differences are more obvious. The BENESCO model assumes a one-time cost for smoking cessation assistance, whereas, in our reference analysis, the costs associated with smoking cessation medications or other forms of support are projected to increase from an average of about \$US260 per patient in year 1, to \$US1,850 after 20 years, and \$US2,160 over a lifetime.

Our model is not without its limitations. For one, only four smoking-related diseases are considered: lung cancer, COPD, MI and stroke. Furthermore, the simulation does not currently account for any benefits associated with quitting smoking once these conditions occur. For example, subjects developing COPD over the course of the simulation are subject to the same mortality risk, regardless of their smoking status. The model also relies on a number of different predictive equations derived from various data sources, including surveys, clinical trials, and other public

data sources. While the model projections seem reasonable, and certainly more in line with what one would expect than models assuming a single quit attempt, validation against an external dataset, and possible refinement of the equations would be of great value. For example, a report based on data from the National Health Interview Surveys showed that the mean number of quit attempts over a lifetime for current smokers aged 18 and over is around 6 and 9 attempts for males and females, respectively [59]. The STOP model predicts an average of just over nine lifetime quit attempts over the course of the simulation, closer to the upper bound of the cited range. The reliance on clinical trial data to simulate success and relapse rates in the year following initiation of a quit attempt is also a limitation of the current analyses, although the simulation allows for alternative success rates and short as well as long-term relapse rate inputs. Finally, the analyses presented in this manuscript are based largely on inputs derived for the US, which limits the generalizability of projections to other countries. In particular, patterns of smoking cessation strategies, the frequency of quit attempts, which were based on US survey data, as well as the profile of smokers, are likely to vary significantly across countries.

5 Conclusion

Despite the limitations addressed above, we believe the STOP simulation represents a significant advancement in the modelling of smoking cessation strategies, and provides a solid platform for evaluating not only individual, one-off interventions, but also more complex strategies, including policies which may encourage earlier or more frequent quit attempts. Given that the vast majority of previous models have restricted evaluations to a single quit attempt [13], the multiple quit attempt aspect of STOP by itself provides a better evaluation framework. By simulating at the individual level, the model produces a rich dataset of simulated patient trajectories, allowing for a better understanding of the experience of subgroups of subjects, as well as the timing and consequences of various events.

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Conflicts of interest Denis Getsios, Nikhil Revankar, Alexandra J. Ward, and K. Jack Ishak are employees of United BioSource

Corporation, who were paid consultants to Pfizer Inc. in connection with the development of the manuscript at the time of study conduct. James G. Xenakis was an employee of United BioSource Corporation at the time the model was being designed and developed. Jenő P. Marton, Dale Rublee, and Richard J. Willke were employees of Pfizer Inc. at the time of study conduct.

Author contributions DG, JPM, NR, AW, RW, DR, KJI, and JX participated in the design of the model, identification of data sources, conduct of data analyses, and implementing the design. Each author also contributed to the interpretation of data and results, drafting the manuscript, and has approved the final version. Denis Getsios will serve as a guarantor for the overall content of the manuscript.

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