Consequences of Marketing Modified Risk Tobacco Product: Population Effects Estimated with the Dynamic Population Modeler

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1 Introduction

Statistical models and simulation programs can be used to provide estimates of the health effects expected to result from changes in the distribution of a harmful exposure in a given population. Such changes can occur due to natural trends or to regulatory actions. If the projected changes are due to regulatory action, then modeled results allow direct comparison of the health impacts of alternative policies that might affect the distribution of the exposure in different ways, thus supporting the selection of one policy over another (Levy, Bauer, et al. 2006). Desirable features of such models are the clarity with which the underlying assumptions are stated, and the ability of the model to delineate the relationship between the estimates it produces and the assumptions underlying the model (Garrison 2003; Weinstein, O'Brien, et al. 2003).

ENVIRON International Corporation (ENVIRON) developed a comprehensive and flexible dynamic population modeler (DPM). The DPM estimates all-cause mortality for a hypothetical population of never tobacco users who, as they age, may transition into and out of different tobacco exposure states. These states include current and former cigarette smoking or modified-risk tobacco product (MRTP) use. The DPM allows for different exposure transitions, e.g., switching between cigarettes and MRTP and, among former tobacco users, relapsing to prior use states. It estimates the difference between the number of survivors in a base case (little or no MRTP use in the population) and a counterfactual exposure scenario (more widespread MRTP use). All-cause mortality risk estimated by the DPM depends on age, duration of exposure, and duration of removal from exposure. Markov chain Monte Carlo techniques estimate the variability of the results, which depends on the certainty specified for the input data (Bachand and Sulsky 2013).

The DPM builds on approaches described by others (Hoogenveen, van Baal, et al. 2008; Kulik, Nusselder, et al. 2012; Levy and Friend 2002; Tengs, Ahmad, et al. 2004; Tengs, Ahmad, et al. 2005; Tengs, Osgood, et al. 2001) but provides additional flexibility, with all parameters defined by the DPM user. It improves on the validity of previous models by accounting for age- and time-dependent changes in risks. Furthermore, most other dynamic models focusing on risks associated with use of tobacco products were developed to estimate changes in population-level risk due to changes in proportions of never, current and former smokers resulting from increasing smoking cessation rates and/or decreasing smoking initiation rates; they do not consider the effect of introducing a new product to a population (Hoogenveen, van Baal, et al. 2008; Kulik, Nusselder, et al. 2012; Levy and Friend 2002; Tengs, Ahmad, et al. 2004; Tengs, Ahmad, et al. 2005; Tengs, Osgood, et al. 2001).

Two published models were designed to estimate the effects of introducing a MRTP to a population of never, current and former smokers, but the range of questions they can address is limited because they hold smoking initiation and cessation rates constant and do not allow transition probabilities to depend on age (Apelberg, Onicescu, et al. 2010; Mejia, Ling, et al. 2010). Specifically, the model proposed by Apelberg, Onicescu, et al. allows for very few transitions, assumes that transition probabilities do not depend on age and that mortality risk depends only on current tobacco exposure status and no other exposure metric. The model

proposed by Mejia, Ling et al. also assumes that risk depends only on current tobacco exposure status (with no other exposure metric) and uses a limited number of exposure states and transitions (e.g., quitters of tobacco cannot revert to tobacco use); it uses the same initiation, cessation and transition rates for the entire hypothetical population, regardless of age; and, quantifies the risk of tobacco related health by a health index that is assumed to be the same regardless of duration of tobacco use or cessation. The health index itself does not seem to be based on empirical data.

The validity of the DPM for estimating survival in the base case model was evaluated by comparing the DPM results against the 2006 US life table for men. Mortality rates for the DPM were based on published data for men participating in the Kaiser Permanente (KP) cohort study (Friedman, Tekawa, et al. 1997). Transition probabilities were based on annual smoking initiation rates (SAMHSA 1999) and cessation rates (Messer, Pierce, et al. 2007) among US males and females in 1980 (Appendix A, Table 1). Using exposure distributions from 1980 provided an induction period for initiation- and cessation-related deaths to have occurred by 2006. No age- *and* sex-specific estimates of smoking initiation or cessation rates were available. Mortality estimated by the DPM for the base case was within 0.2% of mortality estimated using data from the US life table (Appendix A, Table 2).

Similarly, the validity of the DPM for estimating survival under counterfactual scenarios was assessed by comparing the DPM results against the 2006 Swedish life table for men. Transition probabilities were based on Swedish incidence and prevalence of use of cigarettes and snus, a low nitrosamine, smokeless tobacco product that could be considered an example MRTP (Foulds, Ramstrom, et al. 2003; Lundqvist, Sandstrom, et al. 2009). Transition probabilities developed to estimate tobacco exposure patterns in Sweden in the 1990s are shown in Appendix A, Table 3.

Mortality data similar to the KP data were unavailable for Sweden; therefore, to validate the counterfactual scenario based on estimated Swedish exposure transition probabilities, we used the KP data after accounting for differences from the US in tobacco-related and background mortality. We specified the excess relative risk (ERR) for current snus users versus current smokers as 0.11; this value is conservative, based on a published consensus estimate of the risk of current snus use compared to current smoking (Levy, Mumford, et al. 2004). More recent data suggest that the actual risks associated with snus use may be lower than suggested by this ERR, although they cannot be used to estimate the comparative risk of all-cause mortality for snus users vs. cigarette smokers because they focus on specific diseases or causes of death, and/or because they do not provide data for risks comparing snus with cigarettes (Arefalk, Hergens, et al. 2012; Boffetta, Aagnes, et al. 2005; Colilla 2010; Critchley and Unal 2004; Foulds, Ramstrom, et al. 2003; Haglund, Eliasson, et al. 2007; Hansson, Galanti, et al. 2012; Hansson, Pedersen, et al. 2009; Lee 2007; Lee 2010; Lee 2013; Luo, Ye, et al. 2007; Nordenvall, Nilsson, et al. 2011; Nordenvall, Nilsson, et al. 2013; Ostenson, Hilding, et al. 2012; Overland, Skogen, et al. 2013; Rodu and Cole 2009; Roosaar, Johansson, et al. 2008; Roth, Roth, et al. 2005). There was no estimate in the literature for risks of all-cause mortality among former snus users versus former smokers, or for current or former dual users (i.e., those using both cigarettes and snus during the same time period). We set those ERRs to 0.11, 1.0 and 1.0, respectively, indicating that former snus users have the about 11% of the risk of all-

cause mortality compared to former smokers (i.e., the same proportionate decrease in risk as experienced by current snus users vs. current smokers), and that current and former dual use carries the same risk as being a current or former smoker. Mortality estimated by the DPM for the counterfactual scenario, that included the possibility of exposure to cigarettes and snus, was within 0.3% of mortality estimated using data from the Swedish life table (Appendix A, Table 4). The close correspondence between the mortality estimates produced by the DPM and those produced by actual population life tables indicates that the DPM can be used validly to evaluate the potential effect on population mortality of the introduction of a modified risk tobacco product. This is accomplished by defining the base case to reflect the smoking initiation and cessation rates in the population of interest, and defining a series of counterfactual scenarios in which the same population also has access to the MRTP. Comparing the number of survivors in the base case and counterfactual scenarios provides an estimate of the expected population-level effect on all-cause mortality. Although the DPM was developed to determine the effect on mortality of introducing a lower risk product (the MRTP) to a population, there are exposure scenarios that could cause an increase in harm, i.e., fewer survivors in the counterfactual compared with the base case. This occurs in scenarios with an overall increase in the number of tobacco users or in the duration of tobacco use in the counterfactual scenario compared with the base case.

The results generated by the DPM also can be used to estimate tipping points. We defined a tipping point as the proportion of the population that experiences a beneficial change in tobacco exposure that increases the number of survivors relative to the base case that is necessary to offset the survival deficit due to a given harmful change in tobacco exposure. Because large shifts in tobacco use behaviors are unlikely, at least within short time periods, the magnitude of the tipping points allows for an assessment of how responsive the initial harm may be to the effect of possible alternative exposure patterns.

2 Methods

2.1 Addressing the MRTP Application Guidance

The draft guidance document for MRTP applications that was prepared by the US Food and Drug Administration (FDA)[1] outlines a number of potential exposure scenarios affecting different population segments. Many of these scenarios can be translated into base case and counterfactual exposure scenarios that can be analyzed using the DPM. Analyses of those exposure scenarios are presented in this report, along with identification of tipping points based on alternative counterfactual scenarios.

We defined a hypothetical population of 1,000,000 12-year old male never tobacco users, followed from age 13 to 72 in 5-year intervals, with age-specific mortality rates for never, current and former smokers calculated from the Kaiser-Permanente Cohort Study data (Friedman, Tekawa, et al. 1997) and the 2000 US census with coefficients modeled as fixed values. Follow-up could have continued beyond age 72, but the dwindling number of survivors at older ages in any exposure scenario reduces the value of further comparisons. For the base case, age category-specific exposure transition probabilities were based on 2009 cigarette smoking initiation rates[2] and smoking cessation[3] rates for 2005-2008 observed for US males and females (Appendix A, Table 5): there were no estimates of smoking initiation and cessation rates available that were both age- *and* gender-specific, and no more recent smoking cessation rate estimates were available. Using recent smoking initiation and cessation rates to define the base case allows us to address possible effects occurring in the future, after the introduction of a new product to the population. To allow for comparisons of a series of counterfactual scenarios to a specific base case defined by US smoking initiation and cessation rates, we modeled smoking initiation and cessation rates as fixed. The hypothetical cohort could have included women, but prevalence of use of oral tobacco products among women in the US is extremely low, 1% or less in every US state except Alaska[4]. Unrealistically large increases in use thus would have to be assumed in any counterfactual exposure scenario that aimed to estimate changes in health due to uptake of snus by women.

The estimated ERR for the hypothetical MRTP compared to cigarette smoking was set to 0.11. As noted above, this is a conservative estimate based on a published consensus estimate of the ERR comparing current snus use to current cigarette smoking, and likely represents the worst case.[5] We ran 10,000 iterations of the model after a burn-in of 2000 iterations. We considered a

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[1] http://www.fda/gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm

[2] http://www.samhsa.gov/data/NSDUH/2k10ResultsTables/NSDUHTables2010R/HTM/Sect4peTabs1to16.htm#Tab4, 3B

[3] http://www.samhsa.gov/data/2k10/172/172smokingcessation.htm

[4] http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5943a2.thm#tab3

[5] Consistent with estimates provided by an expert Health Panel, impaneled by the Institute of Medicine to examine and develop a consensus estimate for the mortality risk associated with long-term use of low-nitrosamine smokeless tobacco (specifically, Swedish snus) relative to conventional cigarettes and no tobacco use. Consensus estimates for total mortality (adjusted mean; smokeless tobacco use compared to cigarette smoking) among those aged 35-49 and

Markov chain to have converged if the Monte Carlo error was less than 5% of the sample standard deviation. Differences between the numbers of survivors in the base case compared with the counterfactual exposure scenario were estimated after each of the model iterations and the estimates were summarized over all iterations using means and 95% posterior intervals.

We identified tipping points in two ways: A tipping point based on the point estimate was identified when the mean difference between survivors in the base case and counterfactual exposure scenarios was approximately zero. A tipping point based on statistical significance was identified when results changed from a statistically significant mean difference between survivors in the base case and the counterfactual exposure scenario to a difference that was not statistically significant based on the 95% posterior intervals (PIs) around the mean difference (i.e., the 2.5th and 97.5th percentile of the distribution). The first of method of identifying a tipping point is more stringent (i.e., requires a larger shift in exposure) than the second method.

Section VI of the FDA MRTP application guidance document[6] describes seven population segments and exposure patterns of concern. Four of the seven can be analyzed using the DPM, as shown in the next section ("Results"). The three exposure patterns that cannot be analyzed with the DPM focus on:

- Use of medications approved to assist with cessation of tobacco use: The DPM was developed to compare survival in a population exposed to cigarettes with survival in the same population exposed additionally to an MRTP. In order to substitute a different base case exposure for cigarettes, i.e., smoking cessation medications, it would be necessary to construct a new version of the DPM using a data set that provides mortality risks by age and person-years of exposure and removal of exposure from the medication. No such data exist.
- Health risks experienced by non-users: The DPM estimates only the direct effects of exposure to higher and lower risk products, and does not account for changes to second-hand smoke exposures due to changes in the proportions of cigarette smokers in the population. It can be inferred, however, that counterfactual scenarios that include fewer cigarette smokers will reduce environmental tobacco smoke, and thus may provide larger scale benefits that include non-users of tobacco in addition to users.
- Dual use of MRTP and cigarettes: Because mortality risks in the DPM are dependent on duration of exposure and duration of removal from exposure, and because the ERR is an adjustment factor applied to the mortality risks calculated for current and former cigarette smokers, the DPM assumes current and former dual product users have the same all-cause mortality risk as current and former smokers, respectively. Therefore, results of DPM analyses of dual users would not provide useful information about the specific subgroup of dual users, because they would be counted the same as cigarette smokers. If

aged 50+ years were 11.0 and 8.2 (100-point scale), respectively (Levy et al., Cancer Epidemiol Biomarkers Prev 2004;13:2035-2042).

[6] http://www.fda/gov/TobaccoProducts/GuidanceComplianceRegulatoryInformation/default.htm

dual use resulted in decreased exposure to cigarettes, the mortality risk for dual users would likely be overestimated by the DPM.

2.2 Counterfactuals Based on Tobacco Use Patterns Estimated for Sweden

We developed a series of analyses to estimate the effect on US mortality if a MRTP were available and was used in patterns similar to the patterns of cigarette and snus use observed in Sweden in the 1990s. For the base case, exposure transition probabilities were based on US 2009 cigarette smoking initiation rates and smoking cessation rates for 2005-2008 (Appendix A, Table 5). The counterfactual exposure scenarios were selected to investigate potential effects on mortality in the US population if MRTP use was 10%, 25%, 50% and 100% as popular in the US as it was in Sweden in the 1990s (Appendix A, Table 6). Scenarios were run using an estimated ERR for MRTP compared to cigarette smoking of 0.11, as above, and also using an ERR half as large, i.e., 0.055. As described above, we ran 10,000 iterations of the model after a burn-in of 2000 iterations and considered a Markov chain to have converged if the Monte Carlo error was less than 5% of the sample standard deviation. Differences between the numbers of survivors in the base case compared with the counterfactual exposure scenario were estimated after each of the model iterations and the estimates were summarized over all iterations using means and 95% posterior intervals.

3 Results

3.1 Data to address the MRTP Application Guidance

The seven statements from the draft MRTP application guidance that describe the population segments and exposure patterns of concern are quoted here, and labeled A through G. Each of the seven statements is followed by one or more numbered statements that describe the pertinent DPM analyses, if any (see above). A summary of the specific analyses and their results follow the numbered statements, with detailed results provided in Appendix B. Single changes in the exposure pattern are evaluated first, followed by relevant tipping point analyses.

A. "Tobacco users who switch from other commercially marketed tobacco products to the proposed product."

i. Some base case continuing smokers switch to the MRTP and continue MRTP use (Appendix B, Table 1)

For this analysis, 1, 5 or 10% of cigarette smokers in each age category who would have continued to smoke in the base case instead switched to and then continued the MRTP in the counterfactual scenario. We observed an increased number of survivors in all age categories. For example, if 1% (5%; 10%) of current smokers who would have continued to smoke instead switched to and then continued to use the MRTP, there would be an estimated 1,527 (7,000; 12,620) additional survivors in the 68-72 years age interval.

ii. Some base case smoking quitters switch to the MRTP and continue MRTP use (Appendix B, Table 2)

Here, 1, 5 or 10% of cigarette smokers who would have quit smoking in the base case instead switched to and then continued the MRTP in the counterfactual scenario. We observed a decreased number of survivors in all age categories. For example, if 1% (5%; 10%) of current smokers who would have quit smoking instead switched to and then continued to use the MRTP, there would be an estimated 38 (188; 376) fewer survivors in the 68-72 years age interval.

iii. Combinations of i and ii to estimate a tipping point: Base case continuing smokers switch to and continue MRTP use (beneficial exposure pattern) vs. base case smoking quitters switch to MRTP and continue MRTP use (harmful exposure pattern) (Appendix B, Table 3.1- 3.3 and Appendix C, Figure 1)

For this analysis, 1%, 5%, 10% of base case smoking quitters instead switched to the MRTP and continued MRTP use in the counterfactual scenario. In addition, some cigarette smokers who would have continued to smoke in the base case instead switched to and then continued to use the MRTP in the counterfactual scenario.

When 1% of those who would have quit smoking in the base case instead switched to the MRTP, the decrease in survivors (38 additional deaths) at age 68-72 was counterbalanced, i.e., the difference was smaller and no longer statistically significant if there was a concurrent increase of about 0.025% in the number of smokers who switched to MRTP use instead of continuing to smoke (Appendix C, Figure 1.1). If at least approximately 0.05% of base case smokers switched to MRTP use instead of

continuing to smoke, there was a statistically significant increase in the number of survivors in the counterfactual scenario (Appendix B, Table 3.1 and Appendix C, Figure 1.1). If 5% of those who would have quit smoking in the base case instead switched to the MRTP (Appendix B, Table 3.2 and Appendix C, Figure 1.2), the decrease in survivors (188 additional deaths) at age 68-72 was smaller and no longer statistically significant when there was a concurrent increase of about 0.125% in the number of smokers who switched to and remained MRTP users, instead. There was a statistically significant increase in the number of survivors at age 68-72 in the counterfactual compared with the base case if there was a concurrent shift of at least 0.15% of base case continuing smokers switching to and remaining MRTP users (Appendix B, Table 3.2 and Appendix C, Figure 1.2).

If 10% of smokers who would have quit in the base case instead switched to the MRTP, the survival deficit (-376) was no longer observed when approximately 0.25% of base case continuing smokers switched to and remained MRTP users. There was a statistically significant increase in survivors at age 68-72 if this proportion was about 0.275% (Appendix B, Table 3.3 and Appendix C, Figure 1.3).

Results for other age categories were also obtained. However, while different in magnitude, they showed the same pattern as the results in Table 3.1-3.3 and Appendix C, Figure 1, and therefore they are not presented separately.

B. "Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk."

1. Switching from smoking to MRTP among base case continuing smokers followed by switching back to smoking

   i. Some base case continuing smokers switch to the MRTP and some revert to smoking in a subsequent age category

      a. All revert to smoking, then some quit smoking (Appendix B, Table 4)

         For this analysis, 1, 5 or 10% of cigarette smokers who would have continued to smoke in the base case instead switched to MRTP use and then reverted to smoking in the next age category in the counterfactual scenario, for an average of five years' exposure to MRTP. Subsequent smoking cessation occurred at the age-specific smoking cessation rates observed in the US in 2006. We observed an increased number of survivors in all age categories. For example, if 1% (5%, 10%) of current smokers who would have continued to smoke instead switched to MRTP use and then back to smoking, there would be an estimated 323 (1,431; 2,479) additional survivors in the 68-72 years age interval.

      b. 50% of switchers revert to smoking, then some quit smoking, and 50% remain MRTP users (Appendix B, Table 5)

         Here, 1, 5 or 10% of cigarette smokers who would have continued to smoke in the base case instead switched to MRTP use; in each age category, 50% of switchers

reverted to smoking and then quit smoking at the age-specific smoking cessation rate observed in the US in 2006, and 50% remained MRTP users for at least the current age category. We observed an increased number of survivors in all age categories in the counterfactual scenario compared with the base case. For example, if 1% (5%, 10%) of current smokers who would have continued to smoke instead switched to MRTP use, with 50% of switchers reverting to smoking (with some quitting) and 50% remaining MRTP users for at least the current age category in the counterfactual scenario, there would be an estimated 563 (2,515; 4,397) additional survivors in the 68-72 years age interval.

ii. Some smokers who would have quit smoking in the base case instead switch to the MRTP; some revert to smoking in a subsequent age category

a. All revert to smoking, then some quit smoking (Appendix B, Table 6)

For this analysis, 1, 5 or 10% of cigarette smokers who would have quit in the base case instead switched to MRTP use and then reverted to smoking in the next age category in the counterfactual scenario, and subsequently quit smoking at the age-specific smoking cessation rates observed in the US in 2006. We observed a decreased number of survivors in all age categories. For example, if 1% (5%, 10%) of current smokers who would have quit instead switched to MRTP use and then reverted back to smoking, there would be an estimated 208 (1,041; 2,081) fewer survivors in the 68-72 years age interval.

b. 50% of switchers revert to smoking, then some quit smoking, and 50% remain MRTP users (Appendix B, Table 7)

Here, 1, 5 or 10% of cigarette smokers who would have quit in the base case instead switched to MRTP use; in each age category, 50% of switchers reverted to smoking, then quit smoking at the age-specific rates observed in the US in 2006, and 50% remained MRTP users in the counterfactual scenario. We observed a decreased number of survivors in all age categories. For example, if 1% (5%, 10%) of current smokers who would have quit instead switched to MRTP use and 50% reverted to smoking and 50% remained MRTP users in the counterfactual scenario, there would be an estimated 172 (862; 1,724) fewer survivors in the 68-72 years age interval.

iii. Combinations of i and ii to estimate a tipping point: Base case continuing smokers switch to MRTP (and revert to smoking) vs. base case smoking quitters switch to MRTP (and revert to smoking)

a. All revert to smoking, then some quit smoking (Appendix B, Tables 8.1 - 8.3 and Appendix C, Figure 2)

For this analysis, 1%, 5%, 10% of base case smoking quitters switched to the MRTP in the counterfactual scenario, and reverted to smoking in the next age category. In addition, some cigarette smokers who would have continued to smoke in the base

case instead switched to the MRTP in the counterfactual scenario, and then reverted to smoking in the next age category. All cigarette smokers quit smoking at the age-specific smoking cessation rates observed for the US in 2006.

When 1% of those who would have quit smoking in the base case switched to the MRTP and no continuing smokers switched to MRTP instead (Appendix B, Table 8.1, row 1), we observed a statistically significant decrease of 208 survivors in the 68-72 years age interval. If, however, there was a concurrent 0.6% increase in the number of base case smokers who switched to MRTP use instead of continuing to smoke, the difference in the number of survivors was near zero even though the MRTP switchers reverted to smoking in the next age category (Appendix B, Table 8.1 and Figure 2.1). If about 0.8% of those who would have continued to smoke in the base case instead switched to MRTP use (and then reverted to smoking in the next age category), there was a statistically significant increase in the number of survivors in age category 68-72 (Appendix B, Table 8.1 and Appendix C, Figure 2.1).

If 5% of those who would have quit smoking in the base case instead switched to the MRTP and then reverted to smoking in the next age category, the initial survival deficit was overcome if approximately 3% of those who would have continued to smoke in the base case instead switched to the MRTP (and then reverted to smoking) in the counterfactual. If 4% or more of those who would have continued to smoke in the base case switched to the MRTP and reverted to smoking in the next age category, there was a statistically significant increase in the number of survivors in the counterfactual exposure scenario (Appendix B, Table 8.2 and Appendix C, Figure 2.2).

If 10% of those who would have quit smoking in the base case switched to the MRTP and then reverted to smoking in the next age category, the number of survivors in the base case was about the same as the number of survivors in the counterfactual when approximately 6% of base case continuing smokers instead switched to MRTP use and reverted to smoking in the next age category. There was a statistically significant increase in survivors in the counterfactual scenario if at least 8% of base case continuing smokers switched to the MRTP and then reverted to smoking in the next age category (Appendix B, Table 8.3 and Appendix C, Figure 2.3).

b. 50% of switchers revert to smoking, then some quit, and 50% remain MRTP users (Appendix B, Tables 9.1-9.3 and Appendix C, Figure 3)

For this analysis, 1%, 5%, 10% of those who would have quit smoking in the base case switched to the MRTP in the counterfactual scenario; in each age category, 50% reverted to smoking, and subsequently quit smoking at the age-specific smoking cessation rates observed for the US in 2006. The other 50% remained MRTP users. In addition, some cigarette smokers who would have continued to smoke in the base case instead switched to the MRTP in the counterfactual scenario; in each age category, 50% of switchers reverted to smoking, then quit at the 2006 US age-specific rates, and 50% remained MRTP users.

When 1% of base case smoking quitters switched to the MRTP and there was no switching among continuing smokers (Appendix B, Table 9.1, row 1), we observed 172 fewer survivors in the 68-72 years age interval. The number of survivors was almost the same for the base case and counterfactual exposure scenario if there was a concurrent 0.3% increase in the number of base case smokers who switched to MRTP use instead of continuing to smoke, even if 50% of these switchers reverted to smoking and 50% remained MRTP users (Appendix B, Table 9.1 and Figure 3.1). If 0.4% or more of those who would have continued to smoke in the base case instead switched to MRTP use (50% of switchers reverted to smoking and 50% remained MRTP users), there was a statistically significant increase in the number of survivors in the counterfactual compared with the base case (Appendix B, Table 9.1 and Appendix C, Figure 3.1).

If 5% of those who would have quit smoking in the base case instead switched to the MRTP, it was necessary for approximately 1.5% of base case continuing smokers to switch to the MRTP (50% of switchers reverted to smoking and 50% remained MRTP users) to eliminate the deficit of 862 survivors in the counterfactual compared to the base case. There was a statistically significant increase in survivors in the counterfactual compared with the base case if at least 1.75% of those who would have continued to smoke in the base case instead switched to the MRTP, with 50% of them reverting to smoking and 50% remaining as MRTP users (Appendix B, Table 9.2 and Appendix C, Figure 3.2).

If 10% of those who would have quit smoking in the base case switched to the MRTP, then approximately 3% of base case continuing smokers must switch to MRTP (50% of switchers reverted to smoking and 50% remained MRTP users) to result in a difference in the number of survivors near zero. There was a statistically significant increase in survivors in the counterfactual compared with the base case if at least 3.5% of those who would have continued to smoke in the base case switched to the MRTP with 50% of switchers reverting to smoking and 50% remaining MRTP users. (Appendix B, Table 9.3 and Appendix C, Figure 3.3).

2. Initiating MRTP among base case never tobacco users followed by switching to smoking

   i. Some base case **never tobacco users** initiate the MRTP and then **switch** to smoking <u>in a subsequent age category</u>

      a. All switch to smoking, then some quit (Appendix B, Table 10)

      For this analysis, 1, 5 or 10% of never tobacco users in the base case instead initiated MRTP use and then switched to smoking in the counterfactual scenario, subsequently quitting smoking at the age-specific cessation rates seen in the US in 2006. We observed a decreased number of survivors in all age categories. For example, if 1% (5%, 10%) of never tobacco users instead initiated MRTP use and then switched to smoking, there would be an estimated 2,041 (9,833; 18,760) fewer survivors in the 68-72 years age interval.

b. 50% of switchers revert to smoking, then some quit, and 50% remain MRTP users (Appendix B, Table 11)

Here, 1, 5 or 10% of never tobacco users in the base case instead initiated MRTP use in the counterfactual scenario; in each age category, 50% of MRTP users switched to smoking while 50% remained MRTP users in the counterfactual scenario. The smokers quit at the US 2006 age-specific smoking cessation rates, and the MRTP users did not quit MRTP use. We observed a decreased number of survivors in all age categories. For example, if 1% (5%, 10%) of never tobacco users in the base case instead initiated MRTP use and 50% of these MRTP users switched to smoking while 50% remained MRTP users in the counterfactual scenario, there would be an estimated 1,927 (9,282; 17,700) fewer survivors in the 68-72 years age interval.

ii. Some base case **smoking initiators** initiate the MRTP instead and then **switch** to smoking <u>in a subsequent age category</u>

a. All switch to smoking, then some quit (Appendix B, Table 12)

For this analysis, 1, 5 or 10% of those who would have begun smoking in the base case instead initiated tobacco use with the MRTP, switched to smoking in the next age category and subsequently quit smoking at the age-specific smoking cessation rates observed in the US in 2006. We observed an increased number of survivors in all age categories. For example, if 1% (5%, 10%) of those who would have been smoking initiators in the base case instead initiated tobacco use with the MRTP and then switched to smoking, there would be an estimated 21 (105, 209) additional survivors in the 68-72 years age interval.

b. 50% of switchers revert to smoking, then some quit, and 50% remain MRTP users (Appendix B, Table 13)

Here, 1, 5 or 10% of those who would have begun smoking in the base case instead initiated MRTP use in the counterfactual scenario; in each age category, 50% of MRTP users switched to smoking while 50% remained MRTP users in the counterfactual scenario. The smokers quit at the US 2006 age-specific smoking cessation rates. We observed an increased number of survivors in all age categories. For example, if 1% (5%, 10%) of smoking initiators in the base case instead initiated MRTP use and 50% of these MRTP users switched to smoking while 50% remained MRTP users in the counterfactual scenario, there would be an estimated 32 (162, 323) additional survivors in the 68-72 years age interval.

iii. Combination of i and ii to estimate a tipping point: Base case **never tobacco users initiate** MRTP (and some **switch** to smoking) vs. base case **smoking initiators** initiate MRTP (and some **switch** to smoking)

a. All switch to smoking, then some quit (Appendix B, Tables 14.1-14.3)

For this analysis, 1%, 5%, 10% of base case never tobacco users instead initiated the MRTP in the counterfactual scenario, and switched to smoking in the next age category. In addition, some who would have initiated smoking in the base case instead became MRTP users, and then switched to smoking in the next age category. All cigarette smokers quit smoking at the age-specific smoking cessation rates observed for the US in 2006.

When 1% of base case never tobacco users instead became MRTP users, and none who would have initiated smoking in the base case chose to use MRTP instead (Appendix B, Table 14.1, row 1), we observed 2,041 fewer survivors in the 68-72 years age interval. If 100% of those who would have initiated smoking in the base case instead initiated the MRTP in the counterfactual, and then switched to smoking in the next age category, the difference in the number of survivors was positive, i.e., there were more survivors in the counterfactual than in the base case, but near zero and not statistically significant, meaning there was no survival benefit to this exposure pattern. If a larger proportion of those who would never have been smokers in the base case instead initiated use of the MRTP in the counterfactual and then switched to smoking, the survival deficit in the counterfactual scenario could not be eliminated (Appendix B, Table 14.2 and 14.3). This is because the total number of smoking initiators in the base case was less than the difference in the number of survivors in the counterfactual compared with the base case.

b. 50% of switchers revert to smoking, then some quit, and 50% remain MRTP users (Appendix B, Table 15.1-15.3)

For this analysis, 1%, 5%, 10% of those who would been never smokers in the base case instead initiated the MRTP in the counterfactual scenario; in each age category, 50% of MRTP users switched to smoking while 50% remained MRTP users. In addition, some who would have initiated smoking in the base case instead initiated tobacco use with the MRTP in the counterfactual scenario. In each age category, 50% of MRTP users switched to smoking while 50% remained MRTP users. All cigarette smokers quit smoking at the age-specific smoking cessation rates observed for the US in 2006.

When 1% of those who would never have been tobacco users in the base case initiated tobacco use with the MRTP and there was no MRTP initiation instead of smoking initiation (Appendix B, Table 15.1, row 1), we observed 1,927 fewer survivors in the 68-72 years age interval. If about 60% of those who would have initiated smoking in the base case instead initiated tobacco use with the MRTP and if, in each age category, 50% of MRTP users switched to smoking while 50% remained MRTP users, the difference in the number of survivors comparing the base case with the counterfactual exposure scenario was near zero. However, we did not observe a statistically significant increase in the number of survivors under these exposure patterns.

If 5% or 10% of base case never tobacco users initiated tobacco use with the MRTP, and, in each age category, 50% of MRTP users switched to smoking while 50% remained MRTP users, the survival deficit in the counterfactual exposure scenario could not be eliminated (Appendix B, Table 15.2 and 15.3). The total number of smoking initiators in the base case was less than the difference in the number of survivors in the counterfactual compared with the base case.

C. "Tobacco users who opt to use the proposed product rather than cease tobacco use altogether."

This analysis is addressed in section A.ii above.

D. "Tobacco users who opt to use the proposed product rather than an FDA approved tobacco cessation medication."

This analysis cannot be performed with the DPM, because age- and use-specific mortality rates for tobacco cessation medications are not known.

E. "Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users."

1. MRTP initiation among base case never tobacco users followed by continued MRTP use

   i. Some base case **never tobacco users** instead become MRTP users and **continue** MRTP use

      a. Constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (Appendix B, Table 16)

         For this analysis, 1, 5 or 10% of never tobacco users in the base case instead initiated and then continued MRTP use in the counterfactual scenario. MRTP initiation rates were assumed to be constant over the first 3 age categories; no initiation was allowed to take place thereafter. We observed a decreased number of survivors in all age categories. For example, if 1% (5%, 10%) of never tobacco users instead initiated and then continued MRTP use, there would be an estimated 640 (3,082; 5,873) fewer survivors in the 68-72 years age interval.

      b. MRTP initiation rate doubled in the first age category; no initiation after age category 3 (Appendix B, Table 17)

         To estimate the effect of MRTP disproportionately attracting youth, the MRTP initiation rate among base case never smokers is set to 2, 10 or 20% in the first age category, and remains at 1, 5 or 10% of never tobacco users in the subsequent two age categories. There is no MRTP initiation after the third age category, and all MRTP users remain as MRTP users in the counterfactual scenario. Under this counterfactual exposure pattern, we observed a decreased number of survivors in all age categories relative to the base case. For example, if the MRTP initiation rate among never tobacco users in the base case is set to 2% (10%, 20%) in the first age

category and 1% (5%, 10%) in the next two age categories (with all MRTP users continuing to use MRTP), there would be an estimated 862 (4,109; 7,730) fewer survivors in the 68-72 years age interval.

ii. Some base case **smoking initiators** initiate the MRTP instead and **continue** MRTP use

a. Constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (Appendix B, Table 18)

For this analysis, 1, 5 or 10% of smoking initiators in the base case instead initiated and then continued MRTP use in the counterfactual scenario. MRTP initiation rates were set to be constant over the first 3 age categories; no initiation was allowed to take place thereafter. We observed an increased number of survivors in all age categories. For example, if 1% (5%, 10%) of smoking initiators instead initiated and then continued MRTP use, there would be an estimated 161 (805; 1,609) additional survivors in the 68-72 years age interval.

b. MRTP initiation rate doubled in the first age category; no initiation after age category 3 (Appendix B, Table 19)

Here, MRTP initiation in the first age category is set to 2, 10 or 20% among those who would have begun smoking in the base case, and is set to 1, 5 or 10% in the next two age groups, and no MRTP initiation occurred thereafter. All MRTP users in the counterfactual continue using the MRTP until the end of follow-up in the counterfactual scenario. We observed an increased number of survivors in all age categories. For example, if 2% (10%, 20%) of smoking initiators in the base case instead initiated and then continued MRTP use in the first age category in the counterfactual scenario, followed by 1% (5%, 10%) in the next two age categories, there would be an estimated 261 (1,303; 2,606) additional survivors in the 68-72 years age interval.

iii. Combination of i and ii to estimate a tipping point: Base case **never tobacco users initiating** MRTP vs. base case **smoking initiators** initiating MRTP (and **continue** MRTP use)

a. Constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (Appendix B, Table 20.1-20.3 and Appendix C, Figure 4)

For this analysis, 1%, 5%, 10% of base case never tobacco users initiated and continued the MRTP in the counterfactual scenario. In addition, some smoking initiators in the base case instead initiated the MRTP and continued its use in the counterfactual scenario. When 1% of base case never tobacco users initiated the MRTP and there was no MRTP initiation instead of smoking initiation (Appendix B, Table 20.1), we observed 640 fewer survivors in the 68-72 years age interval. If 4% of smoking initiators chose the MRTP instead of cigarettes, the difference in the number of survivors was near zero. If 7% of smoking initiators chose the MRTP

instead of cigarettes, we observed a statistically significant increase in the number of survivors.
If 5% of base case never tobacco users initiated the MRTP and then continued its use, the difference in the number of survivors was near zero if 20% of base case smoking initiators chose the MRTP instead. There was a statistically significant increase in the number of survivors in the counterfactual compared with the base case if at least 30% of base case smoking initiators instead chose the MRTP and then continued its use (Appendix B, Table 20.2).

If 10% of base case never tobacco users initiated the MRTP and then continued its use, the difference in the number of survivors was near zero if 40% of base case smoking initiators chose the MRTP instead of cigarettes. There was a statistically significant increase in survivors compared with the base case if at least 60% of base case smoking initiators instead initiated the MRTP and continued its use (Appendix B, Table 20.3). For these scenarios we assumed constant MRTP initiation rates in the first 3 age categories and no initiation thereafter.

b. MRTP initiation rate doubled in the first age category to estimate the effect of MRTP disproportionately attracting youth; no initiation after age category 3 (Appendix B, Table 21.1 – 21.3 and Appendix C, Figure 5)

In these analyses, the counterfactual scenario consists of 2%, 10% and 20% of base case never tobacco users initiating and continuing to use the MRTP in the first age category, with 1%, 5%, 10% initiating and continuing to use the MRTP in the next two age groups (and no MRTP initiation thereafter). In addition, some who would have initiated smoking in the base case instead initiated tobacco use with the MRTP, and continued its use in the counterfactual scenario.

When 2% of base case never tobacco users in the first age group and 1% in the next two age groups initiated the MRTP, and there was no MRTP initiation instead of smoking initiation, we observed 862 fewer survivors in the counterfactual compared with the base case in the 68-72 years age interval. If, in addition, 5% of smoking initiators initiated the MRTP instead of cigarettes, the difference in the number of survivors was near zero. If 9% of smoking initiators initiated the MRTP instead of cigarettes, we observed a significant increase in survivors (Appendix B, Table 21.1).

If 10% of base case never tobacco users initiated and continued to use the MRTP in the first age category and 5% initiated and continued to use the MRTP in the next two age categories, the difference in the number of survivors was near zero if 25% of those who would have initiated tobacco use with cigarettes initiated tobacco use with the MRTP instead. There was a statistically significant increase in survivors in the counterfactual compared with the base case if at least 45% of those who would have initiated smoking in the base case instead initiated the MRTP and continued its use (Appendix B, Table 21.2).

If 20% of base case never tobacco users initiated and continued to use the MRTP in the first age category, and 10% initiated and continued to use the MRTP in the next two age categories, the difference in the number of survivors was near zero if 50% of those who would have initiated smoking in the base case initiated tobacco use with the MRTP instead of cigarettes. There was a statistically significant increase in survivors in the counterfactual compared with the base case if at least 80% of base case smoking initiators instead initiated with the MRTP instead of cigarettes, and continued its use (Appendix B, Table 21.3).

2. MRTP initiation among base case never tobacco users followed by quitting and restarting MRTP use

   i. Some base case **never tobacco users** initiate the MRTP; then some **quit**; some of the quitters **restart** and then continue MRTP use.

      a. 25% of MRTP quitters resume MRTP use (Appendix B, Table 22)

         For this analysis, 1, 5 or 10% never tobacco users in the base case instead initiated MRTP use in the counterfactual scenario; some quit MRTP use at the same age-specific quit rates as the smokers quit smoking; and, in each age category, 25% of MRTP quitters resumed MRTP use. MRTP initiation rates were assumed to be constant over the first 3 age categories; no initiation was allowed to take place thereafter. We observed fewer survivors in the counterfactual compared with the base case in all age categories. For example, if 1% (5%, 10%) of never tobacco users instead initiated MRTP use, some quit the MRTP and, in each age category, 25% of MRTP quitters resumed MRTP use, there would be an estimated 350 (1,679; 3,183) fewer survivors in the counterfactual scenario compared with the base case in the 68-72 years age interval.

      b. 50% of MRTP quitters resuming MRTP use (Appendix B, Table 23)

         Here, 1, 5 or 10% never tobacco users in the base case instead initiated MRTP use in the counterfactual scenario; some quit MRTP use at the same age-specific quit rates as smokers quit smoking; and, in each age category, 50% of MRTP quitters resumed MRTP use. MRTP initiation rates were assumed to be constant over the first 3 age categories; no initiation was allowed to take place thereafter. We observed fewer survivors in the counterfactual scenario compared with the base case in all age categories. For example, if 1% (5%, 10%) of never tobacco users instead initiated MRTP use, some quit MRTP use and, in each age category, 50% of MRTP quitters resumed MRTP use, there would be an estimated 431 (-2,071; -3,936) fewer survivors in the counterfactual scenario compared with the base case in the 68-72 years age interval.

   ii. Some base case **smoking initiators** instead initiate with the MRTP; some **quit** and some of the quitters **restart** and then continue MRTP use.

a. 25% of MRTP quitters resume MRTP use (Appendix B, Table 24)

For this analysis, 1, 5 or 10% smoking initiators in the base case instead initiated MRTP use in the counterfactual scenario; some quit at the same quit rates as smokers; and, in each age category, 25% of MRTP quitters resumed MRTP use. MRTP initiation rates were assumed to be constant over the first 3 age categories; no initiation was allowed to take place thereafter. There were more survivors in the counterfactual compared to the base case in all age categories. For example, if 1% (5%, 10%) of smoking initiators instead initiated MRTP use, some quit and, in each age category, 25% of MRTP quitters resumed MRTP use, there would be an estimated 192 (958; 1,917) additional survivors in the 68-72 years age interval.

b. 50% of MRTP quitters resume MRTP use (Appendix B, Table 25)

Here, 1, 5 or 10% of smoking initiators in the base case instead initiated MRTP use in the counterfactual scenario. MRTP cessation occurred at the same age-specific rates as smokers quit smoking; and, in each age category, 50% of MRTP quitters resumed MRTP use. MRTP initiation rates were assumed to be constant over the first 3 age categories; no initiation was allowed to take place thereafter. There were more survivors in the counterfactual scenario compared with the base case in all age categories. For example, if 1% (5%, 10%) of smoking initiators instead initiated MRTP use, and some eventually quit and then, in each age category, 50% of MRTP quitters resumed MRTP use, there would be an estimated 183 (914; 1,830) additional survivors in the 68-72 years age interval in the counterfactual scenario compared with the base case.

iii. Combination of i and ii to estimate a tipping point: Base case **never tobacco users initiating** MRTP vs. base case **smoking initiators initiating** MRTP; some MRTP users **quit**; and some of the MRTP quitters **restart** and then continue MRTP use

a. 25% of MRTP quitters resume MRTP use (Appendix B, Tables 26.1–26.3 and Appendix C, Figure 6)

For this analysis, 1%, 5%, 10% of base case never tobacco users initiated the MRTP in the counterfactual scenario, and some quit at the same age-specific rates as smokers quit smoking. In addition, some smoking initiators in the base case instead initiated with the MRTP, with some quitting at the same age-specific rates as smokers quit smoking; in each age category, 25% of MRTP quitters resumed MRTP use.

When 1% of base case never tobacco users instead initiate tobacco with the MRTP and there was no MRTP initiation instead of smoking initiation, we observed 350 fewer survivors in the 68-72 years age interval. If 2% of those who would have initiated smoking in the base case began using the MRTP instead of cigarettes, the difference in the number of survivors in the base case and counterfactual scenario was near zero. If 2.5% of base case smoking initiators instead initiated tobacco use

with the MRTP, we observed a statistically significant increase in survivors in the counterfactual scenario compared with the base case (Appendix B, Table 26.1). If 5% of base case never tobacco users initiated the MRTP, subsequently quitting MRTP use at the same age-specific quit rates as the smokers quit smoking, and if, in each age category, 25% of MRTP quitters resumed MRTP use, the difference in the number of survivors aged 68-72 years in the counterfactual scenario compared with the base case was near zero if 9% of those who would have initiated smoking in the base case initiated tobacco use with the MRTP instead of cigarettes, with subsequent MRTP quitting and relapse rates as described above. There was a statistically significant increase in the number of survivors aged 68-72 years in the counterfactual scenario compared with the base case if 12% of base case smoking initiators instead chose the MRTP, with subsequent MRTP quitting and relapse rates as above (Appendix B, Table 26.2).

If 10% of base case never tobacco users initiated the MRTP in the counterfactual scenario, subsequently quitting the MRTP at the same age-specific quit rates as the smokers quit smoking, and if, in each age category, 25% of MRTP quitters resumed MRTP use, the difference in the number of survivors comparing the counterfactual scenario with the base case was near zero if 18% of base case smoking initiators initiated tobacco use with the MRTP instead of cigarettes. There was a statistically significant increase in survivors aged 68-72 years in the counterfactual compared with the base case if at least 25% of base case smoking initiators instead initiated tobacco use with the MRTP, with quit rates and rates of relapse to MRTP as above (Appendix B, Table 26.3).

b. 50% of MRTP quitters resume MRTP use (Appendix B, Table 27.1-27.3 and Appendix C, Figure 7)

For this analysis, 1%, 5%, 10% of base case never tobacco users initiated the MRTP in the counterfactual scenario, and some quit at the same age-specific rates as smokers quit smoking. In addition, some smoking initiators in the base case instead initiated with the MRTP, with some quitting at the same age-specific rates as smokers quit smoking; in each age category, 50% of MRTP quitters resumed MRTP use.

When 1% of base case never tobacco users instead initiated tobacco use with the MRTP, and there was no MRTP initiation instead of smoking initiation, we observed 431 fewer survivors in the 68-72 years age interval in the counterfactual scenario compared with the base case. If 2.5% of base case smoking initiators instead chose the MRTP, the difference in the number of survivors at age 68-72 was near zero. If 3.5% of smoking initiators chose the MRTP instead of cigarettes, we observed a statistically significant increase in survivors in the last age group, comparing the counterfactual scenario to the base case. (Appendix B, Table 27.1)

If 5% of base case never tobacco users instead initiated tobacco use with the MRTP, with subsequent age-specific quit rates the same as the smoking cessation rates for

smokers, and if, in each age category, 50% of MRTP quitters resumed MRTP use, the difference in the number of survivors at age 68-72 was near zero if 12% of base case smoking initiators instead initiated with the MRTP. There was a statistically significant increase in survivors at age 68-72 in the counterfactual scenario compared with the base case if at least 16% of base case smoking initiators instead initiated tobacco with the MRTP, with and some eventually quitting and 50% of MRTP quitters resuming MRTP use (Appendix B, Table 27.2).

If 10% of base case never tobacco users initiated tobacco use with the MRTP, with subsequent age-specific quit rates the same as the smoking cessation rates for smokers, and, in each age category, 50% of MRTP quitters resumed MRTP use, the difference in the number of survivors at age 68-72 was near zero if 24% of those who would have initiated smoking in the base case instead initiated tobacco use with the MRTP, with some eventually quitting and, in each age category, 50% of MRTP quitters resuming MRTP use. There was a statistically significant increase in survivors at age 68-72 in the counterfactual scenario compared to the base case if at least 30% of base case smoking initiators instead initiated the MRTP, with subsequent quitting and relapse rates as described above (Appendix B, Table 27.3).

F. "Tobacco users who use the product in conjunction with other tobacco products."

DPM analyses of dual users would not be informative, because the mortality risks for current and former dual users are set to be the same as mortality risks for current and former smokers, respectively.

G. "Non-users who experience health risks from the product."

This analysis is not addressed by the DPM.

3.2 Summary results of tipping point analyses

In addition to the detailed results provided in Appendix B, the results of the tipping point analyses are summarized in Appendix C and in the following text.

1. Tipping points for base case continuing smokers switching to MRTP versus base case smoking quitters switching to MRTP. Assume 1% (5%, 10%) of base case **smoking quitters** switch to the MRTP (Appendix D, Table 1)[7].

Survival deficit

Assume that all switchers continue MRTP use. A statistically significant survival deficit is observed if less than 0.01% (0.1%, 0.2%) of base case continuing smokers switch to the MRTP. If 50% of switchers continue MRTP use and 50% revert to smoking, a statistically significant survival deficit is observed if less than 0.25% (1.25%, 2.75%) of base case continuing smokers switch to the MRTP. If all switchers revert to smoking, a statistically significant survival deficit is observed if less than 0.5% (2.5%, 5.75%) of base case continuing smokers switch to the MRTP.

No survival deficit or benefit

[7] It is important to note that the number of continuing smokers is much higher than the number of quitters.

Assume that all switchers continue MRTP use. The survival deficit is eliminated if 0.025% (0.125%, 0.25%) of base case continuing smokers switch to the MRTP. If 50% of switchers continue MRTP use and 50% revert to smoking, the survival deficit is eliminated if 0.3% (1. 5%, 3.0%) of base case continuing smokers switch to the MRTP. If all switchers revert to smoking, the survival deficit is eliminated if 0.6% (3.0%, 6.0%) of base case continuing smokers switch to the MRTP.

Survival benefit

Assume that all switchers continue MRTP use. A statistically significant survival benefit is observed if more than 0.05% (0.15%, 0.275%) of base case continuing smokers switch to the MRTP. If 50% of switchers continue MRTP use and 50% revert to smoking, a statistically significant survival benefit is observed if more than 0.4% (1.75%, 3.5%) of base case continuing smokers switch to the MRTP. If all switchers revert to smoking, a statistically significant survival benefit is observed if more than 0.8% (4.0%, 8.0%) of base case continuing smokers switch to the MRTP.

2. Tipping points for base case never tobacco users initiating MRTP versus base case smoking initiators choosing MRTP instead of cigarettes. Assume 1% (5%, 10%) of base case **never tobacco users** initiate the MRTP. (Appendix D, Table 2).[8]

Survival deficit

Assume that all MRTP users continue MRTP use. We modeled 4 different scenarios:

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; no MRTP quitting

  A statistically significant survival deficit is observed if less than 3% (14%, 25%) of base case smoking initiators choose the MRTP instead of cigarettes.

- MRTP initiation rates doubled in the first age category and no initiation thereafter; no MRTP quitting

  A statistically significant survival deficit is observed if less than 4% (20%, 35%) of base case smoking initiators choose the MRTP instead of cigarettes.

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; some MRTP quitting; 25% of quitters resume MRTP use

  A statistically significant survival deficit is observed if less than 1.5% (7%, 14%) of base case smoking initiators choose the MRTP instead of cigarettes.

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; some MRTP quitting; 50% of quitters resume MRTP use

  A statistically significant survival deficit is observed if less than 1.75% (9%, 18%) of base case smoking initiators choose the MRTP instead of cigarettes.

[8] It is important to note that the number of never tobacco users is much larger than the number smoking initiators.

Now assume that 50% of MRTP users continue MRTP use and 50% switch to smoking. A statistically significant survival deficit is observed if < 40% (≤100%, ≤100%) of base case smoking initiators choose the MRTP instead of cigarettes. If all MRTP users switch to smoking, a statistically significant survival deficit is observed if <80% (≤100%, ≤100%) of base case smoking initiators choose the MRTP instead of cigarettes.

No survival deficit or benefit

Assume that all MRTP users continue MRTP use.

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; no MRTP quitting

  The survival deficit is eliminated if 4% (20%, 40%) of base case smoking initiators initiate the MRTP

- MRTP initiation rates doubled in the first age category and no initiation thereafter; no MRTP quitting

  The survival deficit is eliminated if 5% (25%, 50%) of base case smoking initiators initiate the MRTP

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; some MRTP quitting; 25% of quitters resume MRTP use

  The survival deficit is eliminated if 2% (9%, 18%) of base case smoking initiators initiate the MRTP

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; some MRTP quitting; 50% of quitters resume MRTP use

  The survival deficit is eliminated if 2.5% (12%, 24%) of base case smoking initiators initiate the MRTP

Now assume that 50% of MRTP users continue MRTP use and 50% switch to smoking. In this case the survival deficit is eliminated if 1% of base case never tobacco users initiate the MRTP and 60% of base case smoking initiators choose the MRTP instead of cigarettes. If 5% or 10% of base case never tobacco users initiate the MRTP, the survival deficit cannot be eliminated. Finally, if all MRTP users switch to smoking, the survival deficit cannot be eliminated.

Survival benefit

Assume that all MRTP users continue MRTP use.

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; no MRTP quitting

  A statistically significant survival benefit is observed if more than 7% (30%, 60%) of base case smoking initiators initiate the MRTP

- MRTP initiation rates doubled in the first age category and no initiation thereafter; no MRTP quitting

  A statistically significant survival benefit is observed if more than 9% (45%, 80%) of base case smoking initiators choose the MRTP instead of cigarettes

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; some MRTP quitting; 25% of quitters resume MRTP use

  A statistically significant survival benefit is observed if more than 2.5% (12%, 25%) of base case smoking initiators choose the MRTP instead of cigarettes

- Constant MRTP initiation rates in the first 3 age categories and no initiation thereafter; some MRTP quitting; 50% of quitters resume MRTP use

  A statistically significant survival benefit is observed if more than 3.5% (16%, 30%) of base case smoking initiators choose the MRTP instead of cigarettes

If 50% of MRTP users continue MRTP use and 50% switch to smoking or if all MRTP users switch to smoking, a statistically significant survival benefit is never observed.

3.3 Data for Counterfactuals Based on Tobacco Use Patterns Estimated for Sweden

A. “Swedish counterfactual” vs. US base case

We observed a statistically significant survival benefit if the US population used cigarettes and an MRTP in patterns similar to those observed in Sweden in the 1990s (Appendix A, Table 3). If the ERR for the MRTP compared with cigarettes is assumed to be 0.11, then there are approximately 16,500 more survivors than if cigarettes were the only form of tobacco available, as in the base case. If the ERR is assumed to be half as large, 0.055, there are approximately 17,500 more survivors in the “Swedish counterfactual” compared to the US base case (Appendix E, Table 1).

B. Alternative “Swedish counterfactual” with reduced MRTP initiation vs. US base case

Reducing the probability of MRTP initiation by non-tobacco users and by those who would have become cigarette smokers in the base case to 10%, 25%, or 50% of the Swedish value, and leaving the probabilities of exposure transitions following MRTP initiation unchanged compared to the “Swedish counterfactual” affects the results very little. For ERR=0.11, the survival benefit of the counterfactual scenario versus the base case at the end of follow-up is approximately 16,600; 16,700 and 16,800, respectively (Appendix E, Table 2a). For ERR=0.055, there are approximately 17,400 more survivors compared with the base case (Appendix E, Table 2b). While these scenarios decrease the proportions of base case non-tobacco users initiating MRTP, the same proportional reduction is applied to base case smoking initiators. Thus, compared to the “Swedish counterfactual”, there are more persons who remain never tobacco users rather than initiating MRTP, resulting in fewer deaths compared to the “Swedish counterfactual”. At the same time, there are more current smokers and fewer persons who initiate tobacco use with MRTP instead of cigarettes, resulting in more deaths compared to the

"Swedish counterfactual". The small increases and decreases in numbers of deaths due to these shifts in exposure are nearly balanced.

C. Alternative "Swedish counterfactual" with reduced MRTP initiation and gateway effect doubled, vs. US base case

Using the same probabilities of MRTP initiation (10%, 25% or 50% of the Swedish value) but doubling the gateway effect, such that twice the proportion of those who initiate tobacco use with the MRTP switch to cigarettes, again provides similar survival differences versus the base case compared with those resulting from the "Swedish counterfactual" if ERR=0.11 (Appendix E, Table 3a). Setting the ERR for MRTP vs. cigarette smoking to 0.055 slightly increases the number of survivors compared with the base case to approximately 17,000 (Appendix E, Table 3b). The small effect of doubling the gateway effect in the "Swedish counterfactual" can be explained by the fact that the proportion of snus users who switch to cigarettes in the "Swedish counterfactual" is quite small in each age group (Appendix A, Table 3), so doubling that rate has little impact on survival.

D. Alternative "Swedish counterfactual" with reduced switching to MRTP

If the proportions of those who would have quit smoking in the base case who instead switch to the MRTP is reduced compared to the "Swedish counterfactual", the number of survivors at the end of follow-up are still larger than in the base case, but smaller than in the "Swedish counterfactual", ranging from about 7,000 for 10% of the proportion switching to MRTP in the" Swedish counterfactual" to about 12,000 for 50% of the proportion switching to MRTP in the" Swedish counterfactual" if ERR=0.11 (Appendix E, Table 4a). As may be expected, when these scenarios are modeled with ERR=0.055, the difference in the number of survivors compared to the base case is somewhat increased. In the last age category of follow-up, there are just under 8,000 additional survivors compared with the base case when the proportion switching to MRTP is 10% of that in the "Swedish counterfactual", just under 10,000 when the proportion switching to MRTP is 25% of that in the "Swedish counterfactual", and about 13,000 when the proportion switching to MRTP is 50% of that in the "Swedish counterfactual" (Appendix E, Table 4b).

E. Alternative "Swedish counterfactual" with reduced switching to MRTP and returning to smoking doubled, vs. US base case

Using the same probabilities of switching to MRTP (10%, 25% or 50% of the Swedish value) but doubling the proportion of MRTP users returning to smoking among those who initiate tobacco use with smoking but subsequently switch to MRTP provides smaller survival differences versus the base case compared with those resulting from the "Swedish counterfactual" if ERR=0.11(Appendix E, Table 5a). Setting the ERR for MRTP vs. cigarette smoking to 0.055 slightly increases the number of survivors compared with the base (Appendix E, Table 5b). The results are almost identical to the results from the scenario described in paragraph D. The small effect of doubling the proportion of MRTP users returning to smoking among those who initiate tobacco use with smoking but subsequently switch to MRTP can be explained by the fact that this proportion is quite small in the "Swedish counterfactual" (Appendix A, Table 3), so doubling that rate has little impact on survival.

While these scenarios decrease the proportion of the population switching to MRTP from cigarettes, the same relative decrease is applied to those who would have remained smokers in the base case and to those who would have quit smoking in the base case. Compared to the "Swedish counterfactual", these scenarios include more smokers and fewer MRTP users, resulting in more deaths compared to the base case than was estimated for the unadjusted "Swedish counterfactual". Although the number of persons quitting smoking rather than switching to MRTP is also increased, the absolute increase is too small to make a difference in survival, because there are many fewer people who would have quit smoking than the number who would have continued to smoke. Overall, these exposure scenarios result in more deaths compared with the unadjusted "Swedish counterfactual" and a smaller benefit compared to the US base case.

4 Discussion

The use of modified risk products, as opposed to combusted cigarettes, should serve to reduce harmful exposure to individuals. While reducing individual level exposures is expected to lead to reduced population level mortality risk, increases in population level risk might occur if more people begin using tobacco, and/or if fewer people stop using tobacco because of the availability of products bearing the MRTP label. The analyses presented here examined the potential for unintended consequences to arise from granting a modified risk tobacco product label.

Section VI of the FDA MRTP application guidance document describes seven population segments and exposure patterns that might cause an increase in harm at the population level, were they to occur. Four of the seven can be analyzed using the DPM, and analyses addressing them are provided in this document. The three exposure patterns that the DPM cannot be used to analyze focus on: use of medications approved to assist with cessation of tobacco use, not MRTP; risks experienced by non-users, not the direct effects of MRTP; and dual use of MRTP and cigarettes.

- To address risks of MRTP compared with pharmaceutical quit aids, a version of the DPM would have to be constructed that incorporates mortality risks by age and person-years of exposure and removal of exposure from the medication. No such data exist.
- The DPM does not provide estimates of health risks experienced by non-users. In the case of non-combusted products such as Swedish snus, non-users have no exposure. It can be inferred, however, that counterfactual scenarios that include fewer cigarette smokers will reduce environmental tobacco smoke, and thus may provide larger scale benefits that include non-users of tobacco in addition to users.
- The DPM does not provide useful information on the potential effects of dual use because mortality risks in the DPM are dependent on duration of smoking and duration of smoking cessation. Thus, the DPM assumes current and former dual product users have the same all-cause mortality risk as current and former smokers, respectively. If dual use resulted in decreased exposure to cigarettes, the mortality risk for dual users would likely be overestimated by the DPM

The results generated by the DPM also can be used to estimate tipping points. We defined a tipping point as the proportion of the population that experiences a beneficial change in tobacco exposure, resulting in increases in the number of survivors relative to the base case, necessary to offset the survival deficit due to a given harmful change in the tobacco exposure pattern. The tipping point analyses included in this report were developed specifically to address the potentially harmful scenarios outlined by FDA in the MRTP Application Guidance document. Each tipping point analysis consists of a series of incremental changes in the exposure pattern to identify the point at which the effect of the harmful exposure pattern was negated (i.e., the number of survivors in the base case and the counterfactual scenario was about the same) and the point at which the harmful exposure pattern was reversed (i.e., no longer statistically significant, or replaced by a statistically significant survival benefit in the counterfactual scenario

compared to the base case). Because large shifts in tobacco use behaviors are unlikely, at least within short time periods, the magnitude of the identified tipping points allows for an assessment of how responsive the initial population-level harm may be to reasonable alternative exposure patterns.

Most of the tipping points identified in these analyses occurred when less than 1% of the population made a beneficial change to counteract the effect of the harmful exposure pattern. In some cases, however, larger behavioral shifts, as measured by proportions, were needed to overcome the harm. When modeling a gateway effect, such that base case never tobacco users instead initiated tobacco use with the MRTP and then switched to smoking cigarettes, there was no situation represented in these analyses in which a statistically significant survival benefit occurred in counterfactual scenarios consisting of base case smoking initiators choosing the MRTP instead of cigarettes. In contrast, the harm from 1% of base case never tobacco users instead choosing to use the MRTP and remaining as lifetime MRTP users is counterbalanced if less than 4% of those who would have initiated smoking in the base case (some of whom would have quit smoking) instead become lifetime MRTP users. If 2% of 13-17 year olds and 1% each of 18-22 and 23-27 years olds who would have been never tobacco users instead become lifetime MRTP users, there is a tipping point (the harm is counterbalanced) if about 5% of those who would have become smokers in the base case, some of whom would subsequently quit smoking, instead become lifetime MRTP users.

The base case distribution of current and former cigarette smoking in this hypothetical cohort was based on the age-specific smoking initiation and cessation rates observed in the US in the mid-2000s. It is important to note that the number of continuing smokers is much larger than the number of quitters, and the number of never tobacco users is much larger than the number of smoking initiators. As a result, there are scenarios in which the absolute number of people in a given exposure group is too small for a tipping point to be realized: the population available for a given exposure transition runs out before the end of follow-up. Similarly, it is important to note that, as the hypothetical population ages, the effect of the age-specific initiation, switching and cessation rates are compounded.

When the distribution of cigarette and MRTP use in the US was set to approximate the distributions observed in Sweden in the 1990s, the DPM estimated a statistically significant survival benefit compared to the base case defined by 2008 US smoking initiation and 2005-2008 US smoking cessation rates. The magnitude of the difference in the number of survivors vs. the base case was not greatly affected by the value selected for the ERR comparing the MRTP to smoking (0.11 or 0.055) or by increasing the gateway effect or reducing the MRTP initiation rate among those who would have otherwise remained as never tobacco users *and* those who would have initiated tobacco use with cigarettes. When the rate of switching to MRTP by those who would have continued to smoke *and* quit smoking in the base case was reduced compared to the rates estimated for the “Swedish counterfactual”, there was still a statistically significant increase in the number of survivors in the counterfactual vs. the base case, but the magnitude of the effect was less than half that observed when the counterfactual exposure scenario approximated Swedish exposure patterns. The greater responsiveness of the results to changes that affected continuing smokers or those who would have quit smoking is a reflection of the relative sizes of the various population subgroups included in the analyses.

DPM results are highly dependent on the input data selected by the DPM user. This dependence on model input is expected, and reflects the time, population- and exposure-specific risks accounted for by the model. By evaluating the magnitude of the proportions involved in a given exposure pattern, the likelihood that risks or benefits will be realized, and that unintended negative consequences of allowing or promoting shifts to alternative exposures may occur, can be evaluated.

A large number of analyses were needed to fully assess the likelihood of harm occurring at the population level given the changes in exposure outlined in the MRTP application guidance document. This is because there are several pathways by which MRTP use could occur in the counterfactual scenario, and because the tipping point analyses describe incremental changes in two or more exposure patterns. Additionally, different analysts might select different potentially off-setting exposures patterns to examine for tipping points. Thus, this document provides many tables and figures in an attempt to be completely clear about the analyses underlying the assessment of possible population level harms and benefits, but is not exhaustive in the analyses carried out.

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Appendix A:

Exposure Probabilities and Validation Results

Table 1: Estimated smoking initiation and cessation probabilities (based on US rate data for men and women, 1980)

Age category	Smoking initiation rate[1]	Smoking cessation rate[2]
13-17	11.25	2.5
18-22	10.00	4.5
23-27	1.25	4.5
28-32	0.25	4.5
33-37	0.00	5.0
38-42	0.00	5.5
43-47	0.00	5.5
48-52	0.00	7.5
53-57	0.00	8.5
58-62	0.00	8.5
63-67	0.00	8.5
68-72	0.00	8.5

[1] Based on: Office of Applied Studies, National Household Survey on Drug Abuse (NHSDA), 1999, Appendix D, table 4.2 (http://www.samhsa.gov/data/NHSDA/tobacco/appendixd.htm)

[2] Based on: Messer et al., 2007

Table 2: Validation of base case exposure scenarios based on US tobacco use patterns in 1980. Age-specific number of survivors estimated from 2006 US life table versus model-based estimates (starting with 1,000,000 12-year old male never tobacco users)[a]

Age category	Survivors based on US life table	Survivors based on base case (US)
38-42	957,654	957,100
43-47	940,866	939,200
48-52	915,745	914,300
53-57	880,470	879,800
58-62	832,268	832,000
63-67	764,922	765,600
68-72	674,217	674,300

[a] Age group 38-42 is the first age group where all possible transitions have occurred

Table 3: Transition probabilities used to approximate Swedish tobacco use patterns, ca. 1990.

Probability of:	
Initiating MRTP instead of remaining never tobacco user	**0.05**
Initiating MRTP instead of initiating smoking	**0.05**
Gateway effect (switching to smoking/dual use from MRTP) among persons who initiated tobacco use with MRTP	**0.01**
Quitting MRTP among persons who initiated tobacco use with MRTP	**0.19**
Continued MRTP use among persons who initiated tobacco use with MRTP	**0.77**
Switching to MRTP instead of quitting	**0.02**
Switching to MRTP instead of continuing to smoke	**0.10**
Switching to smoking from MRTP among persons who initiated tobacco use with MRTP	**0.015**
Quitting MRTP among persons who initiated tobacco use with smoking	**0.217**
Continued MRTP use among persons who initiated tobacco use with smoking	**0.768**

Table 4: Validation of counterfactual exposure scenarios based on approximate Swedish tobacco use patterns, ca 1990. Age-specific number of survivors estimated from the 2006 Swedish life table versus model-based estimates (starting with 1,000,000 12 year-old male never tobacco users)[a]

Age category	Survivors based on Swedish life table	Survivors based on exposure scenario (Sweden)
38-42	980,999	979,274
43-47	972,889	970,010
48-52	959,782	957,276
53-57	936,838	935,677
58-62	902,590	902,104
63-67	846,884	847,362
68-72	764,275	762,582

[a] Age group 38-42 is first age group where all possible transitions have occurred

Table 5: Estimated smoking initiation (based on US rate data for men and women, 2009) and cessation probabilities (based on US rate data for men and women, 2005-2008)

Age interval	Smoking initiation[1]	Smoking cessation[2,4]
13-17	13.75	N/A[3]
18-22	10.00	9.00
23-27	1.00	9.50
28-32	0.00	14.00
33-37	0.00	14.00
38-42	0.00	14.00
43-47	0.00	14.00
48-52	0.00	14.00
53-57	0.00	14.00
58+	0.00	14.00

[1]http://www.samhsa.gov/data/NSDUH/2K10ResultsTables/NSDUHTables2010R/HTM/Sect4peTabs1to16.htm#Tab4.3B

[2]http://www.samhsa.gov/data/2k10/172/172smokingcessation.htm

[3]No smoking cessation allowed in 13-17 years age interval, as smoking duration among quitters in this age interval would only be 2.5 years (on average)

[4]The oldest age category for which smoking cessation data were provided was defined as “35 and older”. Thus, the last seven age categories were assigned the same smoking cessation rate.

Table 6: Transition patterns to develop various counterfactual exposure scenarios based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055

	Initiating MRTP			Transitions following MRTP initiation		
	Scenario	Harmful transition: Probability of initiating MRTP instead of remaining NT user	Beneficial transition: Probability of initiating MRTP instead of initiating smoking	Probability of gateway effect (switching to smoking/dual use)	Probability of quitting MRTP	Probability of continued MRTP use
	Sweden	0.05*	0.05*	0.01	0.19*	0.77
	Variations					
1	**Probabilities of transitions following MRTP initiation unchanged compared to Sweden, and:**					
	Probability of MRTP initiation reduced to					
A	10% of Swedish value	0.005	0.005	0.01	0.19	0.77
B	25% of Swedish value	0.0125	0.0125	0.01	0.19	0.77
C	50% of Swedish value	0.025	0.025	0.01	0.19	0.77
2	**Gateway effect doubled and:**					
	Probability of MRTP initiation reduced to					
A	10% of Swedish value	0.005	0.005	0.02	0.19	0.76
B	25% of Swedish value	0.0125	0.0125	0.02	0.19	0.76
C	50% of Swedish value	0.025	0.025	0.02	0.19	0.76

Table 6 cont.: Transition patterns to develop various counterfactual exposure scenarios based on tobacco use patterns estimated for Sweden, modeled with ERR=0.11 and ERR=0.055

	Switching to MRTP			Transitions following MRTP initiation		
	Scenario	Harmful transition: Probability of switching to MRTP instead of quitting all tobacco use	Beneficial transition: Probability of switching to MRTP instead of continuing smoking	Probability of gateway effect (switching to smoking)	Probability of quitting MRTP	Probability of continued MRTP use
	Sweden	0.02*	0.10*	0.015	0.217*	0.768
	Variations					
3	**Probabilities of transitions following switching to MRTP use unchanged compared to Sweden, and:**					
	Probability of MRTP initiation reduced to					
A	10% of Swedish value	0.002	0.010	0.015	0.217	0.768
B	25% of Swedish value	0.005	0.025	0.015	0.217	0.768
C	50% of Swedish value	0.010	0.050	0.015	0.217	0.768
4	**Gateway effect doubled, and:**					
	Probability of MRTP initiation reduced to					
A	10% of Swedish value	0.002	0.010	0.03	0.217	0.753
B	25% of Swedish value	0.005	0.025	0.03	0.217	0.753
C	50% of Swedish value	0.010	0.050	0.03	0.217	0.753

Appendix B:
Detailed Results Tables

Table 1: A.i. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case continuing smokers switch to the MRTP and continue MRTP use

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	43.78	28.99	60.24	214.50	142.10	295.00	418.20	277.30	574.70
38 - 42	103.00	70.57	139.20	499.20	342.30	674.20	960.50	659.40	1,295.00
43 - 47	206.00	146.30	272.40	987.80	702.50	1,305.00	1,876.00	1,336.00	2,476.00
48 - 52	366.90	270.50	472.90	1,741.00	1,284.00	2,242.00	3,265.00	2,411.00	4,198.00
53 - 57	595.50	454.00	746.20	2,798.00	2,135.00	3,502.00	5,185.00	3,964.00	6,481.00
58 - 62	889.20	700.70	1,084.00	4,139.00	3,266.00	5,040.00	7,587.00	5,995.00	9,229.00
63 - 67	1,221.00	992.60	1,449.00	5,637.00	4,586.00	6,680.00	10,240.00	8,340.00	12,120.00
68 - 72	1,527.00	1,255.00	1,790.00	7,000.00	5,765.00	8,194.00	12,620.00	10,410.00	14,740.00

Table 2: A.ii. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP and continue MRTP use

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	-0.55	-0.72	-0.39	-2.77	-3.62	-1.98	-5.55	-7.24	-3.97
38 - 42	-1.44	-1.84	-1.07	-7.20	-9.21	-5.37	-14.42	-18.42	-10.75
43 - 47	-3.14	-3.93	-2.41	-15.72	-19.67	-12.10	-31.44	-39.34	-24.19
48 - 52	-6.08	-7.44	-4.80	-30.40	-37.21	-24.01	-60.80	-74.42	-48.03
53 - 57	-10.73	-12.86	-8.68	-53.66	-64.28	-43.41	-107.30	-128.60	-86.82
58 - 62	-17.55	-20.55	-14.57	-87.76	-102.80	-72.84	-175.50	-205.50	-145.70
63 - 67	-26.72	-30.78	-22.51	-133.60	-153.90	-112.60	-267.20	-307.80	-225.10
68 - 72	-37.63	-43.34	-31.65	-188.10	-216.70	-158.30	-376.30	-433.40	-316.50

Table 3.1: A.iii. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case smoking quitters switch to the MRTP and continue MRTP use (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0.0	-37.63	-43.34	-31.65
0.1	118.20	96.26	139.40
0.2	273.40	223.70	321.30
0.3	427.90	350.70	502.40
0.4	581.70	477.10	682.60
0.5	734.80	603.00	862.20

Table 3.2: A.iii. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case smoking quitters switch to the MRTP and continue MRTP use (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0.0	-188.10	-216.70	-158.30
0.1	-31.92	-38.43	-26.63
0.2	123.60	96.45	149.70
0.3	278.40	224.10	330.80
0.4	432.60	350.80	511.30
0.5	586.00	477.20	691.00

Table 3.3: A.iii. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case smoking quitters switch to the MRTP and continue MRTP use (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0.0	-376.30	-433.40	-316.50
0.1	-219.60	-250.60	-186.80
0.2	-63.67	-76.65	-53.12
0.3	91.60	62.91	118.10
0.4	246.20	192.10	298.20
0.5	400.10	319.30	478.20

Table 4: B1.i.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case continuing smokers switch to the MRTP; all revert to smoking in the next age category

	1%			5%			10%		
Age	Mean	95%	PI	Mean	95%	PI	Mean	95%	PI
33 - 37	29.10	18.44	41.45	141.80	89.85	201.90	274.60	173.90	390.90
38 - 42	57.56	37.13	81.71	276.70	178.40	392.60	526.60	339.60	747.40
43 - 47	98.25	64.97	137.80	465.60	307.90	653.00	871.30	575.60	1,222.00
48 - 52	150.50	102.30	207.60	703.20	477.50	969.80	1,294.00	877.60	1,784.00
53 - 57	210.20	147.50	282.50	968.60	678.60	1,303.00	1,753.00	1,227.00	2,360.00
58 - 62	268.50	195.40	350.40	1,221.00	886.80	1,594.00	2,175.00	1,576.00	2,845.00
63 - 67	311.70	236.00	393.10	1,398.00	1,056.00	1,769.00	2,456.00	1,850.00	3,113.00
68 - 72	322.80	251.80	397.00	1,431.00	1,116.00	1,762.00	2,479.00	1,927.00	3,059.00

Table 5: B1.i.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case continuing smokers switch to the MRTP; in subsequent age categories, 50% of switchers revert to smoking and 50% remain MRTP users

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	35.71	23.12	49.93	174.50	113.10	244.00	339.10	219.80	473.90
38 - 42	75.90	50.34	105.20	366.20	243.10	507.30	700.60	465.00	970.20
43 - 47	137.30	93.71	187.60	653.90	446.50	893.00	1,231.00	841.10	1,680.00
48 - 52	220.90	155.30	296.40	1,038.00	730.00	1,392.00	1,925.00	1,353.00	2,578.00
53 - 57	322.60	233.50	423.30	1,497.00	1,083.00	1,964.00	2,731.00	1,976.00	3,582.00
58 - 62	429.90	321.90	546.40	1,969.00	1,473.00	2,506.00	3,539.00	2,643.00	4,510.00
63 - 67	520.30	403.50	643.10	2,353.00	1,823.00	2,911.00	4,170.00	3,229.00	5,168.00
68 - 72	562.70	445.70	681.30	2,515.00	1,992.00	3,048.00	4,397.00	3,480.00	5,338.00

Table 6: B1.ii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP; all revert to smoking in the next age category

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	-2.04	-2.63	-1.46	-10.23	-13.16	-7.34	-20.46	-26.32	-14.68
38 - 42	-6.53	-8.30	-4.82	-32.66	-41.52	-24.11	-65.32	-83.04	-48.21
43 - 47	-16.16	-20.26	-12.24	-80.82	-101.30	-61.19	-161.60	-202.60	-122.40
48 - 52	-33.69	-41.52	-26.11	-168.50	-207.60	-130.50	-336.90	-415.20	-261.10
53 - 57	-61.86	-74.73	-49.20	-309.30	-373.70	-246.00	-618.60	-747.30	-492.00
58 - 62	-102.30	-121.10	-83.54	-511.50	-605.70	-417.70	-1,023.00	-1,211.00	-835.40
63 - 67	-153.60	-178.60	-127.80	-767.80	-893.20	-639.10	-1,536.00	-1,786.00	-1,278.00
68 – 72	-208.10	-241.90	-173.00	-1,041.00	-1,210.00	-865.10	-2,081.00	-2,419.00	-1,730.00

Table 7: B1.ii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP; in subsequent age categories, 50% of switchers revert to smoking and 50% remain MRTP users

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	-1.37	-1.76	-0.98	-6.86	-8.82	-4.94	-13.73	-17.66	-9.89
38 - 42	-4.43	-5.60	-3.29	-22.15	-28.02	-16.49	-44.31	-56.03	-32.98
43 - 47	-11.29	-14.04	-8.64	-56.44	-70.18	-43.22	-112.90	-140.40	-86.43
48 - 52	-24.35	-29.73	-19.10	-121.80	-148.70	-95.48	-243.50	-297.30	-191.00
53 - 57	-46.31	-55.43	-37.26	-231.60	-277.20	-186.30	-463.10	-554.30	-372.60
58 - 62	-79.27	-92.99	-65.47	-396.30	-465.00	-327.40	-792.70	-929.90	-654.70
63 - 67	-123.10	-142.10	-103.10	-615.30	-710.40	-515.60	-1,231.00	-1,421.00	-1,031.00
68 - 72	-172.40	-199.20	-144.20	-862.00	-996.20	-720.80	-1,724.00	-1,992.00	-1,442.00

Table 8.1: B1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case smoking quitters switch to the MRTP; all revert to smoking in the next age category (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	**Mean**	**95%**	**PI**
0.0	-208.10	-241.90	-173.00
0.2	-141.00	-161.40	-118.90
0.4	-74.69	-87.15	-60.91
0.6	-9.19	-25.24	11.00
0.8	55.49	28.15	87.89
1.0	119.40	79.07	165.90
1.2	182.50	129.20	243.00

Table 8.2: B1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case smoking quitters switch to the MRTP; all revert to smoking in the next age category (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0	-1,041.00	-1,210.00	-865.10
1	-694.40	-794.80	-585.70
2	-368.20	-429.20	-300.70
3	-60.99	-137.00	35.45
4	228.40	103.30	376.70
5	501.00	323.10	707.30

Table 8.3: B1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case smoking quitters switch to the MRTP; all revert to smoking in the next age category (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0	-2,081.00	-2,419.00	-1,730.00
2	-1,363.00	-1,559.00	-1,150.00
4	-722.30	-841.60	-590.80
6	-151.50	-293.90	27.99
8	357.60	132.90	627.90
10	812.10	499.50	1,176.00
12	1,218.00	822.90	1,669.00
14	1,582.00	1,109.00	2,116.00

Table 9.1: B1.iii.b Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case smoking quitters switch to the MRTP; in subsequent age categories 50% of switchers revert to smoking and 50% remain MRTP users (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0.0	-172.40	-199.20	-144.20
0.2	-56.51	-65.39	-46.51
0.4	58.06	35.72	83.34
0.6	171.30	126.70	219.60
0.8	283.30	215.60	355.00
1.0	394.00	304.00	488.60

Table 9.2: B1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case smoking quitters switch to the MRTP; in subsequent age categories 50% of switchers revert to smoking and 50% remain MRTP users (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	Mean	95%	PI
0	-862.00	-996.20	-720.80
1	-280.90	-324.90	-231.30
2	268.20	161.90	388.90
3	787.00	579.00	1,014.00
4	1,277.00	968.80	1,604.00
5	1,740.00	1,336.00	2,164.00

Table 9.3: B1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case smoking quitters switch to the MRTP; in subsequent age categories 50% of switchers revert to smoking and 50% remain MRTP users (results shown for age category 68-72)

Base case continuing smokers switching to MRTP (%)	**Mean**	**95% PI**	
0	-1,724.00	-1,992.00	-1,442.00
1	-1,124.00	-1,281.00	-952.20
2	-557.40	-644.50	-459.80
3	-21.11	-138.00	118.00
4	486.10	285.50	714.90
5	965.70	672.90	1,293.00

Table 10: B2.i.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case never tobacco users initiate the MRTP; all switch to smoking in the next age category

	1%			5%			10%		
Age	**Mean**	**95% PI**		**Mean**	**95% PI**		**Mean**	**95% PI**	
33 - 37	-135.90	-171.40	-106.80	-665.10	-839.20	-522.40	-1,294.00	-1,634.00	-1,016.00
38 - 42	-279.60	-351.20	-218.80	-1,361.00	-1,711.00	-1,065.00	-2,632.00	-3,312.00	-2,057.00
43 - 47	-493.30	-621.30	-380.40	-2,394.00	-3,017.00	-1,845.00	-4,610.00	-5,815.00	-3,550.00
48 - 52	-782.50	-985.50	-596.20	-3,789.00	-4,775.00	-2,884.00	-7,276.00	-9,177.00	-5,534.00
53 - 57	-1,139.00	-1,435.00	-852.60	-5,505.00	-6,939.00	-4,118.00	-10,550.00	-13,300.00	-7,883.00
58 - 62	-1,528.00	-1,925.00	-1,131.00	-7,375.00	-9,298.00	-5,457.00	-14,110.00	-17,800.00	-10,430.00
63 - 67	-1,872.00	-2,371.00	-1,370.00	-9,028.00	-11,440.00	-6,604.00	-17,250.00	-21,860.00	-12,600.00
68 - 72	-2,041.00	-2,626.00	-1,455.00	-9,833.00	-12,660.00	-7,001.00	-18,760.00	-24,150.00	-13,340.00

Table 11: B2.i.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case never tobacco users initiate the MRTP; in subsequent age categories 50% of MRTP users switch to smoking and 50% remain MRTP users

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	-92.75	-116.80	-72.89	-454.10	-572.00	-356.80	-884.60	-1,115.00	-695.00
38 - 42	-203.00	-253.80	-159.50	-989.10	-1,237.00	-776.40	-1,915.00	-2,397.00	-1,502.00
43 - 47	-379.30	-473.20	-295.80	-1,842.00	-2,299.00	-1,435.00	-3,549.00	-4,435.00	-2,763.00
48 - 52	-632.10	-788.20	-487.10	-3,062.00	-3,821.00	-2,358.00	-5,883.00	-7,347.00	-4,530.00
53 - 57	-960.30	-1,196.00	-733.60	-4,643.00	-5,785.00	-3,545.00	-8,900.00	-11,100.00	-6,793.00
58 - 62	-1,339.00	-1,667.00	-1,012.00	-6,464.00	-8,050.00	-4,884.00	-12,370.00	-15,410.00	-9,340.00
63 - 67	-1,702.00	-2,117.00	-1,285.00	-8,208.00	-10,210.00	-6,194.00	-15,680.00	-19,520.00	-11,820.00
68 - 72	-1,927.00	-2,427.00	-1,429.00	-9,282.00	-11,700.00	-6,875.00	-17,700.00	-22,320.00	-13,100.00

Table 12: B2.ii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking initiators initiate the MRTP instead; all switch to smoking in the next age category

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	10.62	7.75	14.34	53.08	38.80	71.71	106.20	77.59	143.40
38 - 42	14.76	10.49	20.26	73.82	52.47	101.30	147.60	104.90	202.60
43 - 47	19.10	13.20	26.63	95.51	65.98	133.10	191.00	132.00	266.30
48 - 52	23.18	15.52	32.40	115.90	77.58	162.00	231.80	155.20	324.00
53 - 57	26.30	17.03	36.88	131.50	85.14	184.40	263.00	170.30	368.80
58 - 62	27.57	17.28	38.88	137.90	86.38	194.40	275.70	172.80	388.80
63 - 67	26.01	15.33	37.57	130.00	76.63	187.90	260.10	153.30	375.70
68 - 72	20.93	10.49	32.07	104.70	52.47	160.40	209.30	104.90	320.70

Table 13: B2.ii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking initiators initiate the MRTP instead; in subsequent age categories 50% of MRTP users switch to smoking and 50% remain MRTP users

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	16.02	11.95	21.19	80.09	59.75	105.90	160.20	119.50	211.90
38 - 42	23.55	17.10	31.58	117.70	85.49	157.90	235.50	171.00	315.80
43 - 47	31.54	22.23	42.93	157.70	111.20	214.70	315.40	222.30	429.30
48 - 52	39.05	26.54	53.55	195.30	132.70	267.70	390.50	265.40	535.50
53 - 57	44.71	29.14	61.81	223.60	145.70	309.00	447.10	291.40	618.10
58 - 62	46.70	28.75	65.93	233.50	143.70	329.70	467.00	287.50	659.30
63 - 67	43.04	23.73	63.61	215.20	118.60	318.00	430.40	237.30	636.10
68 - 72	32.32	12.55	53.03	161.60	62.74	265.10	323.20	125.50	530.30

Table 14.1: B2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base never tobacco users initiate the MRTP instead; all switch to smoking in the next age category (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	**Mean**	**95%**	**PI**
0	-2,041.00	-2,626.00	-1,455.00
50	-999.20	-1,172.00	-820.10
100	43.17	-459.40	621.40

Table 14.2: B2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case never tobacco users initiate the MRTP instead; all switch to smoking in the next age category (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	**Mean**	**95%**	**PI**
0	-9,833.00	-12,660.00	-7,001.00
50	-8,807.00	-11,140.00	-6,465.00
100	-7,782.00	-9,613.00	-5,924.00

Table 14.3: B2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case never tobacco users initiate the MRTP instead; all switch to smoking in the next age category (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-18,760.00	-24,150.00	-13,340.00
50	-17,750.00	-22,670.00	-12,820.00
100	-16,750.00	-21,190.00	-12,290.00

Table 15.1: B2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%of base case never tobacco users initiate the MRTP instead; in subsequent age categories 50% of MRTP users switch to smoking and 50% remain MRTP users (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-1,927.00	-2,427.00	-1,429.00
50	-317.20	-853.90	273.80
100	1,293.00	-210.20	2,896.00

Table 15.2: B2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5%of base case never tobacco users initiate the MRTP instead; in subsequent age categories 50% of MRTP users switch to smoking and 50% remain MRTP users (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-9,282.00	-11,700.00	-6,875.00
50	-7,696.00	-9,210.00	-6,149.00
100	-6,109.00	-7,018.00	-5,174.00

Table 15.3: B2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10%of base case never tobacco users initiate the MRTP instead; in subsequent age categories 50% of MRTP users switch to smoking and 50% remain MRTP users (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95% PI	
0	-17,700.00	-22,320.00	-13,100.00
50	-16,150.00	-19,820.00	-12,420.00
100	-14,590.00	-17,450.00	-11,670.00

Table 16: E1.i.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter

	1%			5%			10%		
Age	Mean	95% PI		Mean	95% PI		Mean	95% PI	
33 - 37	-22.37	-28.92	-17.12	-108.40	-140.20	-82.85	-208.20	-269.70	-159.00
38 - 42	-44.85	-57.55	-34.63	-216.50	-278.10	-167.00	-414.00	-532.60	-318.80
43 - 47	-82.20	-104.80	-63.99	-396.00	-505.50	-308.10	-755.50	-965.50	-587.20
48 - 52	-140.50	-176.90	-109.80	-676.30	-852.10	-527.70	-1,289.00	-1,626.00	-1,005.00
53 - 57	-226.10	-280.60	-179.00	-1,088.00	-1,351.00	-861.00	-2,071.00	-2,574.00	-1,637.00
58 - 62	-343.00	-417.80	-276.40	-1,650.00	-2,012.00	-1,329.00	-3,142.00	-3,834.00	-2,529.00
63 - 67	-488.00	-582.30	-399.80	-2,348.00	-2,804.00	-1,923.00	-4,471.00	-5,340.00	-3,661.00
68 - 72	-640.50	-757.20	-527.80	-3,082.00	-3,646.00	-2,541.00	-5,873.00	-6,950.00	-4,838.00

Table 17: E1.i.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category (2%, 10%, 20%); no initiation after age category 3

	1%			5%			10%		
Age	**Mean**	**95% PI**		**Mean**	**95% PI**		**Mean**	**95% PI**	
33 - 37	-31.52	-41.18	-23.88	-151.50	-198.20	-114.70	-288.20	-377.90	-217.60
38 - 42	-61.11	-79.28	-46.63	-292.20	-379.80	-222.60	-551.90	-718.80	-419.60
43 - 47	-110.20	-141.80	-84.89	-525.60	-676.90	-404.00	-989.20	-1,277.00	-759.40
48 - 52	-187.20	-238.00	-145.20	-891.50	-1,135.00	-690.10	-1,675.00	-2,136.00	-1,294.00
53 - 57	-300.90	-375.60	-236.30	-1,432.00	-1,789.00	-1,122.00	-2,689.00	-3,365.00	-2,103.00
58 - 62	-457.40	-559.70	-366.50	-2,177.00	-2,667.00	-1,740.00	-4,089.00	-5,019.00	-3,267.00
63 - 67	-653.20	-781.80	-534.00	-3,111.00	-3,725.00	-2,542.00	-5,847.00	-7,008.00	-4,774.00
68 - 72	-862.20	-1,022.00	-708.30	-4,109.00	-4,872.00	-3,375.00	-7,730.00	-9,163.00	-6,347.00

Table 18: E1.ii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking initiators initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	25.48	19.43	33.06	127.40	97.13	165.30	254.80	194.30	330.60
38 - 42	43.22	32.49	56.17	216.10	162.40	280.90	432.20	324.90	561.70
43 - 47	66.48	49.12	86.84	332.40	245.60	434.20	664.80	491.20	868.40
48 - 52	94.48	68.21	123.30	472.40	341.10	616.70	944.80	682.10	1,233.00
53 - 57	124.70	88.05	162.90	623.60	440.20	814.60	1,247.00	880.50	1,629.00
58 - 62	152.10	104.20	200.50	760.40	521.00	1003.00	1,521.00	1,042.00	2,005.00
63 - 67	168.00	110.40	225.80	840.10	552.20	1129.00	1,680.00	1,104.00	2,258.00
68 - 72	160.90	94.34	227.60	804.50	471.70	1138.00	1,609.00	943.40	2,276.00

Table 19: E1.ii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking initiators initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category (2%, 10%, 20%); no initiation after age category 3

	1%			5%			10%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	43.61	33.11	56.79	218.10	165.50	284.00	436.10	331.10	567.90
38 - 42	72.95	54.63	95.17	364.80	273.10	475.80	729.50	546.30	951.70
43 - 47	111.10	81.76	145.60	555.40	408.80	728.00	1,111.00	817.60	1,456.00
48 - 52	156.60	112.70	205.10	783.10	563.30	1,025.00	1,566.00	1,127.00	2,051.00
53 - 57	205.40	144.50	269.10	1,027.00	722.30	1,346.00	2,054.00	1,445.00	2,691.00
58 - 62	249.00	170.00	329.00	1,245.00	850.20	1,645.00	2,490.00	1,700.00	3,290.00
63 - 67	273.60	179.20	368.70	1,368.00	896.00	1,843.00	2,736.00	1,792.00	3,687.00
68 - 72	260.60	152.00	369.60	1,303.00	759.80	1,848.00	2,606.00	1,520.00	3,696.00

Table 20.1: E1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case never tobacco users initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95% PI	
0	-640.50	-757.20	-527.80
2	-320.00	-450.60	-187.00
4	0.48	-234.70	239.70
6	321.00	-35.92	687.70
8	641.50	155.10	1,139.00

Table 20.2: E1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case never tobacco users initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95% PI	
0	-3,082.00	-3,646.00	-2,541.00
5	-2,294.00	-2,799.00	-1,796.00
10	-1,506.00	-2,147.00	-855.70
15	-717.90	-1,591.00	185.20
20	70.23	-1,090.00	1,251.00
25	858.40	-594.00	2,338.00
30	1,647.00	-116.40	3,460.00
35	2,435.00	356.30	4,557.00
40	3,223.00	822.90	5,670.00

Table 20.3: E1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95% PI	
0	-5,873.00	-6,950.00	-4,838.00
25	-2,014.00	-3,476.00	-497.00
50	1,846.00	-1,022.00	4,767.00
75	5,706.00	1,291.00	10,200.00

Table 21.1: E1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case never tobacco users initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category; no initiation after age category 3 (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95% PI	
0	-862.20	-1022.00	-708.30
2	-542.90	-702.70	-379.40
4	-223.70	-470.70	32.02
6	95.62	-269.10	464.70
8	414.90	-68.59	912.30
10	734.20	122.20	1,360.00

Table 21.2: E1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case never tobacco users initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category; no initiation after age category 3 (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95% PI	
0	-4,109.00	-4,872.00	-3,375.00
5	-3,336.00	-4,041.00	-2,649.00
10	-2,563.00	-3,336.00	-1,767.00
15	-1,790.00	-2,755.00	-799.70
20	-1,017.00	-2,223.00	227.60
25	-244.40	-1,725.00	1,262.00
30	528.50	-1,248.00	2,324.00
35	1,301.00	-754.80	3,395.00
40	2,074.00	-281.50	4,495.00
45	2,847.00	186.00	5,583.00

Table 21.3: E1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category; no initiation after age category 3 (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-7,730.00	-9,163.00	-6,347.00
25	-4,023.00	-5,695.00	-2,317.00
50	-314.80	-3,175.00	2,602.00
75	3,393.00	-852.90	7,768.00
100	7,101.00	1,340.00	12,970.00

Table 22: E2.i.a. Mean difference in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior interval; 1%, 5%, 10% of base case smoking initiators initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter

	1%			5%			10%		
Age Category	**Mean**	**95% PI**		**Mean**	**95% PI**		**Mean**	**95% PI**	
33 - 37	-17.98	-23.27	-13.80	-86.79	-112.50	-66.53	-166.00	-215.50	-127.10
38 - 42	-32.78	-42.41	-25.03	-157.50	-204.10	-120.10	-299.50	-388.50	-228.20
43 - 47	-55.18	-71.20	-41.81	-264.50	-341.60	-200.20	-501.00	-648.10	-379.10
48 - 52	-87.86	-112.50	-66.55	-420.50	-539.00	-318.30	-795.30	-1,021.00	-601.80
53 - 57	-133.70	-169.80	-101.60	-639.80	-813.00	-486.00	-1,209.00	-1,538.00	-918.60
58 - 62	-195.00	-244.20	-149.80	-933.20	-1,169.00	-717.00	-1,765.00	-2,211.00	-1,356.00
63 - 67	-270.40	-331.40	-212.10	-1,295.00	-1,587.00	-1,016.00	-2,452.00	-3,005.00	-1,926.00
68 - 72	-350.20	-422.60	-280.10	-1,679.00	-2,026.00	-1,343.00	-3,183.00	-3,839.00	-2,549.00

Table 23: E2.i.b. Mean difference in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior interval; 1%, 5%, 10% of base case never tobacco users initiate the MRTP instead; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter

	1%			5%			10%		
Age Category	**Mean**	**95% PI**		**Mean**	**95% PI**		**Mean**	**95% PI**	
33 - 37	-18.30	-23.66	-14.08	-88.39	-114.40	-67.92	-169.20	-219.30	-129.80
38 - 42	-34.09	-43.94	-26.17	-164.00	-211.60	-125.80	-312.10	-403.30	-239.10
43 - 47	-59.04	-75.65	-45.19	-283.30	-363.40	-216.70	-537.70	-690.60	-411.10
48 - 52	-97.02	-123.30	-74.43	-465.10	-591.80	-356.80	-881.70	-1,123.00	-676.30
53 - 57	-152.50	-191.40	-118.40	-730.90	-917.50	-567.20	-1,385.00	-1,739.00	-1,075.00
58 - 62	-229.00	-282.60	-179.90	-1,098.00	-1,355.00	-862.80	-2,082.00	-2,570.00	-1,636.00
63 - 67	-325.90	-393.00	-261.70	-1,564.00	-1,885.00	-1,256.00	-2,968.00	-3,576.00	-2,385.00
68 - 72	-431.30	-513.10	-352.00	-2,071.00	-2,465.00	-1,692.00	-3,936.00	-4,681.00	-3,216.00

Table 24: E2.ii.a. Mean difference in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior interval; 1%, 5%, 10% of base case never tobacco users initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter

	1%			5%			10%		
Age Category	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	26.07	19.93	33.80	130.30	99.67	169.00	260.70	199.30	338.00
38 - 42	44.72	33.84	58.09	223.60	169.20	290.40	447.20	338.40	580.90
43 - 47	69.69	51.90	90.69	348.40	259.50	453.50	696.90	519.00	906.90
48 - 52	100.50	73.78	130.70	502.60	368.90	653.60	1,005.00	737.80	1,307.00
53 - 57	135.00	97.60	175.00	675.20	488.00	874.80	1,350.00	976.00	1,750.00
58 - 62	168.30	119.40	218.20	841.50	597.20	1,091.00	1,683.00	1,194.00	2,182.00
63 - 67	191.50	133.20	250.80	957.30	666.00	1,254.00	1,915.00	1,332.00	2,508.00
68 - 72	191.70	125.90	258.30	958.50	629.30	1,291.00	1,917.00	1,259.00	2,583.00

Table 25: E2.ii.b. Mean difference in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior interval; 1%, 5%, 10% of base case smoking initiators initiate the MRTP; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter

	1%			5%			10%		
Age Category	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	26.02	19.89	33.74	130.10	99.45	168.70	260.20	198.90	337.40
38 - 42	44.55	33.69	57.86	222.70	168.50	289.30	445.50	336.90	578.60
43 - 47	69.20	51.48	90.11	346.00	257.40	450.50	692.00	514.80	901.10
48 - 52	99.42	72.82	129.50	497.10	364.10	647.30	994.20	728.20	1,295.00
53 - 57	132.90	95.64	172.50	664.40	478.20	862.70	1,329.00	956.40	1,725.00
58 - 62	164.50	116.00	213.90	822.40	579.80	1,070.00	1,645.00	1,160.00	2,139.00
63 - 67	185.40	127.40	244.30	926.80	636.90	1,221.00	1,854.00	1,274.00	2,443.00
68 - 72	183.00	117.00	249.40	914.90	585.10	1,247.00	1,830.00	1,170.00	2,494.00

Table 26.1: E2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case never tobacco users initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-350.20	-422.60	-280.10
1	-159.20	-194.90	-122.60
2	31.70	-46.59	110.80
3	222.60	81.27	365.40
4	413.60	207.50	619.70
5	604.50	332.30	874.50

Table 26.2: E2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case never tobacco users initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-1,679.00	-2,026.00	-1,343.00
2	-1,303.00	-1,548.00	-1,069.00
4	-927.50	-1,107.00	-750.30
6	-551.80	-745.80	-348.10
8	-176.10	-458.20	115.60
10	199.50	-193.00	595.70
12	575.20	61.39	1,096.00
14	950.90	310.80	1,597.00

Table 26.3: E2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case never tobacco users initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-3,183.00	-3,839.00	-2,549.00
5	-2,263.00	-2,679.00	-1,866.00
10	-1,343.00	-1,684.00	-991.50
15	-423.00	-937.10	112.20
20	497.00	-293.40	1,294.00
25	1,417.00	331.10	2,520.00
30	2,337.00	939.30	3,752.00

Table 27.1: E2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% of base case never tobacco users initiate the MRTP instead; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-431.30	-513.10	-352.00
1	-249.00	-300.20	-196.70
2	-66.78	-153.40	23.10
3	115.50	-29.38	264.00
4	297.70	89.32	509.80
5	479.90	207.30	756.10

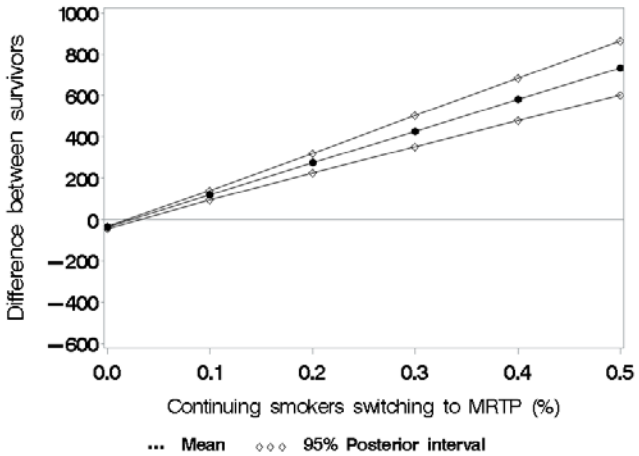
Table 27.2: E2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 5% of base case never tobacco users initiate the MRTP instead; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-2,071.00	-2,465.00	-1,692.00
2	-1,713.00	-2,016.00	-1,420.00
4	-1,354.00	-1,607.00	-1,102.00
6	-995.50	-1,259.00	-720.00
8	-637.00	-968.50	-290.30
10	-278.40	-710.00	168.20
12	80.15	-459.00	634.40
14	438.70	-222.40	1,115.00
16	797.30	17.26	1,592.00
20	1,514.00	479.50	2,565.00

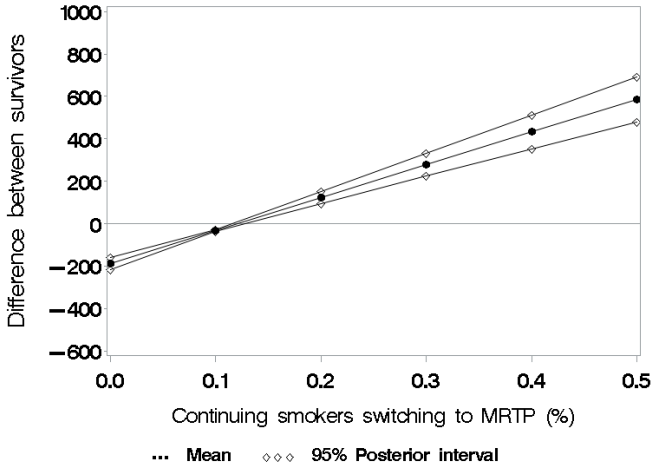
Table 27.3: E2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 10% of base case never tobacco users initiate the MRTP instead; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Base case smoking initiators initiating MRTP (%)	Mean	95%	PI
0	-3,936.00	-4,681.00	-3,216.00
5	-3,058.00	-3,601.00	-2,526.00
10	-2,180.00	-2,661.00	-1,683.00
15	-1,302.00	-1,916.00	-660.10
20	-423.70	-1,284.00	464.50
25	454.30	-677.30	1,606.00
30	1,332.00	-94.43	2,793.00
35	2,210.00	479.00	3,983.00
40	3,088.00	1,039.00	5,171.00

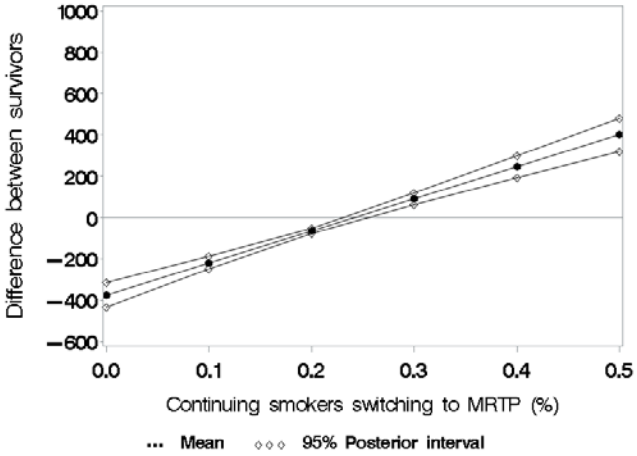
Appendix C:
Selected Graphical Summaries



(1.1) 1% of base case smoking quitters switch to the MRTP

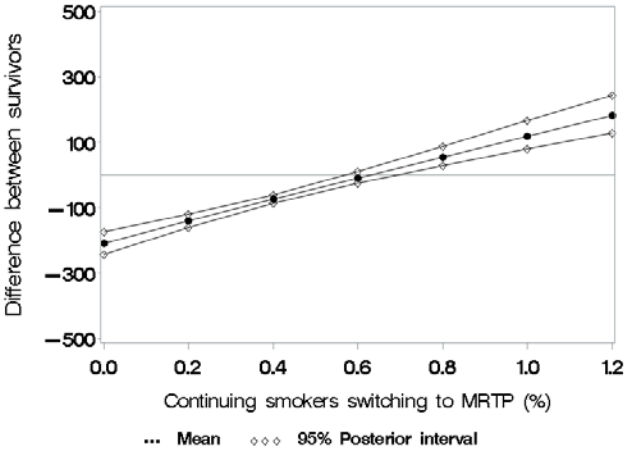


(1.2) 5% of base case smoking quitters switch to the MRTP

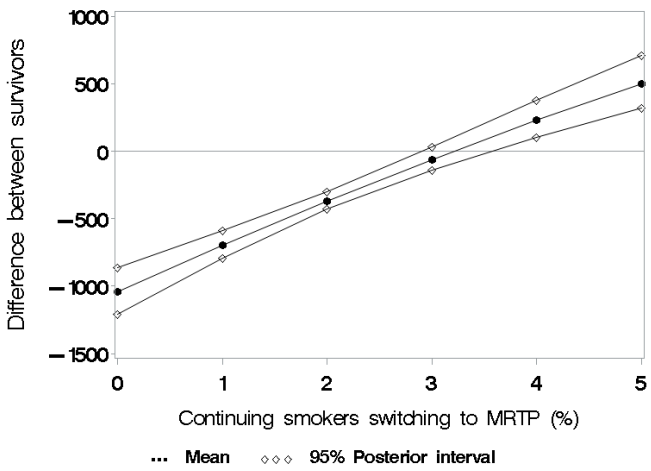


(1.3) 10% of base case smoking quitters switch to the MRTP

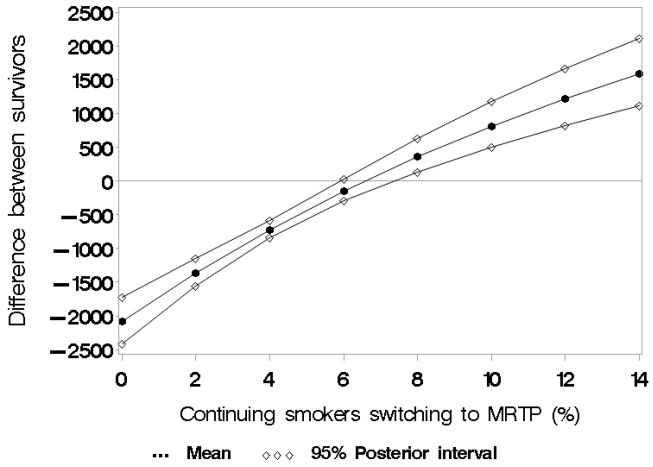
Figure 1: A.iii. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP and continue MRTP use (results shown for age category 68-72)



(2.1) 1% of base case smoking quitters switch to the MRTP

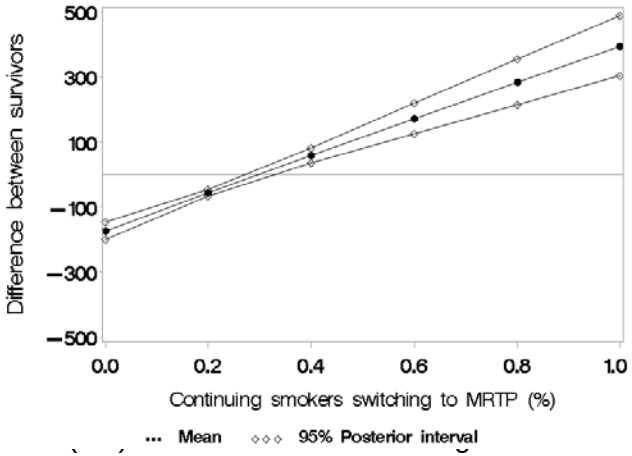


(2.2) 5% of base case smoking quitters switch to the MRTP

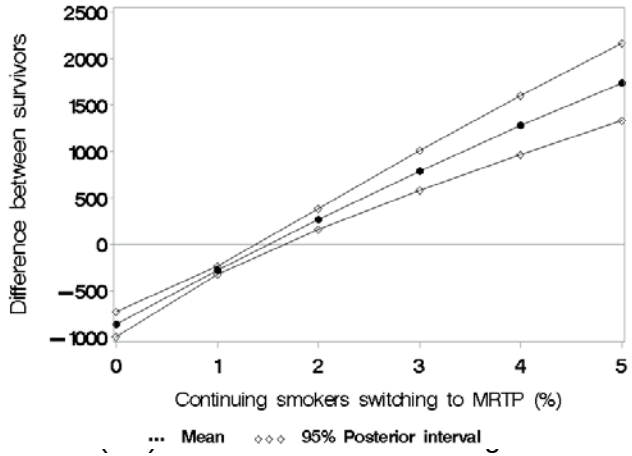


(2.3) 10% of base case smoking quitters switch to the MRTP

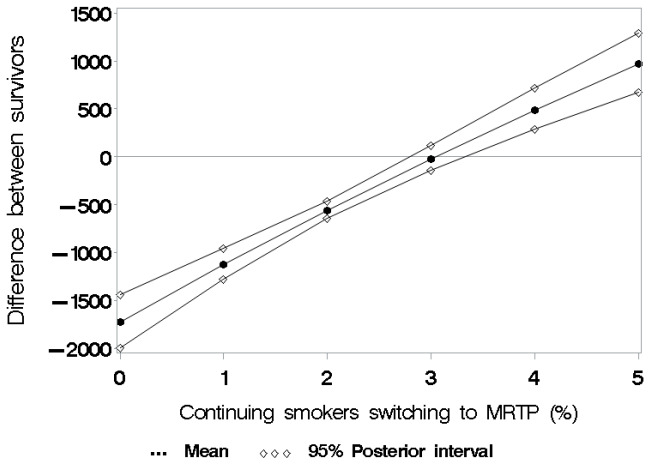
Figure 2: B1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP; all revert to smoking in the next age category (results shown for age category 68-72)



(3.1) 1% of base case smoking quitters switch to the MRTP

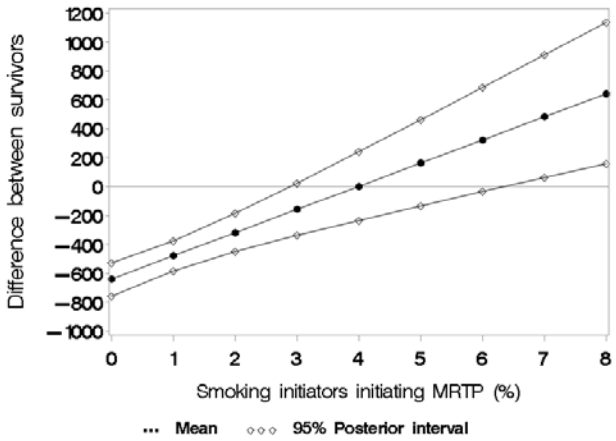


(3.2) 5% of base case smoking quitters switch to the MRTP

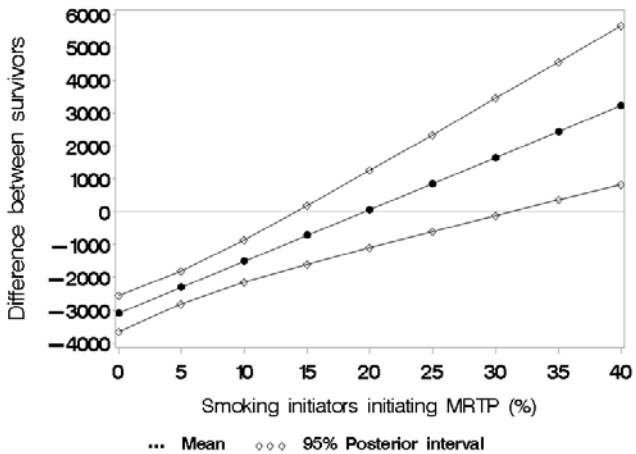


(3.3) 10% of base case smoking quitters switch to the MRTP

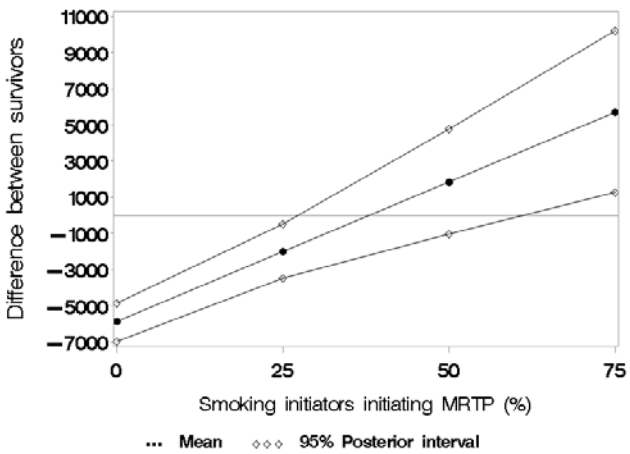
Figure 3: B1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case smoking quitters switch to the MRTP; in subsequent age categories 50% of switchers revert to smoking and 50% remain MRTP users (results shown for age category 68-72)



(4.1) 1% of base case never tobacco users initiate the MRTP

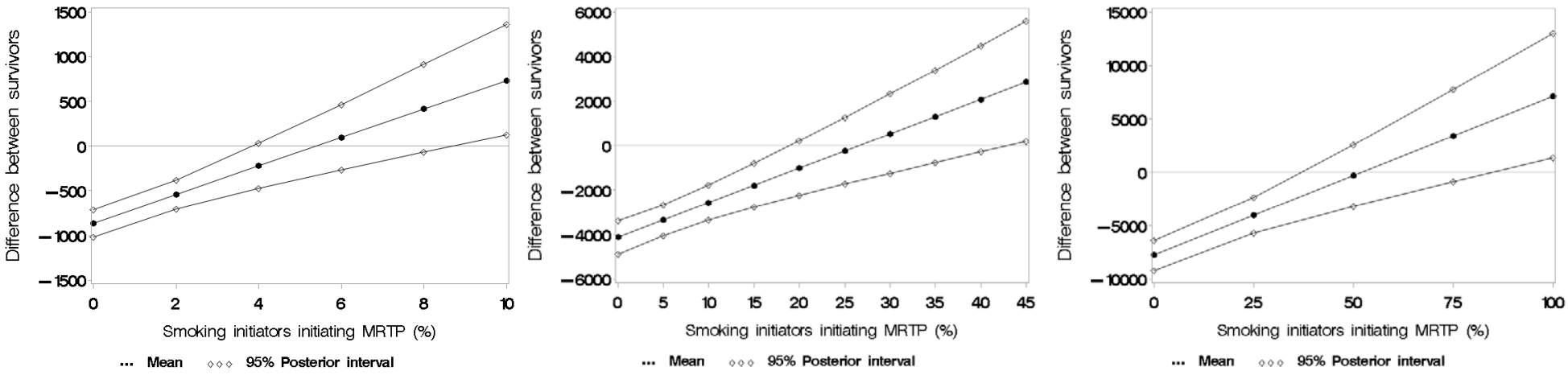


(4.2) 5% of base case never tobacco users initiate the MRTP



(4.3) 10% of base case never tobacco users initiate the MRTP

Figure 4: E1.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1%, 5%, 10% of base case never tobacco users initiate the MRTP instead and continue MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

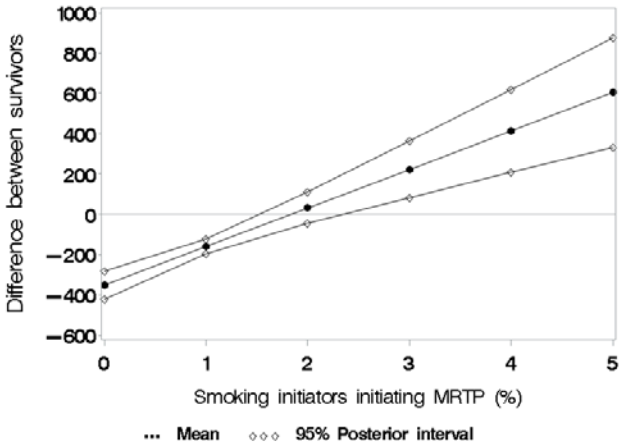


(5.1) 1% of base case never tobacco users initiate the MRTP

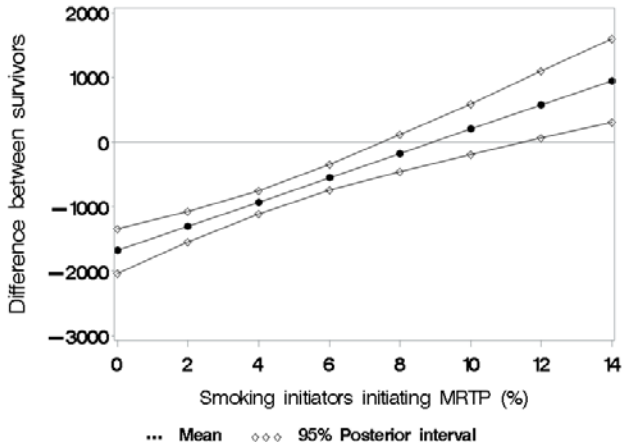
(5.2) 5% of base case never tobacco users initiate the MRTP

(5.3) 10% of base case never tobacco users initiate the MRTP

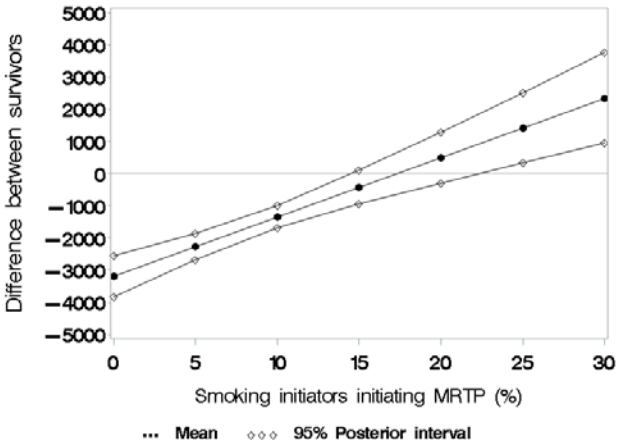
Figure 5: E1.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% (5%, 10%) of base case never tobacco users initiate the MRTP instead and continue MRTP use; MRTP initiation rate doubled in the first age category; no initiation after age category 3 (results shown for age category 68-72)



(6.1) 1% of base case never tobacco users initiate the MRTP

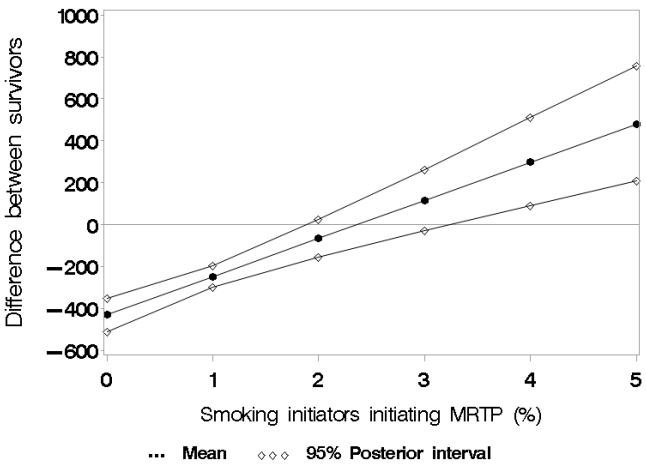


(6.2) 5% of base case never tobacco users initiate the MRTP

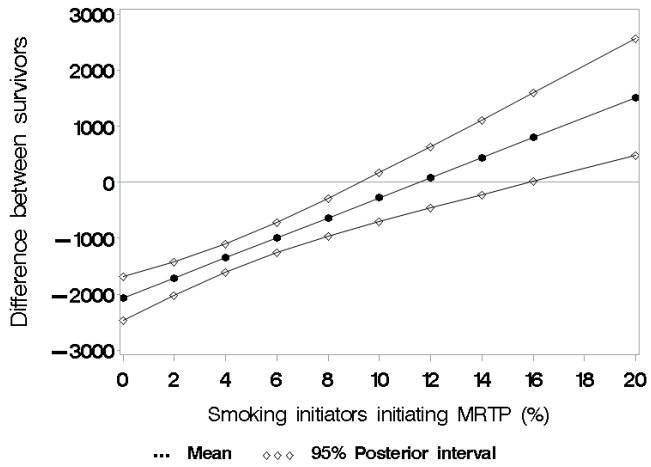


(6.3) 10% of base case never tobacco users initiate the MRTP

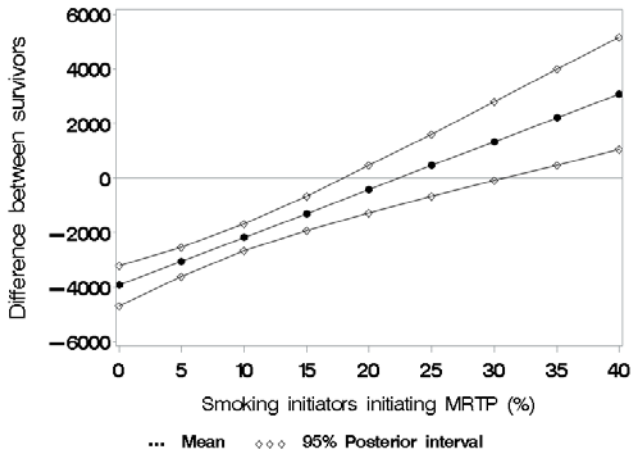
Figure 6: E2.iii.a. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% (5%, 10%) of base case never tobacco users initiate the MRTP instead; 25% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)



(7.1) 1% of base case never tobacco users initiate the MRTP



(7.2) 5% of base case never tobacco users initiate the MRTP



(7.3) 10% of base case never tobacco users initiate the MRTP

Figure 7: E2.iii.b. Mean differences in the number of survivors between the counterfactual and base case scenario at the end of follow-up and 95% posterior intervals; 1% (5%, 10%) of base case never tobacco users initiate the MRTP instead; 50% of MRTP quitters resuming MRTP use; constant MRTP initiation rates in the first 3 age categories; no initiation thereafter (results shown for age category 68-72)

Appendix D:

Selected Tipping Point Analyses

Table 1: Tipping points for base case continuing smokers switching to MRTP versus base case smoking quitters switching to MRTP

Base case smoking quitters switching to MRTP			**1%**			**5%**			**10%**		
			Approximate proportion of base case continuing smokers switching to MRTP needed for								
Scenario	**% reverting to smoking**	**% continuing MRTP use**	**Stat. sign. survival deficit**	**No survival deficit or benefit**	**Stat. sign. survival benefit**	**Stat. sign. survival deficit**	**No survival deficit or benefit**	**Stat. sign. survival benefit**	**Stat. sign. survival deficit**	**No survival deficit or benefit**	**Stat. sign. survival benefit**
A	0%	100%	<0.01%	0.025%	>0.05%	<0.1%	0.125%	>0.15	<0.2%	0.25%	>0.275%
B.1.b	50%	50%	<0.25%	0.3%	>0.4%	<1.25%	1.5%	>1.75	<2.75%	3.0%	>3.5%
B.1.a	100%	0%	<0.5%	0.6%	>0.8%	<2.5%	3.0%	>4.0	<5.75%	6.0%	>8%

Table 2: Tipping points for base case never tobacco users initiating MRTP versus base case smoking initiators initiating MRTP; table entries are the proportion of base case smoking initiators initiating MRTP necessary to eliminate the survival deficit caused by some base case never tobacco users initiating MRTP instead

Base case never tobacco users initiating MRTP			**1%**			**5%**			**10%**		
			Approximate proportion of base case smoking initiators initiating MRTP needed for								
Scenario	**% switching to smoking**	**% continuing MRTP use**	**Stat. sign. survival deficit**	**No survival deficit or benefit**	**Stat. sign. survival benefit**	**Stat. sign. survival deficit**	**No survival deficit or benefit**	**Stat. sign. survival benefit**	**Stat. sign. survival deficit**	**No survival deficit or benefit**	**Stat. sign. survival benefit**
E.1.a[1]	0%	100%	<3.0%	4.0%	>7.0%	<14%	20%	>30%	<25%	40%	>60%
E.1.b[2]	0%	100%	<4.0%	5.0%	>9.0%	<20%	25%	>45%	<35%	50%	>80%
E.2.a[1,3]	0%	100%	<1.5%	2.0%	>2.5%	<7%	9%	>12%	<14%	18%	>25%
E.2.b[2,4]	0%	100%	<1.75%	2.5%	>3.5%	<9%	12%	>16%	<18%	24%	>30%
B.2.b[1,#]	50%	50%	<60.0%	-	-	≤100%	-	-	≤100%	-	-
B.2.a[1,#]	100%	0%	<100.0%	-	-	≤100%	-	-	≤100%	-	-

[1] Constant MRTP initiation rates in the first 3 age categories; no initiation thereafter; no MRTP quitting

[2] MRTP initiation rate doubled in the first age category; no initiation after age category 3; no MRTP quitting

[3] Some MRTP users subsequently **quit** (same age-specific smoking cessation rates as were used in the base case (US 2006 estimates) are applied to the MRTP users) and 25% of MRTP quitters resume MRTP

[4] Some MRTP users subsequently **quit** (same age-specific smoking cessation rates as were used in the base case (US 2006 estimates) are applied to the MRTP users) and 50% of MRTP quitters resume MRTP

[#] Too few smoking initiators to reach a tipping point

Appendix E:

Comparisons Between Counterfactuals Based on Swedish Exposure Distributions and US Base Case

Table 1. Mean difference in number of survivors with 95% posterior intervals (95% PI) for the "Swedish counterfactual[a]" vs. US base case exposure scenario[b]; excess relative risk (ERR) 0.11 and 0.055

	ERR=0.11			ERR=0.055		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 – 37	484.92	312.67	676.14	570.73	384.22	779.32
38 – 42	1,118.75	747.17	1,520.80	1,273.00	882.12	1,703.34
43 – 47	2,206.57	1,525.76	2,928.51	2,456.65	1,745.71	3,221.57
48 – 52	3,887.20	2,791.96	5,040.65	4,263.44	3,133.47	5,473.68
53 – 57	6,261.81	4,658.72	7,896.27	6,794.58	5,145.11	8,491.37
58 – 62	9,331.69	7,189.15	11,447.80	10,045.30	7,859.40	12,227.40
63 – 67	12,901.70	10,317.10	15,448.40	13,802.70	11,165.50	16,418.50
68 – 72	16,448.30	13,398.40	19,424.10	17,506.10	14,421.70	20,532.00

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case is shown in Appendix A, Table 5.

Table 2a: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of MRTP initiation is reduced to 10%, 25%, 50% of Swedish value, vs. the US base case[b]: ERR=0.11

	Proportion of "Swedish counterfactual"[c] MRTP initiation value[c]								
		10%			**25%**			**50%**	
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	475.69	305.75	665.22	476.94	306.61	666.71	479.27	308.31	669.52
38 - 42	1,121.52	750.45	1,521.96	1,120.40	749.40	1,520.93	1,119.12	748.10	1,519.96
43 - 47	2,235.16	1,555.60	2,958.01	2,229.20	1,549.15	2,952.01	2,220.34	1,540.01	2,943.70
48 - 52	3,959.30	2,869.07	5,121.34	3,945.38	2,855.54	5,105.94	3,923.89	2,832.58	5,082.08
53 - 57	6,397.33	4,807.77	8,021.72	6,371.99	4,777.70	7,999.81	6,332.22	4,732.95	7,962.10
58 - 62	9,547.06	7,423.53	11,653.70	9,507.51	7,380.34	11,618.70	9,444.88	7,315.10	11,565.00
63 - 67	13,196.90	10,647.20	15,728.00	13,143.3	10,590.30	15,673.20	13,058.00	10,496.00	15,591.50
68 - 72	16,784.00	13,814.80	19,707.80	16,723.5	13,732.80	19,648.90	16,626.90	13,612.30	19,576.70

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case is shown in Appendix A, Table 5

c. Among base case never smokers and base case smoking initiators

Table 2b: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of MRTP initiation is reduced to 10%, 25%, 50% of Swedish value, vs. the US base case[b]: ERR=0.055

	Proportion of "Swedish counterfactual"[c] MRTP initiation value[c]								
	10%			**25%**			**50%**		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	503.63	326.03	700.74	514.75	335.62	714.05	533.33	352.09	735.54
38 - 42	1,178.79	793.67	1,595.16	1,194.27	807.32	1,612.11	1,220.26	831.10	1,641.99
43 - 47	2,337.95	1,635.15	3,085.97	2,357.26	1,652.62	3,106.84	2,389.86	1,682.87	3,143.88
48 - 52	4,127.57	3,006.05	5,326.62	4,149.38	3,026.72	5,349.46	4,186.49	3,064.09	5,389.51
53 - 57	6,654.10	5,021.49	8,331.23	6,676.24	5,039.87	8,357.50	6,714.29	5,071.43	8,403.37
58 - 62	9,916.44	7,733.54	12,088.60	9,936.18	7,750.65	12,111.30	9,970.64	7,787.48	12,148.60
63 - 67	13,699.60	11,067.30	16,314.40	13,714.70	11,079.50	16,329.60	13,741.80	11,103.80	16,356.60
68 - 72	17,428.10	14,364.10	20,450.00	17,439.10	14,370.20	20,457.10	17,459.20	14,382.00	20,476.10

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case is shown in Appendix A, Table 5

c. Among base case never smokers and base case smoking initiators

Table 3a: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]"where the probability of MRTP initiation is reduced to 10%, 25%, 50% of the Swedish value and the probability of a gateway effect is doubled, vs. the US base case[b]: ERR=0.11

	Proportion of "Swedish counterfactual"[c] MRTP initiation value[c]								
		10%			25%			50%	
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	474.69	304.94	664.07	474.43	304.63	663.83	474.29	304.32	663.74
38 - 42	1,119.04	748.58	1,518.77	1,114.21	744.90	1,513.06	1,106.82	738.33	1,505.72
43 - 47	2,229.95	1,551.24	2,952.00	2,216.23	1,537.99	2,937.27	2,194.60	1,518.56	2,913.54
48 - 52	3,949.57	2,861.10	5,110.52	3,921.18	2,835.28	5,076.48	3,875.87	2,788.90	5,026.37
53 - 57	6,380.75	4,792.96	8,003.68	6,330.74	4,741.74	7,955.07	6,250.43	4,660.17	7,866.34
58 - 62	9,521.01	7,400.09	11,624.20	9,442.72	7,323.22	11,547.40	9,316.47	7,201.34	11,420.60
63 - 67	13,159.30	10,615.00	15,686.00	13,049.80	10,503.10	15,570.80	12,872.70	10,327.10	15,387.40
68 - 72	16,734.80	13,765.30	19,651.80	16,601.30	13,619.20	19,516.20	16,384.80	13,388.30	19,313.00

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case shown in Appendix A, Table 5

c. Among base case never smokers and base case smoking initiators

Table 3b: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of MRTP initiation is reduced to 10%, 25%, 50% of the Swedish value and the probability of a gateway effect is doubled, vs. the US base case[b]: ERR=0.055

	Proportion of "Swedish counterfactual"[c] MRTP initiation value[c]								
	10%			**25%**			**50%**		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	502.57	325.30	699.32	512.11	333.45	710.81	528.08	347.96	729.28
38 - 42	1,176.18	791.52	1,592.25	1,187.77	801.83	1,605.02	1,207.34	819.56	1,626.52
43 - 47	2,332.50	1,630.22	3,079.80	2,343.69	1,641.00	3,092.22	2,362.93	1,659.31	3,112.32
48 - 52	4,117.43	2,997.04	5,314.12	4,124.16	3,005.99	5,322.37	4,136.45	3,018.21	5,332.72
53 - 57	6,636.87	5,005.50	8,310.70	6,633.39	5,004.40	8,306.58	6,629.33	5,003.00	8,301.84
58 - 62	9,889.45	7,705.67	12,057.40	9,869.06	7,689.33	12,032.50	9,837.61	7,666.49	11,999.50
63 - 67	13,660.70	11,032.60	16,271.40	13,618.00	10,995.40	16,222.70	13,550.10	10,935.90	16,147.90
68 - 72	17,377.30	14,316.70	20,394.30	17,312.80	14,247.90	20,320.60	17,209.10	14,148.50	20,212.10

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case shown in Appendix A, Table 5

c. Among base case never smokers and base case smoking initiators

Table 4a: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of switching to MRTP from cigarettes is reduced to 10%, 25%, 50% of the Swedish value vs. the US base case[b]: ERR=0.11

	Proportion of "Swedish counterfactual"[c] value for switching to MRTP [c]								
	10%			25%			50%		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	144.05	93.56	201.27	203.08	131.38	283.49	299.48	193.28	418.12
38 - 42	360.82	237.63	496.42	494.68	327.42	677.71	710.95	472.89	970.44
43 - 47	768.96	521.54	1,036.38	1,027.82	701.55	1,376.49	1,441.61	991.75	1,922.23
48 - 52	1,446.35	1,013.56	1,904.44	1,894.06	1,339.26	2,479.68	2,602.39	1,854.93	3,391.59
53 - 57	2,459.98	1,784.51	3,148.40	3,169.46	2,320.03	4,035.99	4,281.06	3,156.28	5,425.38
58 - 62	3,835.37	2,882.83	4,772.85	4,877.09	3,694.34	6,035.68	6,494.82	4,960.55	8,012.21
63 - 67	5,507.49	4,308.23	6,688.18	6,927.51	5,462.88	8,361.83	9,115.89	7,239.75	10,953.40
68 - 72	7,253.06	5,773.61	8,719.58	9,037.07	7,249.79	10,801.60	11,769.80	9,521.52	13,979.70

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case shown in Appendix A, Table 5

c. Among base case continuing smokers and base case smoking quitters

Table 4b: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of switching to MRTP from cigarettes is reduced to 10%, 25%, 50% of the Swedish value, vs. the US base case[b]: ERR=0.055

	Proportion of "Swedish counterfactual"[c] value for switching to MRTP [c]								
		10%			**25%**			**50%**	
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	211.95	151.13	280.83	274.09	192.25	366.55	375.56	258.82	507.29
38 - 42	476.53	341.65	628.52	617.23	437.20	818.36	844.52	591.53	1,124.91
43 - 47	947.67	687.62	1,236.75	1,219.47	876.33	1,595.28	1,653.85	1,180.39	2,167.65
48 – 52	1,703.13	1,262.20	2,183.31	2,172.93	1,604.68	2,787.59	2,916.05	2,148.11	3,743.62
53 – 57	2,807.25	2,130.25	3,512.37	3,551.65	2,694.05	4,445.14	4,717.71	3,576.07	5,900.24
58 – 62	4,277.97	3,344.22	5,224.91	5,371.52	4,199.79	6,553.66	7,069.35	5,528.40	8,622.42
63 – 67	6,034.07	4,858.74	7,199.57	7,526.63	6,066.06	8,978.15	9,826.26	7,933.60	11,710.40
68 – 72	7,822.78	6,397.17	9,244.79	9,702.17	7,953.26	11,453.80	12,580.40	10,334.50	14,806.00

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case shown in Appendix A, Table 5

c. Among base case continuing smokers and base case smoking quitters

Table 5a: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of switching to MRTP from cigarettes is reduced to 10%, 25%, 50% of the Swedish value and probability of gateway effect is doubled, vs. the US base case[b]: ERR=0.11

	Proportion of "Swedish counterfactual"[c] value for switching to MRTP[c]								
	10%			**25%**			**50%**		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	143.80	93.38	200.93	202.46	130.95	282.72	298.24	192.43	416.56
38 - 42	359.94	236.99	495.29	492.51	325.80	674.94	706.64	469.84	965.14
43 - 47	766.62	519.75	1,033.49	1,022.02	697.21	1,369.47	1,430.19	982.99	1,908.30
48 - 52	1,441.09	1,009.42	1,898.04	1,881.09	1,328.93	2,464.56	2,577.00	1,835.29	3,360.51
53 - 57	2,449.59	1,776.12	3,136.37	3,143.88	2,299.85	4,004.80	4,231.21	3,116.88	5,366.55
58 - 62	3,816.79	2,867.52	4,750.77	4,831.49	3,656.09	5,982.63	6,406.37	4,886.67	7,911.04
63 – 67	5,477.24	4,283.36	6,653.70	6,853.46	5,400.73	8,275.44	8,972.82	7,120.88	10,786.50
68 – 72	7,208.40	5,736.16	8,668.89	8,927.97	7,157.69	10,675.40	11,559.70	9,343.61	13,739.00

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case shown in Appendix A, Table 5

c. Among base case continuing smokers and base case smoking quitters

Table 5b: Mean difference in number of survivors with 95% posterior intervals (95% PI) for alternative "Swedish counterfactuals[a]" where the probability of switching to MRTP from cigarettes is reduced to 10%, 25%, 50% of the Swedish value and probability of gateway effect is doubled, vs. the US base case[b]: ERR=0.055

	Proportion of "Swedish counterfactual"[c] value for switching to MRTP[c]								
	10%			**25%**			**50%**		
Age	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**	**Mean**	**95%**	**PI**
33 - 37	211.69	150.94	280.49	273.45	191.77	365.72	374.27	257.86	505.67
38 - 42	475.62	340.97	627.39	614.97	435.55	815.49	840.05	588.23	1,119.37
43 - 47	945.25	685.84	1,233.82	1,213.46	871.88	1,587.94	1,642.04	1,171.43	2,153.36
48 - 52	1,697.70	1,257.87	2,176.91	2,159.54	1,594.08	2,771.65	2,889.83	2,127.59	3,713.09
53 - 57	2,796.53	2,121.58	3,499.54	3,525.27	2,673.05	4,413.59	4,666.32	3,534.23	5,839.83
58 - 62	4,258.81	3,328.49	5,202.25	5,324.51	4,161.06	6,499.71	6,978.18	5,453.85	8,518.15
63 - 67	6,002.85	4,832.74	7,163.72	7,450.21	6,002.16	8,890.37	9,678.63	7,811.28	11,544.20
68 - 72	7,776.55	6,358.76	9,191.30	9,589.25	7,857.82	11,324.20	12,363.00	10,147.10	14,557.60

a. Exposure distribution for "Swedish counterfactual" is shown in Appendix A, Table 3

b. Exposure distribution for base case shown in Appendix A, Table 5

c. Among base case continuing smokers and base case smoking quitters