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Title

Smoking cessation: a comparison of two model structures

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Abstract

Background

Most economic evaluations of smoking cessation interventions have used cohort state-transition models. Discrete event simulations (DES) have been proposed as a superior approach.

Objective

We developed a state-transition model, and a DES using the Discretely Integrated Condition Event framework and compared the cost-effectiveness results. We performed scenario analysis using the DES to explore the impact of alternative assumptions.

Methods

The models estimated the costs and quality-adjusted life years (QALYs) for the intervention and comparator from the perspective of the UK National Health Service and Personal Social Services over a lifetime horizon. The models considered five comorbidities: chronic obstructive pulmonary disease, myocardial infarction, coronary heart disease, stroke and lung cancer. The state-transition model used prevalence data and the DES used incidence. The costs and utility inputs were the same between two models, and consistent with those used in previous analyses for the National Institute for Health and Care Excellence.

Results

In the state-transition model, the intervention produced an additional 0.16 QALYs at a cost of £540, leading to an incremental cost-effectiveness ratio (ICER) of £3,438. The comparable DES scenario produced an ICER of £5,577. The ICER for the DES increased to £18,354 when long-term relapse was included.

Conclusions

The model structures themselves did not influence smoking cessation cost-effectiveness results, but long-term assumptions did. When there is variation in long-term predictions between interventions, economic models need a structure that can reflect this.

Key points for decision makers

- Two economic models with different structures produced similar results for the cost-effectiveness of a smoking cessation intervention
- Including long-term relapse in one of the economic models dramatically changed the results
- Before building economic models, developers should consider the full treatment pathway of the decision problem

1. Introduction

Economic models may use different structures, and there is much discussion and guidance in the literature on how to choose the model structure[1-4]. The choice of model structure is viewed as important in any disease or health area, including in smoking cessation. Discrete event simulation (DES) models are noted to offer advantages over state-transition models in terms of incorporating history, avoiding limitations of discrete time intervals and facilitating a flexible framework[5]. Commonly cited disadvantages of DESs include the need for additional data, complexity of programming, the need for specialist software, and long run-times.

The Discretely Integrated Condition Event (DICE) simulation framework has been developed to allow modellers to build flexible models in Microsoft Excel[6]. DICE can operate at the individual level or cohort level, and be driven by states (for state-transition modelling) or by events (for DESs). For modellers developing DESs, DICE removes the need to use specialist software and simplifies the coding process. The use of DICE has previously been explored in DES modelling, where it was noted that the DICE produced results almost identical to the original ones[7].

In 2013, Getsios et al reported that models which consider only one smoking cessation attempt lead to biased estimates of cost-effectiveness, and suggest that DES provides a framework for modelling multiple quit attempts in smoking cessation[8]. The majority of economic models in smoking cessation to date have been cohort-level state-transition (Markov) or decision tree models[9, 10]. Indeed, the economic models used in the smoking cessation guidelines produced by the National Institute for Health and Care Excellence (NICE) are all cohort-level models[11-17]. There therefore remains a question as to whether DES models would generate the same results as state-transition models in smoking cessation. A further challenge exists regarding the feasibility of developing DES models in smoking cessation, in terms of data availability and complexity of coding. The purpose of our study was twofold: i) to explore the feasibility of developing a smoking cessation DES model; ii) to compare the results of a cohort-level state-transition and DES model in smoking cessation.

2. Methods

2.1 Model settings

We developed a cohort-level state-transition and a DES model to assess the cost-effectiveness of one intervention versus no treatment. The perspective of the analysis was the UK National Health Service (NHS) and Personal and Social Services (PSS), in accordance with the NICE reference case[18]. The discount rate for costs and benefits was 3.5% annually[18]. As far as possible, we kept all inputs the same between the models[18]. The intervention was a patch plus nasal spray, on which 27% of people had stopped smoking at 12 months[19] and the intervention cost £763.74[20] . No treatment was associated with a background net cessation rate of 2% annually, with no cost[17]. This net rate was also applied annually to people who had not quit on the intervention. The state-transition model used an annual cycle. Both models considered a lifetime horizon to incorporate the long-term health effects of smoking. We considered a cohort of people aged 16 years old, where 50% were male and 50% were female.

2.2 Comorbidities

Both models considered five smoking-related comorbidities: chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), myocardial infarction (MI), stroke and lung cancer. The utilities and costs associated with the comorbidities were based on those used in previous NICE smoking cessation models[11-17], updated with additional searches, are the same in the two models, and are shown in table 1. The state-transition model, like previous NICE smoking cessation models[21] uses prevalence data to model the proportion of the population with each comorbidity. In contrast, the DES considers patients developing a disease and so more naturally uses incidence data. This meant we could not use the same data as the state-transition model, and furthermore we could not obtain equivalent data from the same sources. Sources of incidence and prevalence data for each of the comorbidities are shown in Table 1.

2.3 Utility values

Both models allowed utility to differ by smoker status and by presence of comorbidities. Vogl et al (2012) reported utilities for smokers and non-smokers by age, gender and smoker status [22]. The state-transition model assumed a constant utility for smokers (0.8486) calculated by subtracting the average disutility of light, moderate and heavy smokers from the utility for a never smoker, and a constant utility for former smokers (0.8669), calculated by subtracting the disutility of ex-occasional and ex-regular smokers from the utility for a never smoker. The state-transition model uses utility decrements for each comorbidity, calculated as the difference between the utility for the health state and the utility of the comorbidity in table 1. The DES uses the same source, and has the option to use the same data as the state-transition model or to vary utility by age and gender. In this scenario, the model applies utility data for moderate smokers for smokers and for ex-regular smokers for former smokers, and incorporates age by including an event for utility change which occurs when a person crosses an age band. Vogl et al (2012) provide utility decrements by number of comorbidities: 0.0938 for one, 0.1811 for two, 0.2859 for three and 0.3354 for four or more [22]. The DES can count the number of comorbidities and use this data, or use the specific utility decrement for each comorbidity like the state-transition model.

2.4 Model structures

2.4.1 State-transition model

In the state-transition model, a cohort of people transition between three health states: smoker, former smoker and dead. The prevalence of each comorbidity and the probability of death varied by smoker status. The model structure is shown in Figure 1. The population prevalence of each comorbidity and relative risk for a smoker versus a former smoker were taken from various sources – the sources are shown in Table 1. We combined the population prevalence, relative risk by smoker status, and proportion of smokers in the population to estimate age- and gender-specific prevalence by smoker status for each comorbidity, consistent with the approach taken in previous models[8, 21]. The equation below shows how prevalence in the general population can be decomposed, where *C* is

prevalence, *P* is the proportion within the population, *RR* is relative risk, *general* is general population, *never* is never smokers, *former* is former smokers and *current* is current smokers:

$$C_{general} = C_{never} \times P_{never} + C_{never} \times RR_{former:never} \times P_{former} + C_{never} \times RR_{current:never} \times P_{current}$$

The equation can be rearranged to give the prevalence in the never smoker population, where the other components are known:

$$C_{never} = \frac{C_{general}}{P_{never} + P_{former} \times RR_{former:never} + P_{current} \times RR_{current;never}}$$

2.4.2 Discrete event simulation model

The DES model simulates 5000 hypothetical people, whose individual pathway through the model is determined for each person. Whereas in a state-transition model a proportion of people have each event (or move to a different state) in each time cycle, in a DES each simulated person has each event at their own specific time. They then follow that sequence of events until they die and exit the model. The time at which each event happens depends on the person's characteristics, history and random numbers. Comparing random numbers against probabilities of events occurring ensures that the appropriate proportion of patients have each event at each time point.

The time to each comorbidity uses incidence data, which varies by smoker status. We used the same relative risks for smoker versus former smoker as the state-transition model, and incidence data from various sources (Table 2). Like the state-transition model, we combined the population incidence, relative risk by smoker status and proportion of smokers in the population to estimate incidence by smoker status for each comorbidity.

The model structure is shown in Figure 2. A description of the process in the DES model is provided in the Supplementary Appendix.

Research has shown that relative risks of developing comorbidities decreases with time since cessation, so the DES allows this[23]. The equation to model this has previously been used in smoking DES models[8] and considers age and gender in addition to time since cessation. Utilising

baseline characteristics and history is a known advantage of DES models over state-transition models and this equation was not considered in the state-transition model (although it may be possible with multiple tunnel states). To use the equation in the DES, we needed to adjust background disease incidence to consider the time at which the former smokers in the population had quit smoking. We estimated this using longitudinal data on the proportion of cigarette smokers who had quit by age and gender[24], combined with the proportion of smokers and non-smokers by age and gender[25], using the same approach to that used for estimating prevalence and incidence in the general population. In this case the relative risk for a former smoker is calculated as in the equation below, where γ and η are comorbidity-specific parameters from Getsios et al[8] (we used the MI parameters as a proxy for CHD):

$$1 + \left(RR_{current:never}\right) \times e^{\left(-\gamma \times e^{(-\eta \times |age-50|)} \times time\ since\ cessation\right)}$$

2.5 Mortality

2.5.1 State-transition model

Mortality varied by smoker status, using relative risk data from two studies by Doll[26, 27]. Mortality for former smokers was calculated by applying the relative risks for former and current smokers to the proportion of the UK population who are former and current smokers in a similar way to the equations for prevalence, and using lifetables from the Office for National Statistics (ONS). The relative risk for smokers was applied to the calculated former smoker mortality in the model.

2.5.2 Discrete event simulation model

Smoking cessation models which consider disease incidence may link comorbidity presence to mortality[28] rather than linking smoker status to mortality as the state-transition model does. The DES has the flexibility to either link comorbidity presence or smoker status to mortality, but not both. We calculated the relative risk of death for each comorbidity by combining comorbidity prevalence data (used in the state-transition model) with the number of all-cause deaths and number of deaths from each comorbidity from ONS death registration data[29], using the equation below:

$$RR_{comorbidity:no\ comorbidity} = \frac{number\ of\ \ deaths\ from\ comorbidity}{number\ of\ allcause\ deaths} \div prevalence\ of\ comorbidty$$

2.6 Long-term pathway

The base case analysis considered only one smoking cessation attempt, but long-term effectiveness was explored in scenario analysis. The economic models for NICE guidelines consider only one smoking cessation attempt, and our primary aim was to understand whether using a DES in this scenario would lead to similar results. However, since the inclusion of multiple quit attempts has been highlighted as important[8], we considered a scenario in the DES whereby people who have quit smoking may later relapse. We used the annual long-term relapse probabilities considered in a previous UK economic evaluation of smoking cessation interventions: 0.129 for >1 to <5 years post cessation, 0.0331 for ≥5 to <`10 years post cessation, 0.00112 for >10 years post cessation [28].

2.7 Scenarios considered

We ran the state-transition model for the described settings, and considered several scenarios in the DES, as follows:

1. Mortality linked to smoker status, relative risk of comorbidities does not vary by time since cessation, utility data same as YHEC model.
2. Same as Scenario 1, except mortality linked to comorbidity. As we believe this scenario is more realistic, we consider this as the basis for Scenarios 3-5.
3. Same as Scenario 2, except relative risk of comorbidities varies by time since cessation.
4. Same as Scenario 2, except vary utility by age and gender and using utility decrements for number of comorbidities.
5. Same as Scenario 2, except considering long-term relapse.

3. Results

In both models and in all scenarios, the intervention was associated with higher costs, more life years and more quality-adjusted life years (QALYs) than the comparator. This is because the intervention

leads to fewer comorbidities and improves survival compared with no treatment, and so increases life years and QALYs. By reducing comorbidity occurrence, the intervention has some cost-offsets, so the incremental cost is less than the initial intervention cost. Results for all scenarios are shown in table 2.

3.1 State-transition model

In the state-transition model, the incremental costs are £540, and incremental QALYS are 0.16, leading to an incremental cost-effectiveness ratio (ICER) of £3,438/QALY. This is well below the £20,000 - £30,000/QALY range generally considered cost-effective by NICE[18]. It therefore appears that the intervention is good value for money.

3.2 DES: Scenario 1

In the DES, when mortality is linked to smoker status, the incremental costs are £47 and incremental QALYs are 0.12 yielding an ICER of £399/QALY. The total costs for intervention and comparator are much higher than in the state-transition model because people with costly comorbidities are not assumed to have any reduction in life expectancy, so accrue high costs.

3.3 DES: Scenario 2

The DES scenario linking mortality to comorbidities gives total and incremental results that are more comparable to the state-transition model. In this scenario, the people who develop comorbidities die sooner than the people who do not, and so do not incur such high costs. The number of people developing comorbidities does differ from the state-transition model, as might reasonably be expected for different data sources. A breakdown of comorbidity costs is shown in Table 3.

3.4 DES: Scenario 3

In the scenario where the relative risk of comorbidities varies by time since cessation, there are higher incremental QALYs and lower incremental costs, leading to a lower ICER than in Scenario 2. This is because the benefit of quitting smoking increases over time, and the smokers who quit do so at a young age in the model. The underlying incidence has changed in this scenario as we have adjusted the background incidence in the population to account for time since quitting in the background population.

3.5 DES: Scenario 4

In the scenario where the number of, and not type of, comorbidity is linked to utility decrement, the total costs are unchanged and the QALYs increase in both arms. The incremental QALYs increase by 0.03 and so the ICER decreases by £1,300 compared with Scenario 2. Accounting for the relative frequency of each comorbidity, the average comorbidity decrement in the base case is 0.20, which is higher than the decrement of 0.09 from Vogl et al (2012)[22]. When Vogl et al (2012) is used, the average utility increases, and so there are more QALYs gained from the incremental survival with the intervention. The effect is not large because the QALYs gained from former smokers generally having higher utility than smokers is unchanged. This scenario indicates that this change does not make a large difference to the results.

3.6 DES: Scenario 5

When long-term relapse is added in, the incremental costs remain relatively unchanged but the incremental QALYs decrease substantially, leading to a much higher ICER of £18,354. This is because the cost of the intervention remains the same, but the benefit is much reduced – by 10 years almost 40% of the people who had quit have restarted smoking. This means that they only have a temporary benefit of abstaining for a short period of time.

4. Discussion

We found that the state-transition and DES models reported similar results, but that varying long-term assumptions in the DES dramatically changed the results. Whilst costs and QALYs were not sensitive to model structure or utility decrements, they were sensitive to the inclusion of a long-term relapse rate. This is despite using different underlying approaches and sources for modelling comorbidities.

Leaviss et al (2014) noted that a DES would be needed to incorporate multiple quit attempts following relapse[28]. We note that the average number of quit attempts is 6-30, indicating how important it may be to incorporate more than one quit attempt, to accurately reflect reality[30]. That said, if the sequence of subsequent treatments is identical between intervention and comparator, then a model may only need to capture the time period between the first quit attempt and relapse. However, the

probability of successfully quitting on later treatments may depend on factors such as age, number of and time since previous quit attempts[31], which may then vary between the arms.

To our knowledge, we are the first to directly compare state-transition and DES structures in smoking cessation. Claxton et al (2014)[32] compared a patient level simulation model with a cohort state-transition model in ophthalmology and found that the difference in results was relatively small using a simple patient level simulation, but much greater using more sophisticated patient level simulations. Claxton et al (2014) [32]noted that patient level simulations are better able to accurately represent the real-world in ophthalmology. Simpson et al (2009) [33] compared a DES with a state-transition model in HIV and found that the results were similar but not identical, and that the DES had better long-term predictive validity. Stevenson et al (2016)[34] reviewed six economic models developed by manufacturers of biologics in rheumatoid arthritis, where three used DES, two used cohort-level state-transition models and one used an individual patient simulation model with fixed cycle lengths. The six models used similar data and assumptions and reported broadly similar results. In an independent analysis using a DES, Stevenson et al (2016) [34] found that long-term assumptions about disease progression had a large influence on the cost-effectiveness results.

The DICE framework can be used to build state-transition or DES models, so in future researchers could compare multiple model structures within one Microsoft Excel workbook. We show that where long-term treatment effectiveness and the downstream pathway does not vary between treatments, state-transition and DES models give comparable results and may be considered equally valid. State-transition models can make use of rich data sources such as Doll's study reporting mortality by smoker status. On the other hand, a DES model would give the same results as a state-transition model for one line of treatment, so the structure is not expected to introduce bias when used for multiple lines or sequences of treatments.

We have demonstrated the feasibility of building a DES using readily available data, mostly using inputs that would be identified for a standard state-transition model. The DES did however require

additional data sources for calculating inputs, such as for time since cessation and mortality risk by comorbidity. This increased the workload associated with developing the model, and increased the parameter uncertainty as more data sources were used – although we did strive to use recent, large, national datasets as far as available. The additional flexibility of the DES framework means that it could now be updated as data becomes available or as the decision problem develops, whereas adapting state-transition models to include additional health states or patient characteristics can be time consuming[5]. The flexibility of the DES means that it can use consistent data sources where available – for example in using utility data from Vogl to consider the impact of smoker status and comorbidity from one dataset rather than combining from multiple sources which may not necessarily be valid.

The main limitations of our current analysis lie within the data inputs used in the DES. Firstly, although the DES can link mortality to either smoker status or to comorbidity prevalence, neither approach is perfect. When mortality was linked to smoker status (in Scenario 1), people with comorbidities did not have any reduction in life expectancy and so incurred high costs. In the state-transition model which links mortality to smoking status, using population prevalence adjusts for this by considering a relatively lower proportion of people with comorbidities in advanced age. Using incidence in the DES model does not do this, suggesting that the results and approach in this scenario may not be valid. Linking mortality to comorbidities may be more appropriate, but we considered only five comorbidities, and it is possible that other comorbidities may also impact on mortality, for example through wound complications[35, 36]. It is possible that, individually, each additional comorbidity would have too small an impact on mortality to have been demonstrated in the literature but, cumulatively, the impact of several different comorbidities could have a meaningful clinical effect. By linking smoking status itself with mortality, this would be captured, whereas explicitly linking mortality to five comorbidities could underestimate the true effect. Secondly, the use of empirical frequencies for incidence and death mean that the model can only sample the time to event to the nearest year, and looking up event probabilities from a table increases the model run time compared with sampling from a probability distribution. Thirdly, that the information on long-term

relapse and intervention effectiveness are from separate studies and do not necessarily consider identical patient populations. Despite this, we consider that our analyses provide a pragmatic comparison of two model structures. Our analysis indicates that smoking cessations may be less likely to be cost-effective when a longer pathway is modelled. Previously, most economic evaluations using one year quit rates as a proxy for long-term cessation have found individual smoking cessation interventions to be cost-effective [11-14, 37, 15-17, 28]. This is unsurprising when we consider the substantial health benefits and cost-offsets gained by each individual quitter. However, if we were evaluating the addition of one intervention, with long-term relapse, to a pathway of treatments, then this may not be true. Therefore, it is important that the economic model captures the relevant pathway, and that the positioning of a new intervention within the pathway is understood.

5. Conclusion

We have found that model structures themselves do not influence smoking cessation cost-effectiveness results, but that long-term assumptions do. Before building an economic model, developers should first consider the full treatment pathway in the decision problem. They should then develop a model to incorporate the long-term differences between treatment and comparator. The choice of model structure is only important inasmuch as it allows all relevant outcomes to be incorporated. When there is variation in long-term predictions, economic models need a structure that can reflect this.

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Figure captions and legends

Figure 1: State-transition model structure

CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction

Figure 2: DES model structure

CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction

Table 1: Comorbidity data

Comorbidity	Cost	Cost source*	Utility value	Utility value source	Relative risk data source	Prevalence data source	Incidence data source
Stroke	£5,504	NICE CG92 Full guideline[38]	0.48	Tengs and Wallace[39]	Myint *et al.* (2008) [40]	Bhatnagar *et al.* (2015)[41]	British Heart Foundation (2009) [42]
Lung cancer	£9,254	Cancer Research UK[43]	0.61	Bolin et al. (2009) [10]	Pesch *et al.* (2012) [44]	Maddams *et al.* (2009) [45]	Office for National Statistics (2014) [46]
MI	£1,012	Godfrey *et al[47].*	0.80	Tengs and Wallace [39]	Prescott *et al.* (1998) [48]	Bhatnagar *et al.* (2015) [41]	British Heart Foundation (2012) [49]

CHD	£1,323	British Heart Foundation. Cardiovascular Disease Statistics[50]	0.80	Stevanovic[51]	Shields *et al.* (2013) Shields, 2013 #8}	Liu *et al.* (2002) [52]. Assumed that 12 to 15 year olds had 0% prevalence.	British Heart Foundation (2012) [49]
COPD	£546	NICE CG101[53]	0.73	Rutten-van Molken *et al.* 2006 [54]	Lokke et al. (2006) [55]	Public Health England data set. Assumed 12 to 15 year olds had 0.1% prevalence. (1.28%) [56]	British Lung Foundation (2016) [57]

*All costs inflated to 2014/15 using PSSRU[58]

CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, MI: myocardial infarction, NICE: National Institute for Health and Care Excellence

Table 2: Cost-effectiveness results

Scenario	**Intervention**	**Total Cost**	**Total QALYs**	**Incremental Cost**	**Incremental QALYs**	**ICER**
State-transition	Patch + spray	£4,809	21.83			
	No treatment	£4,270	21.67	£540	0.16	£3,438
DES Scenario 1	Patch + spray	£9,530	19.67			
	No treatment	£9,484	19.55	£47	0.12	£399
DES Scenario 2	Patch + spray	£4,213	19.94			
	No treatment	£3,595	19.83	£618	0.11	£5,577
DES Scenario 3	Patch + spray	£4,392	19.93			
	No treatment	£3,948	19.75	£444	0.18	£2,467
DES Scenario 4	Patch + spray	£4,213	20.26			
	No treatment	£3,595	20.12	£618	0.14	£4,266
	Patch + spray	£3,941	19.85			

DES Scenario 5	No treatment	£3,317	19.81	£623	0.03	£18,354

CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, DES: discrete event simulation, ICER: incremental cost-effectiveness ratio, MI: myocardial infarction, QALY: quality adjusted life year

Table 3: Cost breakdown

Cost element	Intervention costs						Comparator costs					
	State-transition	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**	**Scenario 5**	**State-transition**	**Scenario 1**	**Scenario 2**	**Scenario 3**	**Scenario 4**	**Scenario 5**
Stroke Cost	£1,746	£805	£883	£943	£883	£309	£1,817	£613	£671	£721	£671	£308
Lung cancer Cost	£268	£7,195	£1,760	£1,867	£1,760	£2,054	£296	£8,040	£2,053	£2,302	£2,053	£2,174
MI Cost	£240	£45	£51	£53	£51	£52	£250	£47	£53	£55	£53	£52
CHD Cost	£1,157	£221	£235	£199	£235	£190	£1,182	£215	£227	£206	£227	£192
COPD Cost	£634	£500	£520	£565	£520	£572	£725	£569	£590	£664	£590	£592
Intervention cost	£764	£764	£764	£764	£764	£764	£0	£0	£0	£0	£0	£0
Total cost	£4,809	£9,530	£4,213	£4,392	£4,213	£3,941	£4,270	£9,484	£3,595	£3,948	£3,595	£3,317

CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, DES: discrete event simulation, ICER: incremental cost-effectiveness ratio, MI: myocardial infarction, QALY: quality adjusted life year

Supplementary appendix: description of DES

Each person is assigned a sex and age according to baseline distributions. Their smoker status is initially set to smoker. A utility value is assigned, depending on the person's sex and smoker status (and age, depending on selected settings). The time to each of the comorbidities and death is randomly sampled from its distribution. The time to utility change depends on the age of the person, or may be infinite if utility is not chosen to vary by age. The person then moves immediately into a Quit Attempt, where a treatment (intervention or comparator) is assigned.

In the Quit Attempt, a random number is compared with the probability of successfully quitting on that treatment. If the random number is less than or equal to that probability, then the time to the event Success is set to the duration of the treatment and the time to the event Failure is set to be infinite. If the random number is greater than that probability, then the time to the event Failure is set to the duration of the treatment and the time to the event Success is set to be infinite.

There is then a 'Delay' before the next event – which may be Failure, Success, Utility Change (if included), any of the Comorbidities or Death, depending on which has the shortest time. This 'Delay' happens between any two events, and during this period the person accrues QALYs and costs.

In the Failure event, the person is still a smoker so their smoker status does not change, nor does their utility value nor time to any subsequent events. The time to next Quit Attempt is sampled, since the person may attempt to quit smoking again.

In the Success event, the person has now become a non-smoker, so their smoker status changes to be a non-smoker. Since utility value and time to Comorbidities (and Death, depending upon settings) vary by smoker status, these are then updated. Where long-term relapse is included, the time to Relapse after Success is sampled.

In the Relapse event, the person becomes a smoker again, so their smoker status, utility value and time to Comorbidities (and Death, depending upon settings) are updated. The time to next Quit Attempt is sampled.

In the Utility Change event, if included, the person's utility value changes because they have crossed an age band. The time to next Utility Change is calculated.

In each of the Comorbidity events (MI, CHD, Stroke, COPD and Lung Cancer), the person's status for that comorbidity is updated. Their utility value therefore changes, and they incur annual costs associated with that comorbidity. Since each person can only have each comorbidity once, the time to that Comorbidity is then set to be infinite. In the scenarios where comorbidities are associated with increased mortality, the time to death is resampled.

In the Death event, the time to End is set to be the current die, the person dies and exits the model.

In the End event, all results are reported.

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