PNLSC

Simulation and Sensitivity Analysis Report

PHIM System
Population Health Impact Model

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EXECUTIVE SUMMARY

A Population Health Impact Model (PHIM) has been developed to estimate the reduction in mortality from the four major smoking-related diseases (lung cancer, IHD, stroke and COPD) that would occur over a period following the introduction of a Modified Risk Tobacco Product (MRTP). All the analyses described in this report are based on simulated samples of the US population aged 10-79 years, which in 1990 had a distribution of conventional cigarette (CC) smoking habits based on national data, individual smoking histories then being updated annually for 20 years using Tobacco Transition Probabilities (TTPs) under two alternative scenarios. In the NULL Scenario, where the MRTP is not introduced, there are three smoking groups (never, current, former smokers) and three TTPs (initiation, cessation and re-initiation). In the MRTP Scenario, there are five tobacco use groups (never, current CC, current MRTP, current dual, former) and 15 TTPs, three each for initiation, quitting and re-initiation and six for switching between current tobacco use groups. (Note that in this Executive Summary we use the terms "MRTP users" and "CC smokers" to refer to those who predominantly use the relevant product, with "dual users" being those with a substantial use of both products. Note also that tobacco use refers only to the use of the two products of interest, CCs and MRTPs.)

Based on these simulated tobacco use histories, downloaded national data on population size and mortality, published estimates of the current smoking relative risk and the half-life for quitting (the time following quitting when the excess risk associated with continuing smoking is halved), and estimates of the effective dose relative to CC smoking for MRTP use (F-factor) and for dual use (G-factor), the number of deaths associated with smoking at age 30-79 years can then be estimated under the NULL and MRTP scenarios. The difference between the two estimates then represents the reduction in mortality associated with MRTP introduction.

For the NULL Scenario, predictions of national smoking prevalence up to 2010 derived using the TTPs were shown to be reasonably consistent with published estimates of smoking prevalence over this period from International Smoking Statistics (ISS). Differences observed may partly be due to lack of representativeness in a simulated population followed for 20 years and assumed not to die. The overall percentages of deaths from the four causes of interest which were attributable to smoking estimated by PHIM for the NULL Scenario were also reasonably consistent with estimates published in 2014 by the US Surgeon General. Variations result from the US Surgeon General including deaths at ages 80 or over, and using different RR estimates from ours, particularly for COPD, despite our RR estimates being derived from extensive meta-analyses. The differences do not invalidate the PHIM, seem unlikely to affect conclusions from the simulation and sensitivity analyses, and do not cast doubt on the parameter estimates used for the NULL Scenario.

The sensitivity analyses conducted tested the effect on the estimated reduction in mortality associated with MRTP introduction of varying a wide range of parameters. These included the effective dose factors, the relative risks, the half-lives, the factors by which TTPs are affected by previous tobacco use history, as well as the TTPs used in the MRTP Scenario. The TTPs used in the NULL Scenario, which were found to predict smoking distributions reasonably consistent with national data, were not varied.

A basic analysis used a set of parameters thought to be a suitable starting point given the available evidence. These include an 80% reduction in effective dose for MRTP use (F-factor = 0.2) and a 40% reduction for dual use (G-factor = 0.6, consistent with dual users smoking 50% CCs and 50% MRTPs with no increase in total consumption), relative risk and half-life estimates derived from published meta-analyses, and a set of assumed values of the TTPs in the MRTP Scenario derived, in the absence of empirical data, from educated guesses. The magnitude of effect on tobacco use prevalence in the basic analysis is illustrated by men aged 50-54 years in 1990, at which time there were 29.6% never smokers, 30.3% current smokers and 40.1% former smokers. By 2010, when the

men were aged 70-74 years, the proportions of never users in the NULL and MRTP Scenarios remained the same, and the proportions of former users were similar 47.3% NULL and 45.8% MRTP). However, the make-up of current users was different (23.1% CC in the NULL Scenario, and 17.9% CC, 4.6% MRTP and 2.1% dual in the MRTP Scenario).

In this basic analysis MRTP introduction was associated with a reduction in deaths from the four smoking-associated diseases totalling 35,206 in males and 16,403 in females, representing, respectively 1.5% and 1.3% of all deaths attributable to smoking during 1990-2009 in the US population aged 30-79 years. This compares with a reduction of 19.5% in males and 18.7% in females in one extreme situation where CC smoking is totally replaced by MRTP use, and with a reduction of 26.6% in males and 25.5% in females in another extreme situation where all smokers quit immediately at the time of MRTP introduction, with no further initiation or re-initiation.

In the sensitivity analyses one or more parameters were varied from the values assumed in the basic analysis. Some sensitivity analyses (e.g. varying relative risks) did not affect smoking prevalence in the MRTP Scenario but, in those that did, the effects were much as would be expected *a priori*. Thus, increasing initiation rates had most effect on tobacco use prevalence at younger ages, while increasing re-initiation rates had most effect at older ages. Varying rates of quitting and switching between products had a much greater effect on tobacco use distributions than did varying the factors by which TTPs are affected by previous tobacco use, these factors only being applied when multiple changes in tobacco use status occurred.

The largest increases in the estimated reductions in mortality associated with MRTP introduction resulted from decreasing the effective dose factors F and G, increasing rates of switching to MRTP (from CC or dual use), decreasing rates of switching to CC (from MRTP or dual use), and quitting. Effects of varying relative risk and half-life estimates and re-initiation rates were also clearly seen. In analyses involving 4-fold variations in

multiple parameters, decreasing the effective dose factor, F, and increasing the rate of switching to MRTP caused the largest increases in the estimated reductions in mortality, larger than those resulting from decreasing the rate of switching to CC or increasing the rate of quitting from MRTP.

Analyses were also conducted to determine what changes in parameter values might possibly eliminate the estimated reduction in deaths associated with MRTP introduction. Leaving aside the cases where the effective dose for MRTP use and CC smoking is identical, or where there is no uptake of MRTP, which would clearly totally eliminate the reduction in deaths, there were three situations where variation in a parameter might in theory fully eliminate the reduction, but none of these seemed likely to occur in practice. One was where the G-factor, the effective dose for dual users, was increased to 2.8, consistent with 20 a day CC smokers before MRTP introduction becoming users of almost 100 a day (half CC, half MRTP) afterwards. The second was where re-initiation rates increased 2-fold. The third was where quitting rates of CC smokers decreased by about 35%.

Increasing initiation rates 8-fold had a moderate effect on the reduction in deaths, reducing it 30.3% in males and 41.9% in females from that in the basic analysis. It should be noted that initiation was assumed only to occur at age <35 years, so that over the 20-year follow-up period increasing initiation rates would have no effect at all on those aged 55 years or over, where most deaths occur. It should be noted that an 8-fold increase in initiation rates would massively affect the smoking distribution in 30-34 year olds. Thus, comparing 1990 and 2010, the proportion of never users would reduce in males from 44.5% to 2.6%, and in females from 50.8% to 3.0%, while the proportion of current users would increase in males from 34.9% (all CC) to 70.0% (48.4% CC, 13.3% MRTP, 8.3% dual), and in females from 30.5% (all CC) to 72.3% (50.2% CC, 12.4% MRTP, 9.7% dual). Had the follow-up period been longer than 20 years, the effect of such a large, though implausible, increase in initiation rates on the reduction in deaths would clearly have been greater than seen in our analyses.

Compared to increasing the initiation rates, decreasing quitting rates of CC smokers and increasing re-initiation rates has a greater effect, and substantial and rather implausible changes in these would in theory eliminate the reduction in deaths associated with MRTP introduction. While the reduction could in theory be eliminated by making simultaneous multiple smaller changes in these parameters, even these smaller changes seem rather improbable. The fact that MRTP introduction is unlikely to cause an increase in deaths is emphasised by the results of an analysis involving an extreme situation in which, as soon as MRTP was introduced, smokers and non-smokers alike all became continuing MRTP users. Here the effect of MRTP introduction was clearly beneficial in males, and somewhat so in females, the reduction in risk for those who were smokers at the time of the introduction outweighing the increase in risk for those who were non-smokers.

The FDA MRTP guidelines highlight seven population segments and exposure patterns, two of which (**"Tobacco users who opt to use the proposed product rather than an FDA approved tobacco cessation medication"** and **"Non-users who experience health risks from the product"**) are outside the present scope of the model. The analyses presented in this report do, however, provide relevant information on the other segments. Thus **"Tobacco users who switch from other commercially marketed tobacco products to the proposed product"** relates to switching from CCs to MRTPs, **"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"** relates to switching from MRTPs to CCs, **"Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users"** relates to both initiation and re-initiation to MRTPs, and **"Tobacco users who use the product in conjunction with other tobacco products"** relates to dual use and the effective dose for dual users, all well covered by the sensitivity analyses conducted. **"Tobacco users who opt to use the proposed product rather than cease tobacco use altogether"** was considered by a specific analysis in which current CC smokers who would otherwise have switched to MRTP or to dual use quit instead. Here, the reduction in deaths associated

with MRTP introduction was estimated to be about 11 times greater in males and about 13 times greater in females than that for the basic analysis analysis. In practice, however, it seems likely that only a small proportion of CC smokers who elect to use MRTPs would have quit had MRTPs not been on the market.

Overall, we confirm that, given MRTPs have a low effective dose and given a reasonable rate of uptake by smokers, a clear reduction in mortality would be achieved by their introduction, and the detailed results provide estimates of the magnitude of this reduction in various alternative situations. The results also show that a reduction in mortality would still occur given levels of increases in cigarette consumption, risk in dual users, rates of initiation, switching or re-initiation to CC smoking, or reductions in rates of quitting which might plausibly be associated with MRTP introduction.

ABBREVIATIONS AND TERMINOLOGY USED

CC (or C)	Conventional Cigarette
CC only smokers	Those who smoke only CCs or no more than a defined proportion of MRTPs (Referred to as CC smokers in the Executive Summary).
COPD	Chronic Obstructive Pulmonary Disease
D	Dual user
Dual users	Those who smoke CCs and use MRTPs and who are not defined as CC only smokers or MRTP users.
F	Effective dose for MRTP only users, where 1 is that for CC only smokers and 0 that for non-smokers
F	Former smoker (abbreviation only used when defining TTPs)
FDA	Food and Drug Administration
Former tobacco users (or former users)	Those who have previously used CCs or MRTPs but do not now do so
G	Effective dose for dual users
H	Half-life for quitting; the time in years after which the excess risk (RR−1) in quitters is reduced to half that in continuing smokers
IHD	Ischaemic Heart Disease
ISS	International Smoking Statistics
L	Alternative parameter value expected to produce the largest reductions in mortality
MMWR	Morbidity and Mortality Weekly Report
MRTP (or M)	Modified Risk Tobacco Product
MRTP only users	Those who smoke only MRTPs or no more than a defined proportion of CCs. (Referred to as MRTP users in the Executive Summary).
MRTP Scenario	Scenario where MRTP is introduced

N	Never smoker
Never tobacco users (or never users)	Those who have never used either CCs or MRTPs
NHIS	National Health Interview Survey
NULL Scenario	Scenario where MRTP is not introduced
PHIM	Population Health Impact Model
RR	Relative risk
S	Alternative parameter value expected to produce the smallest reductions in mortality
SAD	Smoking Attributable Deaths
SSA	Simulation and Sensitivity Analysis
Tobacco use	Use of CCs and/or MRTPs
TTP	Tobacco Transition Probability
UN	United Nations
USSURG	US Surgeon General
WHO	World Health Organization
Zero benefit analyses	Analyses intended to determine what changes in parameter values might eliminate the reduction in deaths associated with MRTP introduction

1 REPORT HISTORY

1.1 Document Location

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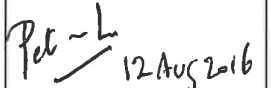
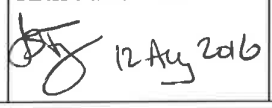
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1.2 Revision History

Revision date	Author	Version	Summary of Changes	Changes marked
12th August 2016	P.N.Lee	1.1	Remove red colour. Remove some unwanted text from the Table of Contents. Correct erroneous cross-references to other sections of the report.	1) On page 1 change "PHIM System", "Population Health Impact Model" and the names of the authors from red to black. 2) Remove unwanted three lines of text in Table of Contents after "4.4 Sensitivity analyses". 3) In first text line of section 8.2.2. change "section 6.3" to "section 6.2". 4) In para "24,25" of section A 2.2.1 change "..Section 2.3." to "..Section 4.4.2." 5) In first text line of section A 4.1 change "section A5.1" to "sections A1 to A3".

1.3 Approvals

This document requires the following approvals:

Name	Title	Date of Issue	Version
P.N.Lee	Director and consultant statistician, P N Lee Statistics and Computing Ltd	12th August 2016 	1.1
J.S. Fry	Statistician and head of computing, P N Lee Statistics and Computing Ltd	12th June 2016 	1.1

Contents

1 REPORT HISTORY 10
1.1 Document Location 10
1.2 Revision History 10
1.3 Approvals 10
2 PURPOSE 28
3 BACKGROUND 28
4 OUTLINE OF ANALYSES CONDUCTED 29
4.1 The basic analysis 29
Text-table 1 Monthly rates per million of initiation, quitting and re-initiation as used in the NULL Scenario 31
Text-table 2 Monthly rates per million of initiation, quitting, re-initiation and switching as used in the MRTP Scenario in the basic analysis 33
4.2 Investigating the appropriateness of the findings from the NULL Scenario 34
4.2.1 Comparison of ISS smoking prevalences with those predicted by the basic analysis 34
4.2.2 Comparison of published estimates of the proportion of deaths attributable to smoking with those predicted by the basic analysis 35
4.3 Simulation analyses 35
4.4 Sensitivity analyses 35
4.4.1 Testing for effect of variation of different parameters, considered one at a time 36
Text-table 3 Current smoker relative risks as reported by the US Surgeon General (USSURG) compared with those used in the basic analysis 39

4.4.2 Testing for the effect of variation in the assumption set for the MRTP Scenario 39
Text-table 4 Switching rates (per million per month) in the MRTP Scenario assumed in the basic model (rates are independent of time of follow-up) 42
4.5 Adjusting for population size 42
4.6 Extreme situation 43
4.7 Varying combinations of parameters – first set of analyses 43
Text-table 5 Definition of alternative analyses for varying combinations of parameters 45
4.8 Varying combinations of parameters – second set of analyses 45
4.9 Zero benefit estimation 45
4.10 Changes in relative and absolute risk by time 46
5 OUTPUT 47
5.1 Detailed output from simulation and sensitivity analyses 47
5.2 Summary results for reductions in mortality associated with MRTP introduction 47
5.3 Summary results for tobacco use prevalence 48
5.4 Extended output for the basic analysis 48
6 RELATIONSHIP TO THE SEVEN FDA POPULATION SEGMENTS 49
6.1 Segments outside the present scope of PHIM 49
6.2 Segments where the analyses conducted do provide some information 50
7 RESULTS AND CONCLUSIONS 53
7.1 The basic analysis 53
Table 1 Tobacco use prevalences (%) - basic analysis 54

Table 2 Reduction in mortality at age 30-79 which is associated with MRTP introduction – variation by year of follow-up (basic analysis) 55

Table 3 Reduction in mortality in 1990 to 2009 which is associated with MRTP introduction – variation by age (basic analysis) 58

7.2 Investigating the appropriateness of the findings from the NULL Scenario 59

7.2.1 Comparison of ISS smoking prevalences with those predicted by the basic analysis 59

Table 4 Comparison of prevalences of current and former smoking as predicted by the PHIM NULL Scenario, and as reported by ISS 60

7.2.2 Comparison of published estimates of the proportion of deaths attributable to smoking with those predicted by the basic analysis 61

Table 5 Comparison of % smoking-attributable mortality between basic analysis (NULL Scenario) and other published estimates 62

7.2.3 Conclusions regarding the appropriateness of the findings from the NULL Scenario 65

7.3 Simulation analyses 65

Table 6 Reduction in deaths per simulation in 1990-2009 at age 30-79 which is associated with MRTP introduction – comparison of results of simulation and basic analyses 66

7.4 Sensitivity analyses 67

7.4.1 Testing for effect of variation of different parameters, considered one at a time 67

Table 7(a) Prevalence (%) of tobacco use in the NULL and MRTP Scenario – comparison of results of simulation and basic analysis – age 30-34 68

Table 7(b) Prevalence (%) of tobacco use in the NULL and MRTP Scenario – comparison of results of simulation and basic analysis – age 50-54 69

Table 7(c) Prevalence (%) of tobacco use in the NULL and MRTP Scenario – comparison of results of simulation and basic analysis – age 70-74 70

Table 8(a) Effect of varying the effective dose for MRTP only users, F, on the reduction in mortality at age 30-79 which is associated with MRTP introduction (effective dose for dual users, G, kept constant at 0.6).....71

Table 8(b) Effect of varying the effective dose for MRTP only users, F, on the reduction in mortality at age 30-79 which is associated with MRTP introduction (effective dose for dual users, G, set at (1+F)/2) 72

Table 9(a) Effect of varying the effective dose for dual users, G, on the reduction in mortality at age 30-79 which is associated with MRTP introduction 74

Table 9(b) Effect of varying the effective dose for dual users, G, on the reduction in deaths at age 30-79 and for the period 1990-2009 which is associated with MRTP introduction 75

Table 10(a) Effect of varying the relative risks, RR, on the reduction in mortality at age 30-79 which is associated with MRTP introduction 77

Table 10(b) Reduction in deaths at age 30-79 for the period 1990-2009 which is associated with MRTP introduction for the basic analysis compared with that using the current smoker relative risks used by the US Surgeon General (USSURG) as given in Text-table 3.....78

Table 10(c) Comparison of percentage smoking-attributable deaths as reported by the US Surgeon General (USSURG) for 2005-2009 for age 35+ (see Table 5) and as estimated by PHIM for the same period for

age 30-79 using the current smoker relative risks given in Text-table 3 79

Table 11 Effect of varying the half-life, H, on the reduction in mortality at age 30-79 which is associated with MRTP introduction....82

Table 12(a) Effect of varying TTP factors and definitions of short-term quitting and use on tobacco use prevalence (%) at age 30-34 in 2010....83

Table 12(b) Effect of varying TTP factors and definitions of short-term quitting and use on tobacco use prevalence (%) at age 50-54 in 2010....84

Table 12(c) Effect of varying TTP factors and definitions of short-term quitting and use on tobacco use prevalence (%) at age 70-74 in 2010....85

Table 13 Effect of varying TTP factors 1, 2 and 3 and the definition of short-term quitting on the reduction in mortality from the four diseases combined in 1990-2009 age 30-79 associated with MRTP introduction....87

Table 14 Comparison of effect of varying different parameters on the estimated % reductions in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction....88

7.4.2 Testing for the effect of variation in the assumption set for the MRTP Scenario....89

Table 15 Effect of varying the relative frequency of initiation and of re-initiation to the three current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010....90

Table 16 Effect of varying the relative frequency of initiation and of re-initiation to the three current tobacco use groups on the reduction

in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction 91

Table 17 Effect of varying initiation and re-initiation rates on tobacco use prevalence (%) for the MRTP Scenario in 2010 93

Table 18 Effect of varying initiation and re-initiation rates on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction 97

Table 19(a) Effect of varying quitting rates of MRTP only users and dual users on tobacco use prevalence (%) for the MRTP Scenario in 2010 99

Table 19(b) Effect of varying quitting rates of CC only smokers on tobacco use prevalence (%) for the MRTP Scenario in 2010....100

Table 19(c) Effect of varying all quit rates on tobacco use prevalence (%) for the MRTP Scenario in 2010 101

Table 20(a) Effect of varying quitting rates of MRTP only users and dual users on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction 102

Table 20(b) Effect of varying quitting rates of CC only smokers on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction 103

Table 20(c) Effect of varying quitting rates of CC only smokers on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction 104

Table 21 Effect of varying switching rates between current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010 107

Table 22 Effect of varying switching rates between current tobacco use groups on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction 111

7.5 Adjusting for population size 113

Table 23 Effect of adjustment for population size on estimates of the reduction in mortality at age 30-79 which is associated with MRTP introduction 114

7.6 Extreme situations 115

Table 24(a) Effect on the reduction in mortality in 1990-2009 at age 30-79 in the first extreme situation where all smokers quit immediately and no initiation or re-initiation occurs 116

Table 24(b) Effect on the reduction in mortality in 1990-2009 at age 30-79 in the second extreme situation where CC smoking is totally replaced by MRTP use 117

Table 24(c) Effect on the reduction in mortality in 1990-2009 at age 30-79 in the third extreme situation where the whole population becomes current MRTP only users 118

Table 24(d) Comparison of reductions in mortality in 1990-2009 at age 30-79 in the basic analysis, and in the fourth extreme situation, where current CC only smokers who would otherwise have switched to MRTP only or to dual use quit instead 119

7.7 Varying combinations of parameters – first analysis 122

Table 25(a) Effect of varying four parameters simultaneously (first analysis) on smoking prevalence (%) at age 30-34 in the MRTP Scenario in 2010 123

Table 25(b) Effect of varying four parameters simultaneously (first analysis) on smoking prevalence (%) at age 50-54 in the MRTP Scenario in 2010 124

Table 25(c) Effect of varying four parameters simultaneously (first analysis) on smoking prevalence (%) at age 70-74 in the MRTP Scenario in 2010 125

Table 26 Effect of varying four parameters simultaneously (first analysis) on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction 126

7.8 Varying combinations of parameters – second analysis 127

Table 27 Effect of varying four parameters simultaneously (second analysis) in the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction 128

7.9 Zero benefit analysis 129

7.10 Changes in relative and absolute risk by time 131

Table 28 Zero benefit analyses. Effect of varying three parameters on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction 132

8 DISCUSSION AND CONCLUSIONS 134

8.1 General conclusions 134

8.2 Conclusions as regards the FDA Segments 137

8.2.1 Segment 1 **"Tobacco users who switch from other commercially marketed tobacco products to the proposed product"** 137

8.2.2 Segment 2 **"Tobacco users and smokers who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk"** 138

8.2.3 Segment 3 **"Tobacco users who opt to use the proposed product rather than cease tobacco use altogether"** 139

8.2.4 Segment 5 **"Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users"** 139

8.2.5 Segment 6 **"Tobacco users who use the product in conjunction with other tobacco products"** 141

9 REFERENCES 143

Figure 1(a) Effect of varying the effective dose for MRTP only, F, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). G is taken as the basic value of 0.6. Source: Appendix 3. Basic analysis value = 0.2 144

Figure 1(b) Effect of varying the effective dose for MRTP only, F, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). G is taken as (1+F)/2. Source: Appendix 3. Basic analysis value = 0.2 145

Figure 2 Effect of varying the effective dose for dual use, G, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 4. Basic analysis value = 0.6 146

Figure 3 Effect of varying TTP Factor 1 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 5. Basic analysis value = 2. The TTP from MRTP to CC is multiplied by TTP Factor 1 if previously used CC..... 147

Figure 4 Effect of varying TTP Factor 2 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 6. Basic analysis value = 2. The TTPs for quitting are multiplied by TTP Factor 2 if previously quit. 148

Figure 5 Effect of varying TTP Factor 3 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 7. Basic analysis value = 2. The TTPs for re-initiation are multiplied by TTP Factor 3 if a short-term quitter. 149

Figure 6 Effect of varying the definition of short-term quitting (years) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 8. Basic analysis value = 2 150

Figure 7 Effect of varying TTP factor 4 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 5. Basic analysis value = 0. The TTPs from MRTP to CCs and to dual use were multiplied by TTP factor 4 if a more than short-term user of MRTP. 151

Figure 8 Effect of varying the definition of short-term use (years) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 5. Basic analysis value = 2 152

Figure 9 Effect of varying the relative risk, RR, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 9. The excess relative risks (RR-1) from the basic analysis are multiplied by 0.8 or 1.2 in the alternative analyses. 153

Figure 10 Effect of varying the half-life, H, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 10. The half-lives from the basic analysis are multiplied by 0.8 or 1.2 in the alternative analyses. 154

Figure 11 Effect of varying the relative frequency of initiation to MRTP only and dual use (with the total initiation rate held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 11. Alternative 1 decreases (and Alternative 2 increases) the frequencies relative to the basic analysis. In the Figure, the results for Alternative 1, basic, and Alternative 2 are given against values of 1, 2 and 3 on the x-axis). 155

Figure 12 Effect of varying the relative frequency of re-initiation to MRTP only and dual use (with the total initiation rate held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 11. Alternative 3 decreases (and Alternative 4 increases) the frequencies relative to the basic analysis. In the Figure, the results for Alternative 3, basic, and Alternative 4 are given against values of 1, 2 and 3 on the x-axis). 156

Figure 13 Effect of varying initiation rates to MRTP only and dual use (with the initiation rate to CC only held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, alternatives 1, 2 and 3 successively increase the initiation rates to MRTP only and dual use. In the Figure, the results for basic, Alternative 1, Alternative 2 and Alternative 3 are given against values of 1, 2, 3 and 4 on the x-axis. 157

Figure 14 Effect of varying initiation rates on the percentage reduction in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, Alternatives 4-8 successively increase

all the initiation rates. In the Figure, the results for basic, Alternative 4, Alternative 5, Alternative 6, Alternative 7 and Alternative 8 are given against values of 1, 2, 3, 4, 5 and 6 on the x-axis. 158

Figure 15 Effect of varying re-initiation rates to MRTP only and dual use (with the re-initiation rate to CC only held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, Alternatives 9-10 successively increase the re-initiation rate to MRTP only and dual use. In the Figure, the results for basic, Alternative 9 and Alternative 10 are given against values of 1, 2 and 3, on the x-axis. 159

Figure 16 Effect of varying re-initiation rates on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, Alternatives 11 to 14 successively increase all the re-initiation rates In the Figure, the results for basic, Alternative 11, Alternative 12, Alternative 13 and Alternative 14 are given against values of 1, 2, 3, 4 and 5 on the x-axis. 160

Figure 17 Effect of varying quitting rates for MRTP only and dual use (with quitting rates for CC only held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 13. The quitting rates from the basic analysis are multiplied by 0.5, 0.75, 1.5 or 2 in the alternative analyses. 161

Figure 18 Effect of varying quitting rates for CC only (with quitting rates for MRTP only and dual use held constant) on the percentage

reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 13. The quitting rates from the basic analysis are multiplied by 0.0, 0.25 or 0.50 in the alternative analyses. 162

Figure 19 Effect of decreasing quitting rates for CC only, and simultaneously increasing quitting rates for MRTP only and dual use so as to keep overall quit rates approximately constant, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 13. In the Figure, the results for basic, Alternative 1 (CC x 0.9, Other x 1.5), Alternative 2 (CC x 0.8, Other x 2.0) and Alternative 3 (CC x 0.7, Other x 2.5) are shown against values of 1, 2, 3 and 4 on the x-axis. 163

Figure 20 Effect of varying switching rates from CC only or dual use to MRTP only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses. 164

Figure 21 Effect of varying switching rates from CC only or MRTP only to dual use on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses. 165

Figure 22 Effect of varying switching rates from MRTP only or dual use to CC only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the

basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses. 166

Figure 23 Effect of varying switching rates from CC only to MRTP only or dual use on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses. 167

Figure 24 Effect of varying switching rates from MRTP only to CC only or dual use on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses. 168

Figure 25 Effect of varying switching rates from dual use to CC only or MRTP only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses. 169

Figure 26 Effect of varying switching rates from MRTP only or dual use to CC only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 20, 50, 100 or 150 in the alternative analyses with the TTP Factor 1 set to 1....170

Figure 27 Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of lung cancer for an

individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.....171

Figure 28 Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of IHD for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.....172

Figure 29 Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of stroke for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.....173

Figure 30 Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of COPD for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.....174

Figure 31 Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of lung cancer for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.....175

Figure 32 Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of IHD for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.....176

Figure 33 Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of stroke for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.....177

Figure 34 Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of COPD for an individual

starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all....178

ANNEX A Appendices for Simulation and Sensitivity Analyses 179

A1 Introduction....179

A2 Format of a typical output....179

A2.1 Headings for each page....179

A2.2 Headings for each run....180

A2.2.1 Run and control file details....180

A2.2.2 TTP Values....181

A2.2.3 Relative risk values....182

A2.2.4 Half–life values....182

A2.3 Results....183

A2.3.1 Tobacco use prevalences....183

A2.3.2 Reductions in mortality....184

A3 Content of Appendices 1-19....185

A3.1 APPENDIX 1 - Basic analysis....185

A3.2 APPENDIX 2 - Ten simulations basic analysis....185

A3.3 APPENDIX 3 - Varying F....186

A3.4 APPENDIX 4 - Varying G....186

A3.5 APPENDIX 5 - Varying TTP Factor 1 and TTP Factor 4....186

A3.6 APPENDIX 6 - Varying TTP Factor 2....187

A3.7 APPENDIX 7 - Varying TTP Factor 3....187

A3.8 APPENDIX 8 - Varying short-term definition....187

A3.9 APPENDIX 9 - Varying RR....187

A3.10 APPENDIX 10 - Varying H....188

A3.11 APPENDIX 11 - Varying starting and re-starting proportions....188

A3.12 APPENDIX 12 - Varying starting and re-starting rates....189

A3.13 APPENDIX 13 - Varying quitting rates....189

A3.14 APPENDIX 14 - Varying switching between products....189

A3.15 APPENDIX 15 - Adjusting for population size 190
A3.16 APPENDIX 16 - Extreme situations 190
A3.17 APPENDIX 17 - Varying parameter combinations – first analyses 191
A3.18 APPENDIX 18 – Varying parameter combinations – second analyses 193
A3.19 APPENDIX 19 – Zero benefit estimation 193
A4 Appendices 20 to 24 194
A4.1 Reductions in mortality associated with MRTP Introduction 194
A4.2 Summary tables for tobacco use prevalence 195
A4.3 Extended output for the basic analysis 196

2 PURPOSE

The purpose of this document is to present the Simulation and Sensitivity Analysis (SSA) Report for the Population Health Impact Model (PHIM). Some of the findings described herein are planned to be used in a paper for publication describing the PHIM software.

3 BACKGROUND

A Population Health Impact Model has been developed to estimate the reduction in the death rate and in the number of deaths that would occur over a period following the introduction of an MRTP. This was carried out as there are no population level data available before marketing authorization.

PHIM is based on an estimate, F, of the relative exposure from an MRTP compared to that from conventional cigarettes (CCs), along with publicly available data on the prevalence of smoking, and on the relationship of mortality from the most common smoking-related diseases to various aspects of CC smoking. It allows consideration of a wide range of possibilities regarding the effect that introducing an MRTP might have on the prevalence of smoking of CCs or using MRTPs, individually or in combination. By comparing attributable deaths where the MRTP is introduced ("MRTP Scenario") and where it is not ("NULL Scenario"), the PHIM provides estimates of the number of deaths attributable to CC smoking and MRTP use, as well as an estimate of the reduction in the number of attributable deaths resulting from MRTP introduction.

This report is based on a set of Simulation and Sensitivity Analyses run on the tested version 4.0 of the PHIM. It provides information on the robustness of the PHIM, summarizes the effect that varying the model inputs has on the estimates of smoking distributions and changes in deaths associated with the introduction of the MRTP, and interprets and discusses the findings.

4 OUTLINE OF ANALYSES CONDUCTED

4.1 The basic analysis

The basic analysis, the results of which are given in **Appendix 1**, involves two runs, one for males and one for females. Each run concerns the following:

Country: USA

Follow-up period: 1990-2009 (2010), and

Age range: Risk reductions associated with MRTP introduction are estimated for the age range 30-79 years, based on tobacco use histories generated from age 10 years.

Note that the tobacco use distribution of the simulated populations, based initially on International Smoking Statistics (ISS) data for 1990, is updated annually 20 times using the specified tobacco transition probabilities (TTPs), so that tobacco use prevalences are available up to 2010. The reduction in deaths associated with MRTP introduction is calculated only for the 20 year period 1990 to 2009, based on the tobacco use prevalences at the beginning of each year.

The analyses use population estimates provided by the United Nations (UN), mortality estimates from the World Health Organization (WHO), current and former smoking prevalence estimates from ISS, and data on distribution of quit times from the National Health Interview Survey (NHIS), which do not vary in any of the simulation and sensitivity analyses, which are described more fully in "Notes on data files for PHIM project". The current and former smoking prevalences are for any product rather than specifically CCs, it being thought that material bias will not be produced by assuming that the small proportion of cigar and pipe smokers have the same risk of disease as do CC smokers.

The analyses also use a standard set of monthly TTPs in the NULL Scenario. As mentioned in the "Notes" document, there are three TTPs in this scenario:

Initiation rate: the probability, P_{NC}, that someone who has never smoked (N) becomes a cigarette smoker (C).

Quitting rate: the probability, P_{CF}, that a cigarette smoker becomes a former smoker (F).

Re-initiation rate: the probability, P_{FC}, that a former smoker becomes a cigarette smoker.

These rates only refer to the smoking of conventional cigarettes and it is assumed that only one transition is possible in a month. Thus the TTP from never smoker to former smoker (P_{NF}) is assumed to be zero.

These rates were initially derived as educated guesses reflecting age-specific patterns of cigarette initiation, quitting and re-initiation which seemed plausible and which produced not unreasonable estimates of the prevalence of current and former smoking at different ages. They were used in the initial testing of the PHIM. Subsequently, Weinberger *et al.* (2014) described results of a 3-year longitudinal study in a representative US population. Comparing rates from this study and those we had used, it was concluded that the initially derived rates of initiation and quitting were satisfactory, but the re-initiation rates should be increased by a factor of 2.4. The actual rates used, which do not vary by period of follow-up or sex, are shown in Text-Table 1. The initiation rate, 2000 per million per month at age 10-14, rises to a maximum of 3500 at age 15-19 and then falls steadily, being assumed to be zero at age 35+. The quitting rate starts at 500 per million per month at age 10-14, and then rises to a constant 2000 between ages 20-24 and 50-54, before rising again to 4000 at age 75-79. Re-initiation rates are 48% of quitting rates.

In the MRTP Scenario, two additional possible states are considered. Thus there are now five tobacco use states – never (N), current CC only (C), current MRTP only (M), current dual (D), and former (F) – and 15 TTPs. Three TTPs (P_{NC}, P_{NM}, P_{ND}) relate to initiation, three (P_{CF}, P_{MF}, P_{DF}) to quitting, three (P_{FC}, P_{FD}, P_{FM}) to re-initiation, and six (P_{CM}, P_{CD}, P_{MC}, P_{MD}, P_{DC}, P_{DM}) to switching between the current tobacco use groups. Note that while we use the term “MRTP only” smoker in this report, it is recognized that, in

practice, MRTP only users may be defined to include those with a limited use of CCs. Similar considerations apply to the term "CC only" smokers.

Text-table 1 Monthly rates per million of initiation, quitting and re-initiation as used in the NULL Scenario

Period of follow-up (months)	Age (years)	Initiation P_{NC}	Quitting P_{CF}	Re-initiation P_{FC}
1-3	10-14	2000	500	240
	15-19	3500	1500	720
	20-24	2000	2000	960
	25-29	1000	2000	960
	30-34	500	2000	960
	35-39	0	2000	960
	40-44	0	2000	960
	45-49	0	2000	960
	50-54	0	2000	960
	55-59	0	2500	1200
	60-64	0	2500	1200
	65-69	0	3000	1440
	70-74	0	3500	1680
	75-79	0	4000	1920
4+	10-14	2000	500	240
	15-19	3500	1500	720
	20-24	2000	2000	960
	25-29	1000	2000	960
	30-34	500	2000	960
	35-39	0	2000	960
	40-44	0	2000	960
	45-49	0	2000	960
	50-54	0	2000	960
	55-59	0	2500	1200
	60-64	0	2500	1200
	65-69	0	3000	1440
	70-74	0	3500	1680
	75-79	0	4000	1920

Initial estimates of the TTPs were educated guesses, though they were revised for various reasons. First, initial estimates of re-initiation rates were found to be low, as judged by results from a recent paper (Weinberger et al., 2014), so were revised upwards. Second, output generated using earlier TTP estimates suggested that they overestimated likely MRTP uptake. The rates were developed so that, 10 years after MRTP introduction, current users would be distributed approximately 84% CC, 10% MRTP and 6% dual, considered to be a plausible level of uptake. Third, the rates were designed to reflect the fact that younger people were considered less likely than older people to initiate with or switch to the MRTP, because of cost consideration.

To ensure comparability with the rates on the TTP_NULL file various constraints were applied:

1. Initiation rates. The sum of the three TTPs for initiation is equal to that for P_{NC} in the NULL Scenario. As for the NULL Scenario, the initiation rates are age-dependent, rising to a maximum for age 15-19 years and then falling to age 30-34 years, subsequently being zero.
2. Re-initiation rates. The sum of the three TTPs for re-initiation is equal to that for P_{FC} in the NULL Scenario. The three TTPs for re-initiation (P_{FC}, P_{FM}, P_{FD}) are in the ratio 60:20:20 for 1-24 months after MRTP introduction, and 40:40:20 for 25+ months after. As for the NULL Scenario, re-initiation rates rise with age.
3. Quitting. The three TTPs for quitting (P_{CF}, P_{MF}, P_{DF}) are each set equal to that for P_{CF} in the NULL Scenario, so do not vary by time of follow-up. As for the NULL Scenario, quitting rates rise with age.
4. Switching. The six TTPs which relate to switching between current tobacco use status do not vary by period of follow-up, and only two of them (P_{CM} and P_{CD}) vary by age, rising from age 10-14 to age 25-29 and then being constant.

The set of TTPs used in the basic analysis for the MRTP Scenario are shown in Text-table 2. The effect of varying these TTPs is considered in section 4.4.2.

Text-table 2 Monthly rates per million of initiation, quitting, re-initiation and switching as used in the MRTP Scenario in the basic analysis

Period of follow-up (months)	Age (years)	Initiation			Quitting			Re-initiation		
		P_{NC}	P_{NM}	P_{ND}	P_{CF}	P_{MF}	P_{DF}	P_{FC}	P_{FM}	P_{FD}
1-24	10-14	1840	80	80	500	500	500	144	48	48
	15-19	2940	280	280	1500	1500	1500	432	144	144
	20-24	1520	240	240	2000	2000	2000	576	192	192
	25-29	680	160	160	2000	2000	2000	576	192	192
	30-34	300	100	100	2000	2000	2000	576	192	192
	35-39	0	0	0	2000	2000	2000	576	192	192
	40-44	0	0	0	2000	2000	2000	576	192	192
	45-49	0	0	0	2000	2000	2000	576	192	192
	50-54	0	0	0	2000	2000	2000	576	192	192
	55-59	0	0	0	2500	2500	2500	720	240	240
	60-64	0	0	0	2500	2500	2500	720	240	240
	65-69	0	0	0	3000	3000	3000	864	288	288
	70-74	0	0	0	3500	3500	3500	1008	336	336
	75-79	0	0	0	4000	4000	4000	1152	384	384
25+	10-14	1680	160	160	500	500	500	96	96	48
	15-19	2380	560	560	1500	1500	1500	288	288	144
	20-24	1040	480	480	2000	2000	2000	384	384	192
	25-29	360	320	320	2000	2000	2000	384	384	192
	30-34	100	200	200	2000	2000	2000	384	384	192
	35-39	0	0	0	2000	2000	2000	384	384	192
	40-44	0	0	0	2000	2000	2000	384	384	192
	45-49	0	0	0	2000	2000	2000	384	384	192
	50-54	0	0	0	2000	2000	2000	384	384	192
	55-59	0	0	0	2500	2500	2500	480	480	240
	60-64	0	0	0	2500	2500	2500	480	480	240
	65-69	0	0	0	3000	3000	3000	576	576	288
	70-74	0	0	0	3500	3500	3500	672	672	336
	75-79	0	0	0	4000	4000	4000	768	768	384

Period of follow-up (months)	Age (years)	Switching within current tobacco use groups					
		P_{CM}	P_{CD}	P_{MC}	P_{MD}	P_{DC}	P_{DM}
1-24	10-14	150	30	400	400	400	400
	15-19	200	40	400	400	400	400
	20-24	300	60	400	400	400	400
	25-29	450	90	400	400	400	400
	30-34	450	90	400	400	400	400
	35-39	450	90	400	400	400	400
	40-44	450	90	400	400	400	400
	45-49	450	90	400	400	400	400
	50-54	450	90	400	400	400	400
	55-59	450	90	400	400	400	400
	60-64	450	90	400	400	400	400
	65-69	450	90	400	400	400	400
	70-74	450	90	400	400	400	400
	75-79	450	90	400	400	400	400

Period of follow-up (months)	Age (years)	Switching within current tobacco use groups					
		P_{CM}	P_{CD}	P_{MC}	P_{MD}	P_{DC}	P_{DM}
25+	10-14	150	30	400	400	400	400
	15-19	200	40	400	400	400	400
	20-24	300	60	400	400	400	400
	25-29	450	90	400	400	400	400
	30-34	450	90	400	400	400	400
	35-39	450	90	400	400	400	400
	40-44	450	90	400	400	400	400
	45-49	450	90	400	400	400	400
	50-54	450	90	400	400	400	400
	55-59	450	90	400	400	400	400
	60-64	450	90	400	400	400	400
	65-69	450	90	400	400	400	400
	70-74	450	90	400	400	400	400
	75-79	450	90	400	400	400	400

The sensitivity analyses involve varying one (or more) parameters at a time, the meaning of the parameters, and the values assumed in the basic analysis, becoming clear in the sections below which describe the sensitivity analyses.

4.2 Investigating the appropriateness of the findings from the NULL Scenario

Preliminary analyses involve checking that the parameters used for the NULL Scenario produce predictions reasonably consistent with what is known for the US population, as regards both the distribution of smoking habits and the proportion of deaths due to smoking.

4.2.1 Comparison of ISS smoking prevalences with those predicted by the basic analysis

As regards smoking habits, age- and sex-specific distributions generated by the PHIM during the 20 year follow-up from the start time of 1990 are compared with the corresponding ISS estimates. Differences are expected to be minor for 1990 between the distribution of the simulated samples of 10,000 of each sex and the actual ISS values, as the age- and sex-specific probabilities of being a current, former or never smoker are derived from US data for that year taken from ISS. Subsequently, however, the distribution of the simulated sample will change as a result of applying the NULL

Scenario TTPs. However, exact correspondence is not to be expected for various reasons including: (a) variation due to the simulation process; (b) inaccuracies in the ISS estimates; (c) ISS estimates for the USA not yet currently being available past 2005, the estimates for later years being taken to be the same as in 2005; and (d) the simulation process assuming that the initial sample survives throughout follow-up, with no account taken of differential mortality by smoking habit, or of immigration or emigration.

4.2.2 Comparison of published estimates of the proportion of deaths attributable to smoking with those predicted by the basic analysis

The output from the NULL Scenario, for each of the four diseases of interest, provides estimates of the proportion of deaths attributable to smoking. These are compared with published estimates for the USA, and any major differences commented on. Differences seen are expected to arise from differences between the relative risk (RR) estimates we used, which were derived from major meta-analyses, and those used for the published estimates.

4.3 Simulation analyses

Whereas all other analyses are based on a single simulation of 10,000 individuals, the simulation analyses are conducted using 10 simulations, each of 10,000 individuals. These analyses, the results of which are given in **Appendix 2,** aim to give support for using the smaller sample size for the other analyses described in this report, and provide information on variability of the results.

4.4 Sensitivity analyses

The analyses conducted are generally based on comparison of results obtained using a fixed NULL Scenario with a variable MRTP Scenario.

4.4.1 Testing for effect of variation of different parameters, considered one at a time

Effects of variation are initially considered one parameter at a time, with estimates of the distribution of smoking habits and of the reduction in mortality associated with the introduction of MRTP based on a standard value of the parameter compared with estimates based on alternative values. Below, each parameter considered is described, with the value considered in the basic analysis, and the alternatives considered in the sensitivity analyses made clear. Note that, for some parameters, some alternatives chosen are intended to assist in determining how high or low the parameter has to be for any advantage in switching to MRTP to be lost ("zero benefit" estimation).

Effective dose for current MRTP only users (F) F is expressed on a scale where 1 is equivalent to current CC smoking, and 0 is non-smoking (including quitters). Thus, the value of F used in the basic analysis of 0.2 is equivalent to an 80% reduction in effective dose, and would imply that the reduction in excess risk of a disease associated with switching from CCs to MRTPs would be 80% of the reduction associated with quitting CCs. The 11 alternative values tested in the sensitivity analysis are 0, 0.05, 0.1, 0.15, 0.25, 0.3, 0.35, 0.4, 0.5, 0.6 and 0.7. The range of values chosen will allow estimation of the reduction in mortality associated with estimates of F to be derived from clinical studies. Note that the set of 24 runs (2 sexes x 12 F values) were carried out twice. In the first set, G (the effective dose for dual users) was held at the basic analysis value of 0.6. In the second, G was taken as (1+F)/2. The results of the sensitivity analyses are given in **Appendix 3**.

Effective dose for dual users (G) The value of G used in the basic analysis is 0.6, the alternatives tested being 0.4, 0.8, 1.0, 1.2, 1.5 and 2.0. Assuming the basic value of F of 0.2 and linearity of dose-response, G = 0.6 corresponds to dual users using 50% CCs and 50% MRTPs, while G = 0.4 corresponds to dual users using 25% CCs and 75% MRTPs, and G = 0.8 to using 75% CCs and 25% MRTPs. G = 1 and G = 1.2 allow for increased consumption. Thus, G = 1.2 corresponds to a 20-a-day CC smoker becoming a dual user of 20 a day of each product. The results of these analyses are presented in **Appendix 4**.

G = 1.5 and 2.0 are intended to assist in zero benefit estimation, as described in section 4.9. Note that G values may correspond to varying alternative consumptions of CCs and MRTPs. Thus, assuming 20 a day for CC smokers before MRTP introduction and the basic F of 0.2, a G value of 0.6 corresponds not only to dual use of 10 a day of each product, but alternatively to dual use of 11.25 CCs and 3.75 MRTPs a day, or of 7.5 CCs and 22.5 MRTPs a day.

TTP Factor 1 and TTP Factor 4 The TTP associated with the transition from MRTP to CC is multiplied by TTP Factor 1 if the individual has previously used CCs. In the basic analysis, TTP factor 1 is set at 2, with alternative values of 1, 1.5, 2.5 and 3 tested in the sensitivity analyses.

The TTPs associated with both the transition from MRTPs to CCs and that from MRTPs to dual use are multiplied by TTP factor 4 if the individual has used MRTP continuously for more than a defined period. Note that if TTP factor 4 is set to a value and an individual uses MRTP continuously for more than the defined period, TTP factor 1 is not applied. However, the user has the option to ignore (not set) TTP factor 4, in which case TTP factor 1 is applied regardless of how long MRTP has been used. The basic value of TTP Factor 4 is taken to be 0, with alternative values of 0.5, 1 and "ignore" to be tested in the sensitivity analyses (with the defined period taken as 2 years). (See **Appendix 5**).

Definition of short-term use TTP factor 4 requires the user to define short-term use. In the basic analysis, short-term use is assumed to be for a period of 2 years, with alternative values tested at 1, 3 and 4 years (with TTP factor 4 taken as 0). (See **Appendix 5**).

TTP Factor 2 The TTP associated with quitting is multiplied by TTP factor 2 if the individual has previously quit. This applies to both the NULL and MRTP Scenarios. As for TTP factor 1, TTP factor 2 is set at 2 in the basic analysis, with alternative values of 1, 1.5, 2.5 and 3 tested in the sensitivity analyses. (See **Appendix 6**).

TTP Factor 3 The TTP associated with re-initiation is multiplied by TTP factor 3 if the individual is a short-term quitter. This applies to both the NULL and MRTP Scenarios. As for TTP factor 1, TTP factor 3 is set at 2 in the basic analysis, with alternative values of 1, 1.5, 2.5 and 3 tested in the sensitivity analyses. (See **Appendix 7**).

Definition of short-term quitting TTP factor 3 requires the user to define short-term quitting. In the basic analysis, short-term quitters are assumed to be those who have quit for up to 2 years, with alternative values of up to 1 year and up to 3 years tested in the sensitivity analyses. (See **Appendix 8**).

Relative risks (RR) The RR estimates used in the basic analyses are from dataset PNLEST of the RR file, and were derived from meta-analyses. For the sensitivity analyses, one alternative dataset (PNLLOW) was created with each RR replaced by 1 + 0.8 (RR-1) = 0.8 RR + 0.2, giving a 20% reduction in the excess RR. Another alternative dataset (PNLHIGH) replaced each RR by 1 + 1.2 (RR-1) = 1.2 RR – 0.2, giving a 20% increase in the excess RR. A third alternative (USSURG) was based upon the RR estimates for current smoking given in Table 12.3 of the 2014 US Surgeon General's Report (US Surgeon General, 2014). The estimates are shown in Text-table 3. Note that the Surgeon General's RRs for former smokers are not used as our risk estimations depend on time of quit and the half-life associated with quitting. (Results are presented in **Appendix 9**).

Half-lives (H) For a given disease, H is the estimated time after quitting when the excess risk (RR−1) declines to half that for a continuing smoker. The estimates of H used in the basic analysis (data set PNLEST) were derived from meta-analyses and are not dependent on sex. For stroke (H = 4.78) and COPD (H = 13.32), they are independent of age. The H values are 6.98, 10.39, 10.60 and 12.99 for lung cancer and are 1.47, 5.22, 7.48 and 13.77 for IHD for, respectively, ages <50, 50-59, 60-69 and 70-79. For the sensitivity analyses, alternative datasets were created, with each H value replaced by either 0.8 H (dataset PNLLOW) or 1.2 H (dataset PNLHIGH). (See **Appendix 10**).

Text-table 3 Current smoker relative risks as reported by the US Surgeon General (USSURG) compared with those used in the basic analysis

		Males		Females	
Disease	Age (years)	USSURG	Basic	USSURG	Basic
Lung cancer	<55	14.33	11.68	13.30	11.68
	55-64	19.03	11.68	18.95	11.68
	65-74	28.29	11.68	23.65	11.68
	75+	22.51	11.68	23.08	11.68
IHD	<55	3.88	3.38	4.98	3.38
	55-64	2.99	2.32	3.25	2.32
	65-74	2.76	1.70	3.29	1.70
	75+	1.98	1.27	2.25	1.27
Stroke	<55	2.17	2.48	2.27	2.48
	55-64	2.17	2.13	2.27	2.13
	65-74	2.17	1.39	2.27	1.39
	75+	1.48	1.06	1.70	1.06
COPD	<75	29.69	4.56	38.89	4.56
	75+	23.31	4.56	20.96	4.56

Note that the USSURG estimates are applied to age 35+ years, while the basic estimates are applied to age 30-79 years.
[a] The mean of RRs for bronchitis/emphysema and for airways obstruction

Variation in some of the parameters considered above will only affect the estimated reduction in deaths associated with MRTP introduction; - the effective doses for MRTP (F) and dual use (G), the relative risk (RR) estimates, and the half-life (H) estimates. The other parameters considered above will also affect the tobacco use distributions; - TTP factor 1, TTP factor 2, TTP factor 3, TTP factor 4, the defined period of MRTP use for TTP factor 4 to apply, and the definition of short-term quitting in relation to TTP factor 3.

4.4.2 Testing for the effect of variation in the assumption set for the MRTP Scenario

The set of TTP values for the NULL Scenario remains unchanged throughout the sensitivity analyses described here. The sensitivity analyses described here consider how

variation in the set of TTP values used for the MRTP Scenario affect both the estimates of the distribution of tobacco use and the estimated reduction in mortality associated with MRTP introduction.

Varying the relative frequency of initiation and of re-initiation to the three current tobacco use groups

While the set of TTP values for the NULL Scenario (see Text-table 1) remains unchanged throughout the sensitivity analyses, it is important to realize that the basic set of TTP values for the MRTP Scenario (see Text-table 2) was constructed from that for the NULL Scenario. Thus, in each case, the sum of the three rates for the MRTP Scenario is equal to the corresponding rate for the NULL Scenario.

In the sensitivity analyses investigating the effect of varying the relative frequency of initiation in the three current tobacco use groups, the rates P_{NM} and P_{ND} will either be halved (Alternative 1) or multiplied by 1.5 (Alternative 2) while the rate P_{NC} will be correspondingly altered so that the sum of the three MRTP rates P_{NM}, P_{ND} and P_{NC} will equal the NULL rate P_{NC}. Thus, for example, for age 20-24 in the first 24 months of follow-up, the MRTP rates for P_{NC}, P_{NM} and P_{ND}, instead of being 1520, 240 and 240 as in Text-table 2, will become 1760, 120 and 120 in Alternative 1 and 1280, 360 and 360 in Alternative 2. Exceptionally, for age 30-34 for follow-up 25+ months, where multiplying P_{NM} and P_{ND} by 1.5 would make them both 300, and the total more than the rate of 500 for P_{NC} NULL, P_{NM} and P_{ND} will be set to 250, and P_{NC} MRTP to 0.

In the sensitivity analyses investigating the effect of varying the relative frequency of re-initiation in the three current tobacco use groups, the MRTP rates P_{FM} and P_{FD} will either be halved (Alternative 3) or multiplied by 1.5 (Alternative 4) while the MRTP rate P_{FC} will be altered so that the sum of the three MRTP rates will equal the NULL rate. Here there is no case where multiplying the two rates by 1.5 will make the other MRTP rate go negative.

The results of these sensitivity analyses are given in **Appendix 11**.

Varying initiation and re-initiation rates While in the previous analyses the overall rates of initiation and re-initiation are kept constant, with only the relative frequency by type of product (CC only, MRTP only, dual use) varying, in these analyses the overall rates of initiation and re-initiation are varied. 14 alternatives are considered. In alternatives 1-3, initiation rates to MRTP and dual use only are multiplied by 1.5, 2 or 3, while in alternatives 4-8, all initiation rates are multiplied by 1.5, 2, 3, 4 or 8. In alternatives 9 and 10, re-initiation rates to MRTP and dual use only are multiplied by 1.5 or 2, while in alternatives 11-14, all re-initiation rates are multiplied by 1.5, 2, 5 or 10. Alternatives 7 and 8 (increasing initiation rates) and alternatives 13 and 14 (increasing re-initiation rates) relate to the zero benefit estimation. (See **Appendix 12**).

Varying quitting rates In the basic analysis, the rates in the MRTP Scenario for quitting from each of the three current tobacco use groups are set equal to the quitting rate for the NULL Scenario. Here, ten alternative situations are considered. In alternatives 1 to 4, the quitting rate for CC only smokers remains unchanged, but the quitting rates of MRTP only users and dual users are each multiplied by the factors 0.5, 0.75, 1.5 or 2. In alternatives 5 to 7, the quitting rates of MRTP only users and dual users remain unchanged, but the quitting rate of CC only smokers is multiplied by the factors 0, 0.25 or 0.5, relating to zero benefit estimation. In alternatives 1 to 7, the overall quitting rate in the MRTP Scenario will differ from that in the NULL Scenario. In alternatives 8 to 10, the quitting rate in the MRTP Scenario for CC only smokers is multiplied by the factors 0.9, 0.8 or 0.7, while the quitting rate for both MRTP only users and dual users are multiplied by the corresponding factors 1.5, 2.0 and 2.5. Given the relative frequency of CC only smokers and other current users (about 5:1) over the whole study period, this should keep the overall quit rate approximately constant. (See **Appendix 13**.)

Varying switching rates between current tobacco users Of the 15 TTPs in the MRTP Scenario, six relate to switching between current tobacco use groups. The rates assumed in the basic model are shown in Text-table 4.

Text-table 4 Switching rates (per million per month) in the MRTP Scenario assumed in the basic model (rates are independent of time of follow-up)

Age	P_{CM}	P_{CD}	P_{MC}	P_{MD}	P_{DC}	P_{DM}
10-14	150	30	400	400	400	400
15-19	200	40	400	400	400	400
20-24	300	60	400	400	400	400
25+	450	90	400	400	400	400

Here 22 alternatives are investigated, with alternatives

1-3 varying TTPs relating to switching to MRTPs (P_{CM} and P_{DM}),

4-6 varying TTPs relating to switching to dual use (P_{CD} and P_{MD}),

7-9 varying TTPs relating to switching to CCs (P_{MC} and P_{DC}),

10-12 varying TTPs relating to switching from CCs (P_{CM} and P_{CD}),

13-15 varying TTPs relating to switching from MRTPs (P_{MC} and P_{MD}), and

16-18 varying TTPs relating to switching from dual use (P_{DC} and P_{DM}).

In each case the rates shown in Text-table 3 are multiplied by 0.5, 5 or 10. In alternatives 19-22, which relate to zero benefit estimation, the probabilities of switching to CC use are multiplied by 20, 50, 100 and 150. (See **Appendix 14**).

4.5 Adjusting for population size

Other sensitivity analyses make no adjustment for the fact that, because of the reduced mortality in the MRTP Scenario, the population at risk will increase relative to that in the NULL Scenario. **Appendix 15** repeats the basic analysis, but with adjustment made for the change in population size. This only affects the estimations of risk.

4.6 Extreme situation

The basic and alternative analyses provide insight into the reduction in mortality from MRTP introduction. To bring these results into context, it is useful to compare them with four extreme situations.

In the first extreme situation, all current smokers in the MRTP Scenario quit immediately and no further initiation or re-initiation occurs.

In the second extreme situation, CC smoking is totally replaced by MRTP use. Initiation rates in the MRTP Scenario for CC only and for dual use are added to those for MRTP only use and then set to zero. The same applies to the re-initiation rates. Switching within current users is all to MRTP only.

In the third extreme situation, the whole population takes up MRTP at the start of the follow-up, with no further CC only smoking, dual use or quitting.

In the fourth extreme situation, current CC only smokers who would otherwise have switched to MRTP only or to dual use quit instead. Thus, the two TTPs for current CC only smokers switching are added to the quitting rate and then reset to zero. (See **Appendix 16**).

4.7 Varying combinations of parameters – first set of analyses

These analyses concern variation in four sets of parameters found, in preliminary analyses, to have a major effect on the reduction in mortality associated with MRTP;

(i) the effective dose for MRTP only users (F),
(ii) the rate of switching to MRTP only (from CC only and from dual use),
(iii) the rate of switching to CC only (from MRTP only or dual use), and
(iv) the rate of quitting from MRTP only or dual use.

Note that variation in G, the effective dose for dual users, is considered indirectly by taking it as equal to (1 + F)/2 in all the alternatives considered, i.e. assuming, as in the basic analysis, that dual use is 50% CCs and 50% MRTPs, with no increase in overall cigarette consumption.

For each of the four sets of parameters, two alternatives are used, one producing larger and one smaller drops in mortality.

For variation in F, F = 0.1 is used to produce larger reductions in mortality, and F = 0.5 to produce smaller reductions.

For variation in the TTPs for switching to MRTP only, switching rates 10 times the basic rate produce larger reductions in mortality, and switching rates half the basic rate produce smaller reductions.

For variation in the TTPs for switching to CC only, switching rates half the basic rate produce larger reductions in mortality, and switching rates 10 times the basic rate produce smaller reductions.

For variation in the TTPs for quitting from MRTP or dual use, doubling the basic quit rate produces larger reductions in mortality, and halving the basic quit rate produces smaller reductions.

Text-table 5 summarizes the 16 alternative analyses, with Alternative 1 expected to produce the largest reductions in mortality and Alternative 16 the smallest. L indicates the parameter value used to produce larger reductions and S that used to produce smaller reductions.

Text-table 5 Definition of alternative analyses for varying combinations of parameters

Alternative	F	Switching to MRTP	Switching to CC only	Quitting from MRTP or dual use
1	L	L	L	L
2	L	L	L	S
3	L	L	S	L
4	L	L	S	S
5	L	S	L	L
6	L	S	L	S
7	L	S	S	L
8	L	S	S	S
9	S	L	L	L
10	S	L	L	S
11	S	L	S	L
12	S	L	S	S
13	S	S	L	L
14	S	S	L	S
15	S	S	S	L
16	S	S	S	S

L = alternative expected to produce the largest reductions in mortality
S = alternative expected to produce the smallest reductions in mortality

Results of these analyses are presented in **Appendix 17**.

4.8 Varying combinations of parameters – second set of analyses

These analyses are similar to those described in section 4.7, except that the alternatives for each of the four parameters considered vary by fixed ratios (basic value/2, basic value x 2). This allows more direct comparability between the effects of variation in the different parameters. Results of these analyses are presented in **Appendix 18**.

4.9 Zero benefit estimation

Analyses already described are intended to give understanding of which parameter variations might eliminate the effect of MRTP introduction. These relate to:

Dual users increasing consumption	-	Appendix 4
Increasing initiation rates	-	Appendix 12
Increasing re-initiation rates	-	Appendix 12
Decreasing quit rates of CC only smokers	-	Appendix 13
Increasing switching rates to CC only smoking	-	Appendix 14

Based on the results of these analyses, and estimates of the parameter values to individually eliminate the effect of MRTP introduction, further analyses were conducted to give additional insight. Except for parameters proving to have little effect on the estimated drop in deaths associated with MRTP introduction, values for each parameter (V_1, V_2 … V_5) would be selected which successively reduced the estimated drop in deaths and five alternative sets of analyses were run, with the first set using all the V_1 values, the second all the V_2 values and so on. For those parameters where the effect of MRTP introduction could be eliminated by a given value V_E, V_i was taken as $V_B + \alpha_i(V_E - V_B)$, where α_i = 0.1, 0.2, 0.3, 0.4 and 0.5 (i = 1, 2…5). Here V_B is the value in the basic analysis. For other parameters, a similar scheme was adopted.

Results of these analyses are presented in **Appendix 19**.

4.10 Changes in relative and absolute risk by time

Associated with version 4.0 of PHIM is an additional SAS program CALCRISK2 which allows the user to estimate and plot changes in relative and absolute risk over time for individuals with a detailed history of tobacco use. Two sets of eight plots are included in this report. The first set compares individuals, each of which start to smoke CCs at age 16, and then switch to MRTPs at age 25, 40, 55 or not at all. The second set compares individuals, again starting to smoke CCs at age 16, who then quit at age 25, 40, 55 or not at all. For each set, there will be a pair of plots (relative and absolute risk) for each disease.

5 OUTPUT

5.1 Detailed output from simulation and sensitivity analyses

The detailed output is presented in **Appendices 1 to 19** as described above. Associated with this output is **Annex A** "Appendices for Simulation and Sensitivity Analyses" which explains in detail the format of a typical output. In summary, the output for each alternative and for each sex starts by presenting a section specifying the variable parameter values used, a listing of the TTP values used, and then (if other than standard) a listing of the RR and H values used. It then gives details of the distribution of smoking habits by age and period (0, 5, 10, 15, 20 years) separately for the NULL and MRTP Scenarios, and a summary of results for the reduction in mortality associated with MRTP introduction, for every year from 1990 to 2009 and for 1990-2009 combined, and for the four diseases (lung cancer, IHD, stroke and COPD) separately and combined.

The Annex also summarizes the analyses conducted in **Appendices 1-19**, and describes in detail the content of five other **Appendices (20-24)** as summarized below.

5.2 Summary results for reductions in mortality associated with MRTP introduction

As the output described in section 5.1 is so extensive, **Appendix 20** gives some summary information from these analyses, which allows ready comparison between the results for mortality from the various analyses presented in **Appendices 1** to **19**. It brings together results by disease and for the four diseases combined, consisting of the estimated reduction in deaths, as well as the percentage reductions in deaths and in attributable deaths. Results are shown separately for 2000, 2005, 2009 and 1990 to 2009 combined. Data from **Appendix 20** are used to provide many of the tables in this report.

Associated with this is **Appendix 21**, an Excel file allowing the user readily to produce plots showing how the percentage reductions in deaths and in attributable deaths vary by level of the parameters varied in **Appendices 1 to 14**. The user may select the sex, year

(1990-2009 individually or combined) and disease (individually or combined). Some of the plots are shown in this report, the interested reader being referred to **Appendix 21** for others.

5.3 Summary results for tobacco use prevalence

Corresponding to **Appendix 20** for mortality, **Appendix 22** gives some summary information allowing ready comparison between the results for tobacco use prevalence for ages 30-34, 50-54 and 70-79 from the various analyses presented in **Appendices 1 to 19.** Results are shown separately for 1995, 2000, 2005 and 2010. Data from **Appendix 22** are used to provide many of the tables in this report.

Associated with this is **Appendix 23**, an Excel file allowing the user readily to produce plots showing how the distribution of tobacco use prevalence in the MRTP Scenario varies by level of the parameters varied in **Appendices 1** to **14**. The user may select the age group as 30-34, 50-54 or 70-74, and a year from 1990 to 2010.

5.4 Extended output for the basic analysis

Appendix 24 contains results from an additional run of the basic analysis showing the mortality results by 5-year age group. Some results from this are used in Table 3.

6 RELATIONSHIP TO THE SEVEN FDA POPULATION SEGMENTS

The MRTP Guidance highlights seven population segments and exposure patterns.

1 **Tobacco users who switch from other commercially marketed tobacco products to the proposed product.**
2 **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.**
3 **Tobacco users who opt to use the proposed product rather than cease tobacco use altogether.**
4 **Tobacco users who opt to use the proposed product rather than an FDA approved tobacco cessation medication.**
5 **Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users.**
6 **Tobacco users who use the product in conjunction with other tobacco products.**
7 **Non-users who experience health risks from the product.**

It is important to consider how the sensitivity analyses described above relate to the seven segments. It should be made clear initially that two of the segments are outside the scope of PHIM. For the other five segments the results, though not directly comparing risk in different smoking groups, do provide some information. These points are enlarged upon below.

6.1 Segments outside the present scope of PHIM

Segment 4 "**Tobacco users who opt to use the proposed product rather than an FDA approved tobacco cessation medication"** is not referred to in the paper introducing the PHIM (Weitkunat et al., 2015), which does not formally consider switching to products other than the MRTP of interest. However, it is, in theory, possible to run alternative models with the MRTP Scenario replaced by a tobacco cessation medication (TCM)

Scenario, using estimates of TTPs and effective doses (F) which are considered reasonable for the TCMs rather than for MRTP. Such estimates are, however, not available at the present time. It should be noted, however, that a recent publication (Stanley and Massey, 2016) suggests that nicotine replacement therapy may be ineffective as a smoking cessation aid.

Segment 7 **"Non-users who experience health risks from the product"** is also not considered**.** A paragraph in the discussion of the paper introducing the PHIM (Weitkunat et al., 2015) makes it clear that any risks associated with environmental tobacco smoke (ETS) exposure in never smokers are much lower than those associated with CC smoking, so that whether or not the MRTP reduces the risk from ETS exposure would have little effect on the estimates of the reduction in mortality associated with MRTP introduction.

6.2 Segments where the analyses conducted do provide some information

It is important to realize that PHIM as currently written considers mortality in the whole population according to variation in the input parameters, and does not estimate mortality for specific tobacco use groups. Nevertheless, it is clear that the analyses conducted do provide relevant information for a number of segments.

Segment 1 "**Tobacco users who switch from other commercially marketed tobacco products to the proposed product"** relates to switching from CCs to MRTP and is considered in section 4.4.2, in particular in alternative analyses 10-12, where the switching rates from CC only to MRTP only and to dual use are varied, and less so in alternative analyses 1-3, where the switching rates from CC only or dual use to MRTP only are varied. Also relevant are sections 4.7 and 4.8 where the rate of switching to MRTP only is one of the four parameters varied simultaneously, and the plots of relative and absolute risk described in section 4.10 comparing individuals switching to MRTP only at different times. (See **Appendices 14, 17** and **18** for the detailed results).

As regards segment 2 "**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", t**he MRTP Scenario does not consider tobacco products other than CCs, such as pipes, cigars or smokeless tobacco, as it would make the estimation process overly complex. For the same reason, it does not consider switching from and to CCs with a range of different health risks.

However, the MRTP Scenario does consider switching to or back to CCs, having previously used MRTPs. Here alternative analyses 7-9 and 19-22 described in section 4.4.2, which vary rates of switching to CC only (from MRTP only and from dual use) are particularly relevant, while alternative analyses 13-15, which concern switching rates to CC only and to dual use (from MRTP only), are also of interest. Also relevant are sections 4.7 and 4.8 where the rate of switching to CC only (from MRTP only or dual use) is one of the four parameters varied simultaneously, and section 4.9 where switching to CC only is considered in the zero benefit analyses. (See **Appendices 14, 17, 18** and **19** for the detailed results).

The transition probability from MRTP to CC relates to the "gateway hypothesis", i.e. switching from MRTPs to become a CC smoker for the first time, while multiplying this transition probability by TTP factor 1 relates to switching back from MRTPs to CCs, having smoked CCs previously. (See **Appendix 5** for the effects of varying TTP factor 1, as well as the Appendices referred to in the previous paragraph)**.**

Segment 3 **"Tobacco users who opt to use the proposed product rather than cease tobacco use altogether"** is addressed by contrasting the basic analysis, in which some CC only smokers switch to MRTP only or to dual use, with an alternative situation in which the probability of switching to MRTP only or to dual use is added to the probability of quitting and then reset to zero. This is the fourth extreme situation described in section 4.6. (See **Appendix 16** for the detailed results.)

Segment 5 "**Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users"** is fully covered in the PHIM, with tobacco use histories starting from age 10, and the possibility of initiation of MRTPs in never smokers and of re-initiation to MRTPs by former smokers considered in the MRTP scenario. The analyses varying initiation and re-initiation rates presented in **Appendices 11** and **12** and described in section 4.4.2 are relevant here, as are the zero benefit analyses presented in **Appendix 19**.

Segment 6 "**Tobacco users who use the product in conjunction with other tobacco products"** relates to dual use, and is considered in the analyses presented in **Appendix 4** and described in section 4.4.1. These analyses relate to varying G, the effective dose associated with dual use. They consider not only the possibility that smokers who become dual users do not change the daily amount smoked, only the relative frequency of CCs and MRTPs being varied, but also the possibility that smokers who become dual users increase their overall consumption from when they only smoked CCs. Dual users increasing consumption is also considered in the zero benefit analyses presented in **Appendix 19**. Also relevant are various analyses described in section 4.4.2, where those TTPs are varied which relate to initiation to dual use, re-initiation to dual use, or switching to or from dual use within current tobacco users (see **Appendices 11, 12 and 14**).

7 RESULTS AND CONCLUSIONS

7.1 The basic analysis

A summary of results from the basic analysis is given in **Appendix 1**.

Table 1 gives the tobacco use prevalences (%) predicted by the NULL and MRTP Scenario by sex and 5-year period (1990, 1995, 2000, 2005, 2010) for selected age groups (30-34, 50-54, 70-74).

In males, the prevalence of never use clearly decreases with age and, for a given age group, increases with time of follow-up. The pattern is essentially the same for both the NULL and MRTP Scenarios, as overall initiation rates do not differ between them. Also, the prevalence of former use increases with age, and decreases with time of follow-up within age for both scenarios. The overall prevalence of current use reduces somewhat with age, but varies little by time of follow-up within age. In the MRTP Scenario, the prevalence of current CC only smokers falls from 1990, most clearly seen at younger ages, with the combined number of current MRTP only users and dual users making up the rest, with MRTP users generally exceeding dual only users.

In females, the pattern is less clear, with an increase in never users and a decrease in former users with time of follow-up only being clearly seen at age 30-34. The overall proportion of current users declines with age, but within age only shows a clear decrease over time at younger ages. As for males, the proportion of current MRTP only users and dual users rises over time, with MRTP users outnumbering dual users.

Table 2 gives the reduction in the number of deaths associated with MRTP introduction, together with the percentage reductions in deaths and in attributable deaths, by disease (lung cancer, IHD, stroke, COPD, and for the four diseases combined), sex and period (1995, 2000, 2005, 2009, and overall).

Table 1 Tobacco use prevalences (%) - basic analysis

			NULL Scenario			MRTP Scenario				
Sex	**Age**	**Year**	**Never**	**Current**	**Former**	**Never**	**CC only**	**MRTP only**	**Dual**	**Former**
Male	30-34	1990	44.51	34.90	20.59	44.51	34.90	0.00	0.00	20.59
		1995	45.90	35.20	18.90	46.00	32.77	1.49	0.93	18.81
		2000	52.51	32.25	15.24	52.09	25.99	4.49	2.61	14.82
		2005	58.58	31.58	9.84	57.38	23.93	4.59	4.37	9.73
		2010	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
	50-54	1990	29.58	30.34	40.08	29.58	30.34	0.00	0.00	40.08
		1995	30.48	31.43	38.10	30.48	30.79	1.43	0.88	36.83
		2000	35.86	26.19	37.95	35.86	24.21	2.44	1.40	36.09
		2005	41.73	25.90	32.37	41.73	22.10	2.77	0.82	32.58
		2010	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
	70-74	1990	18.94	22.01	59.05	18.94	22.01	0.00	0.00	59.05
		1995	23.66	19.64	56.70	23.66	15.63	2.01	2.01	56.70
		2000	24.00	25.20	50.80	24.00	20.20	2.80	0.80	52.20
		2005	27.38	24.27	48.35	27.38	16.89	4.47	1.94	49.32
		2010	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
Female	30-34	1990	50.80	30.48	18.72	50.80	30.48	0.00	0.00	18.72
		1995	52.05	29.93	18.02	52.25	28.03	0.70	0.90	18.12
		2000	50.78	31.53	17.69	53.07	22.50	3.13	2.05	19.25
		2005	56.04	32.82	11.14	58.06	22.27	6.40	3.67	9.60
		2010	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
	50-54	1990	47.10	27.10	25.79	47.10	27.10	0.00	0.00	25.79
		1995	48.47	24.80	26.73	48.47	23.51	0.64	0.32	27.05
		2000	52.03	22.56	25.40	52.03	18.87	2.22	0.62	26.26
		2005	51.24	20.52	28.25	51.24	15.88	2.27	1.03	29.59
		2010	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
	70-74	1990	54.94	11.32	33.74	54.94	11.32	0.00	0.00	33.74
		1995	51.95	14.10	33.95	51.95	13.91	1.11	0.19	32.84
		2000	48.51	16.98	34.51	48.51	15.86	2.43	0.75	32.46
		2005	51.23	18.65	30.12	51.23	13.73	1.84	1.64	31.56
		2010	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21

Source : **Appendix 1**

Table 2 Reduction in mortality at age 30-79 which is associated with MRTP introduction – variation by year of follow-up (basic analysis)

Disease	Sex	Year	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	1995	154	0.200	0.251
		2000	446	0.605	0.773
		2005	641	0.903	1.166
		2009	844	1.250	1.628
		1990-2009	7688	0.521	0.663
	Female	1995	22	0.046	0.064
		2000	104	0.206	0.283
		2005	405	0.788	1.081
		2009	890	1.739	2.394
		1990-2009	4508	0.460	0.633
IHD	Male	1995	434	0.274	1.294
		2000	1083	0.676	3.257
		2005	1564	1.151	5.378
		2009	2024	1.653	7.678
		1990-2009	19189	0.640	3.006
	Female	1995	66	0.073	0.551
		2000	277	0.307	2.195
		2005	641	0.894	5.885
		2009	1003	1.678	10.573
		1990-2009	6963	0.422	2.995
Stroke	Male	1995	82	0.245	1.841
		2000	174	0.521	4.043
		2005	231	0.804	5.854
		2009	317	1.170	8.272
		1990-2009	3064	0.488	3.628
	Female	1995	21	0.062	0.655
		2000	87	0.256	2.675
		2005	209	0.749	7.156
		2009	328	1.309	12.032
		1990-2009	2219	0.356	3.620

(table continues)

Table 2 (contd.) Reduction in mortality at age 30-79 which is associated with MRTP introduction –variation by year of follow-up (basic analysis)

Disease	Sex	Year	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
COPD	Male	1995	86	0.248	0.441
		2000	327	0.901	1.661
		2005	460	1.250	2.338
		2009	575	1.558	2.968
		1990-2009	5266	0.739	1.349
	Female	1995	11	0.038	0.083
		2000	45	0.132	0.287
		2005	243	0.685	1.466
		2009	641	1.740	3.723
		1990-2009	2714	0.420	0.915
Four diseases	Male	1995	756	0.249	0.637
		2000	2031	0.668	1.766
		2005	2896	1.063	2.689
		2009	3759	1.481	3.708
		1990-2009	35206	0.606	1.549
	Female	1995	120	0.060	0.190
		2000	512	0.246	0.751
		2005	1498	0.803	2.207
		2009	2862	1.656	4.295
		1990-2009	16403	0.421	1.260

Source : **Appendix 1**

For all four diseases combined, and for the whole of the 20 year follow-up period, there is a reduction of 35,206 deaths in males and 16,403 in females associated with MRTP introduction. In males, the majority, 19,189 are from IHD, with 7,688 from lung cancer, 5,266 from COPD and 3,064 from stroke. In females, IHD is again the main contributor, though less predominantly so, with 6,963 deaths, as against 4,508 from lung cancer, 2,714 from COPD, and 2,219 from stroke. The difference between sexes in the distribution by disease mainly reflects the relative frequency of the diseases in the two sexes. Expressed as a percentage reduction in attributable deaths, there is little difference between the two sexes. However, the percentage reductions are much larger for IHD (males 3.01, females 3.00) and stroke (males 3.63, females 3.62) than they are for lung cancer (males 0.66, females 0.63) and COPD (males 1.35, females 0.92) reflecting the much shorter half-lives for the vascular diseases. The percentage reductions in total deaths are much more similar between the sexes. For all diseases and in both sexes, the reductions, however expressed, show a clear rise with increasing time of follow-up, reflecting the greater time for the switch to MRTP to take effect.

Table 3, extracted from **Appendix 24**, gives additional information on the reduction in mortality by age. Results (by disease and sex) are only shown for the combined 20-year period (1990-2009) and for four age groups (45-49, 55-59, 65-69, 75-79).

In females, the percentage reductions in both attributable deaths and total deaths decrease steadily with increasing age for the four diseases combined, and for each disease individually. This pattern is not, however, seen in males, except for the percentage reduction in total deaths, and then not for lung cancer and COPD. While the reduction in absolute numbers of deaths associated with MRTP introduction clearly rises with age for lung cancer and COPD (except at the highest ages in females), this is not the case for the vascular diseases. These trends depend on the relative frequency of overall deaths by age for the different diseases, the differing half-lives by disease, and the age-dependence of relative risks for IHD and stroke.

Table 3 Reduction in mortality in 1990 to 2009 which is associated with MRTP introduction – variation by age (basic analysis)

Disease	Sex	Age	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	45-49	251	0.511	0.651
		55-59	417	0.273	0.345
		65-69	1304	0.438	0.556
		75-79	2307	0.774	0.996
	Female	45-49	279	0.784	1.044
		55-59	697	0.722	0.963
		65-69	966	0.511	0.692
		75-79	213	0.100	0.146
IHD	Male	45-49	1848	1.345	3.246
		55-59	1842	0.646	2.230
		65-69	2680	0.547	3.130
		75-79	2105	0.281	3.793
	Female	45-49	779	1.956	5.316
		55-59	1174	1.132	4.609
		65-69	955	0.377	2.662
		75-79	64	0.011	0.229
Stroke	Male	45-49	208	0.786	2.389
		55-59	279	0.601	2.263
		65-69	428	0.466	4.616
		75-79	244	0.125	8.482
	Female	45-49	229	1.012	3.504
		55-59	361	0.974	4.338
		65-69	253	0.312	3.812
		75-79	29	0.012	1.345
COPD	Male	45-49	69	0.622	1.184
		55-59	148	0.353	0.641
		65-69	699	0.540	0.971
		75-79	2316	1.000	1.848
	Female	45-49	86	0.782	1.633
		55-59	296	0.775	1.576
		65-69	651	0.570	1.172
		75-79	261	0.122	0.287
Four diseases	Male	45-49	2375	1.061	2.160
		55-59	2686	0.510	1.123
		65-69	5110	0.506	1.273
		75-79	6972	0.473	1.679
	Female	45-49	1373	1.259	2.581
		55-59	2528	0.918	2.023
		65-69	2826	0.443	1.188
		75-79	567	0.045	0.213

Source : **Appendix 24**

7.2 Investigating the appropriateness of the findings from the NULL Scenario

7.2.1 Comparison of ISS smoking prevalences with those predicted by the basic analysis

Table 4 shows the PHIM NULL Scenario and ISS estimates of current and former smoking prevalence and their differences by sex and year for three selected age groups, 30-34, 50-54 and 70-74.

For the years 1990 and 1995, the corresponding PHIM and ISS estimates agree quite well, with differences always less than 4%, though for later years the correspondence is less good. The correspondence is also clearly better for ages 30-34 and 50-54 than for age 70-74. The greatest differences between the two sets of estimates tend to occur in later years and for age 70-74. Thus, for example, in 2005 for males aged 70-74, PHIM overestimates the prevalence of current smoking by 10.9% (24.3% vs 13.4%) and underestimates the prevalence of former smoking by 10.3% (48.4% vs 58.7%).

As noted in section 4.2.1, exact correspondence is not to be expected for various reasons, particularly ISS estimates for the USA not yet being available past 2005 (with 2010 estimates taken to be the same as for 2005), and PHIM not taking into account differential mortality by smoking habit, which will have most effect at older age groups where death rates are highest.

While it would no doubt have been possible to modify the set of TTPs used to slightly improve fit, for example by allowing the TTPs to vary by time, there seemed no strong reason to do so, as it seems unlikely that this would have affected the main conclusions from the simulation and sensitivity analyses.

Table 4 Comparison of prevalences of current and former smoking as predicted by the PHIM NULL Scenario, and as reported by ISS

			Age 30-34			Age 50-54			Age 70-74		
Sex	**Smoking**	**Year**	**PHIM**	**ISS**	**DIFF**	**PHIM**	**ISS**	**DIFF**	**PHIM**	**ISS**	**DIFF**
Male	Current	1990	34.9	34.7	0.2	30.3	30.1	0.2	22.0	18.6	3.4
		1995	35.2	31.5	3.7	31.4	28.0	3.4	19.6	16.0	3.6
		2000	32.3	28.8	3.5	26.2	25.7	0.5	25.2	13.0	12.2
		2005	31.6	29.4	2.2	25.9	24.1	1.8	24.3	13.4	10.9
		2010	32.5	(29.4)	3.1	27.5	(24.1)	3.4	23.1	(13.4)	9.7
		Mean			2.5			1.8			8.0
Female	Current	1990	30.5	29.5	1.0	27.1	25.5	1.6	11.3	14.1	–2.8
		1995	29.9	28.0	1.9	24.8	24.5	0.3	14.1	13.6	0.5
		2000	31.5	23.9	7.6	22.6	22.1	0.5	17.0	12.3	4.7
		2005	32.8	22.7	10.1	20.4	19.3	1.1	18.7	10.5	8.2
		2010	27.3	(22.7)	4.6	23.3	(19.3)	4.0	21.5	(10.5)	11.0
		Mean			5.0			1.5			4.3
Male	Former	1990	20.6	19.7	0.9	40.1	42.2	–2.1	59.1	60.6	–1.5
		1995	18.9	15.6	3.3	38.1	39.1	–1.0	56.7	60.6	–3.9
		2000	15.2	13.6	1.6	38.0	35.9	2.1	50.8	60.6	–9.8
		2005	9.8	14.2	–4.4	32.4	32.8	–0.4	48.4	58.7	–10.3
		2010	8.7	(14.2)	–6.5	29.2	(32.8)	–3.6	47.3	(58.7)	–11.4
		Mean			–1.0			–1.0			–7.4
Female	Former	1990	18.7	18.8	–0.1	25.8	24.8	1.0	33.7	32.1	1.6
		1995	18.0	15.6	2.4	26.7	24.9	1.8	34.0	31.2	2.8
		2000	17.7	12.7	5.0	25.4	24.9	0.5	34.5	30.2	4.3
		2005	11.1	12.7	–1.6	28.3	22.5	5.9	30.1	30.5	–0.4
		2010	8.1	(12.7)	–4.6	26.9	(22.5)	4.4	31.4	(30.5)	0.9
		Mean			0.3			2.7			1.8

Source : **Appendix 1** and ISS
Notes : Cases where the differences between the PHIM and ISS estimates exceed 5% are underlined. ISS estimates to 2010 are not yet available, but are taken to be the same as for 2005
Diff = difference PHIM - ISS

7.2.2 Comparison of published estimates of the proportion of deaths attributable to smoking with those predicted by the basic analysis

Recently, the US Surgeon General (2014) published, in his Table 12.4, estimates of the number of deaths, smoking attributable deaths (SAD), and attributable percentages by disease and sex. These estimates were derived from national estimates of mortality, population and smoking prevalence, coupled with RR estimates based on analyses of Cancer Prevention Study II and updated analyses of the pooled contemporary cohort population described in Thun *et al* (2013) provided to the Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health. These estimates relate to the age group 35 years or older, and are for the period 2005-2009.

Earlier, a Morbidity and Mortality Weekly Report (MMWR) (1993) published a table giving numbers of SAD by sex and disease for the US for 1990 for age 35 years or older. The SAD were calculated similarly to those for 2005-2009, though based on earlier RR estimates given in the report. It should be noted that this report did not give total numbers of deaths or attributable percentages. To calculate these, estimates of the total numbers of deaths were obtained from WHO statistics for lung cancer, IHD and stroke for exactly comparable disease definitions. For COPD, however, data for exactly comparable definitions could not be obtained.

Table 5 compares these results with those from the basic analysis NULL Scenario for 1990, 2005 and 2009. The table shows by sex and disease, the total estimated numbers of SAD and those expressed as a percentage in two ways – firstly, of deaths from the cause and second, of total SAD from the four diseases. The footnotes show the disease definitions used for the published data.

As expected, numbers of SAD are higher for the two published reports than for the PHIM as they include deaths at age 80 or above. However, there are similarities between the direction of the trend between 1990 and 2009 based on the results from the PHIM and on

Table 5 Comparison of % smoking-attributable mortality between basic analysis (NULL Scenario) and other published estimates

Sex	Disease	Source/year[a]	Smoking attributable deaths (SAD)	SAD as % of deaths from cause	SAD as % of SAD from 4 diseases
Male	Lung cancer	MMWR 1990	81179	89.3[b]	40.3
		PHIM 1990	63444	80.5	50.4
		PHIM 2005	54965	77.5	51.0
		PHIM 2009	51823	76.8	51.1
		USSURG 2005-09	74300	83.7	38.2
	IHD	MMWR 1990	65349	26.0[b]	32.5
		PHIM 1990	38383	22.4	30.5
		PHIM 2005	29078	21.4	27.0
		PHIM 2009	26362	21.5	26.0
		USSURG 2005-09	61800	28.2	31.7
	Stroke	MMWR 1990	14978	26.8[b]	7.4
		PHIM 1990	4588	14.0	3.6
		PHIM 2005	3944	13.7	3.7
		PHIM 2009	3827	14.1	3.8
		USSURG 2005-09	8200	15.3	4.2
	COPD	MMWR 1990	39709	(81.5)[b]	19.7
		PHIM 1990	19415	57.1	15.4
		PHIM 2005	19692	53.5	18.3
		PHIM 2009	19372	52.5	19.1
		USSURG 2005-09	50400	82.0	25.9
	Four diseases	MMWR 1990	201215	(45.0)[b]	100.0
		PHIM 1990	125830	39.7	100.0
		PHIM 2005	107679	39.5	100.0
		PHIM 2009	101384	39.9	100.0
		USSURG 2005-09	194700	46.1	100.0

(table continues)

Table 5 (cont) Comparison of % smoking-attributable mortality between basic analysis (NULL Scenario) and other published estimates

Sex	Disease	Source/year[a]	Smoking attributable deaths (SAD)	SAD as % of deaths from cause	SAD as % of SAD from 4 diseases
Female	Lung cancer	MMWR 1990	35741	71.4[b]	35.1
		PHIM 1990	30645	71.8	53.5
		PHIM 2005	37486	72.9	55.3
		PHIM 2009	37202	72.7	55.8
		USSURG 2005-09	56359	80.7	37.3
	IHD	MMWR 1990	33572	14.2[b]	33.0
		PHIM 1990	12647	12.8	22.0
		PHIM 2005	10885	15.2	16.0
		PHIM 2009	9484	15.9	14.2
		USSURG 2005-09	37500	19.4	24.8
	Stroke	MMWR 1990	8303	9.6[b]	8.2
		PHIM 1990	3193	9.5	5.6
		PHIM 2005	2927	10.5	4.3
		PHIM 2009	2723	10.9	4.1
		USSURG 2005-09	7100	8.7	4.7
	COPD	MMWR 1990	24138	(66.4)[b]	23.7
		PHIM 1990	10815	43.7	18.9
		PHIM 2005	16549	46.8	24.4
		PHIM 2009	17214	46.7	25.9
		USSURG 2005-09	50200	75.7	33.2
	Four diseases	MMWR 1990	101754	(24.9)[b]	100.0
		PHIM 1990	57301	28.7	100.0
		PHIM 2005	67847	36.4	100.0
		PHIM 2009	66623	38.6	100.0
		USSURG 2005-09	151159	36.8	100.0

a PHIM data are from basic analysis and for age 30-79 (see **Appendix 1**)
Morbidity and Mortality Weekly Report (MMWR) data are from Anonymous, 1993 and for age 35+. ICD-9 codes used are: lung cancer 162, IHD 410-414, stroke 430-438, COPD 491-492, 496. US Surgeon General (USSURG) data are from US Surgeon General, 2014 and also for age 35+. ICD-10 codes are used: lung cancer C33-C34, IHD I20-I25, Stroke I60-I69, COPD J40- J44.

b Total numbers of deaths by cause for age 35+ were not given, so, in order to calculate the percentage SAD formed of all deaths, WHO data were used. For lung cancer, IHD and stroke, the definitions of the diseases were exactly as used in MMWR. For COPD the definition used differed (ICD9 490-493, 495, 496), so the bracketed results may not be exactly consistent with the numbers of SAD.

those from the two published reports. Thus both sets of data show downward trends for stroke in both sexes, and for lung cancer and IHD in males, and upward trends for lung cancer and COPD in females. However, trends for IHD in females (downward – PHIM, upward – published reports) and for COPD in males (flat – PHIM, upward – the published reports) were not the same. The differing patterns partly reflect changes in the RRs used in the two cases. Thus, for example, the USSURG RRs for current smokers for COPD for males were estimated as 9.7 in 1990 for all ages, but as 29.69 at age 65-74 and 23.01 at age 75+ in 2005-2009. Similarly for females they were 10.5 in 1990 for all ages, but 38.89 at age 65-74 and 20.96 at age 75+ in 2005-2009. The differing patterns may also reflect the effect of including those aged 80 or over in the published data.

Comparing SAD as a percentage of total deaths from the cause, the results for most diseases seem quite similar between PHIM and the published data. However, there is a striking difference for COPD. Thus, for females, PHIM estimates that almost a half of the COPD deaths are attributable to smoking while the USSURG estimates are about three-quarters. The difference arises because of the much larger current smoking RRs for USSURG. Their estimates noted in the previous paragraph can be compared with our estimates of 4.56 for both sexes. Given that our estimates were based on a published meta-analysis (Forey et al., 2011) involving 120 estimates, 39 for North America, and given that only six of the 120 RR estimates exceeded 25 (maximum 46.74), that as many as 80 of the 120 estimates were less than 5, and that the 95% confidence interval for the estimate of 4.56 for North American studies was as narrow as 3.69 to 5.62, the USSURG estimate may be far too high.

Some differences can also be seen when the SAD are expressed as a percentage of total SADs for the four diseases. Thus, compared to USSURG, PHIM gives higher percentages for lung cancer, lower percentages for COPD and more similar estimates for the vascular diseases.

Note that the effect of varying RR estimates on the estimated reduction in mortality is studied in one of the sensitivity analyses, the results of which are discussed later. If our RR estimates are too low, they will tend to underestimate the magnitude of the reduction in deaths associated with MRTP introduction.

7.2.3 Conclusions regarding the appropriateness of the findings from the NULL Scenario

While the results given in the preceding section generally show reasonable consistency between the PHIM and the published sources in smoking prevalence and the estimated percentages of attributable deaths, some differences are seen. Where differences are observed, some appear to be due to weaknesses in the published data (RRs too high for COPD, lack of ISS data for 2010) or to lack of representativeness in a simulated population followed for 20 years and assumed not to die. The differences do not invalidate the PHIM, and seem unlikely to affect conclusions from the simulation and sensitivity analyses.

7.3 Simulation analyses

While the basic analysis involved only a single run of 10,000 individuals per sex, the simulation analysis involved 10 runs per sex. The first run for each sex of the simulation analysis is the same as for the basic analysis, as the process started from the same random number seed, but subsequent runs differ due to the Monte Carlo nature of the process, though based on the same set of variable parameters (other than the initial random number seed).

The main results of the simulation analysis are summarized in **Appendix 2**. Table 6 shows the estimated reduction in deaths per simulation associated with MRTP introduction over the full 20-year follow-up period (1990-2009), both for the simulation analysis and the basic analysis.

Table 6 Reduction in deaths per simulation in 1990-2009 at age 30-79 which is associated with MRTP introduction – comparison of results of simulation and basic analyses

		10 simulations			Basic
Sex	**Disease**	**Mean**	**SE**	**95% CI**	**Estimates**
Male	Four diseases	35473	1627	31793 to 39154	35206
	Lung cancer	7274	342	6501 to 8047	7688
	IHD	20329	977	18118 to 22539	19189
	Stroke	3195	158	2938 to 3552	3064
	COPD	4676	187	4252 to 5099	5266
Female	Four diseases	18479	1478	15137 to 21822	16403
	Lung cancer	5249	458	4212 to 6285	4508
	IHD	7084	492	5970 to 8198	6963
	Stroke	2207	136	1898 to 2515	2219
	COPD	3940	425	2977 to 4902	2714

Source : **Appendices 1 and 2**

The standard error from the simulations, expressed as a percentage of the overall total, ranges from about 4% to 5% in males, and from about 6% to 11% in females. The basic estimate is within the 95% CI of the simulations, except for COPD in males.

Table 7 shows tobacco use prevalences for selected age groups (30-34, 50-54, 70-74 years) and selected years (2000 – 10 years follow-up, and 2010 – 20 years follow-up), separately for the NULL and MRTP Scenarios, comparing results from the simulation and basic analyses. Standard errors, expressed as a percentage of the prevalences, range from about 1% to 3% for current CC smokers and for former smokers, but are higher than this, sometimes exceeding 10%, for current MRTP users and current dual users. The basic estimates are generally reasonably close to the mean from the simulations.

Though clearly carrying out 10 simulations provides greater precision in the estimated means, a single simulation of 10,000 individuals still produces quite an accurate estimate. This suggests that using a single simulation in the sensitivity analyses should allow good understanding of the relative importance of the different parameters.

7.4 Sensitivity analyses

7.4.1 Testing for effect of variation of different parameters, considered one at a time

The results of these sensitivity analyses are presented in **Appendices 3** to **10**. Those four parameters which do not affect the tobacco use prevalences are considered first.

Table 8(a) and Table 8(b) show how variation in the effective dose for MRTP only users, F, affects the estimated reduction in mortality associated with MRTP introduction. Results are shown by disease and sex, and are mainly for the whole follow-up period (1990-2009), though some additional results are given for the final year for the four diseases combined. Results are shown for the lowest, basic, and highest F values tested, respectively 0, 0.2 and 0.7. In Table 8a, the effective dose for dual users, G, is kept constant at 0.6, while in Table 8b it is set equal to (1+F)/2.

Table 7(a) Prevalence (%) of tobacco use in the NULL and MRTP Scenario – comparison of results of simulation and basic analysis – age 30-34

		10 simulations		
		Mean (SE)	95% CI	Basic
NULL Scenario - male				
2000	% current	32.64 (0.49)	31.52 to 33.76	32.25
	% former	15.70 (0.24)	15.16 to 16.23	15.24
2010	% current	30.53 (0.78)	28.77 to 32.29	32.48
	% former	8.20 (0.24)	7.67 to 8.74	8.71
MRTP Scenario - male				
2000	% current CC	27.21 (0.49)	26.10 to 28.32	25.99
	% current MRTP	3.59 (0.22)	3.09 to 4.09	4.49
	% current Dual	2.16 (0.15)	1.82 to 2.50	2.61
	% former	15.70 (0.33)	14.95 to 16.45	14.82
2010	% current CC	17.56 (0.36)	16.75 to 18.37	18.08
	% current MRTP	6.42 (0.20)	5.97 to 6.87	6.58
	% current Dual	4.87 (0.13)	4.58 to 5.16	5.36
	% former	8.65 (0.22)	8.15 to 9.15	8.93
NULL Scenario – female				
2000	% current	29.62 (0.68)	28.08 to 31.16	31.53
	% former	17.96 (0.39)	17.07 to 18.84	17.69
2010	% current	29.84 (0.49)	28.72 to 30.96	27.31
	% former	8.81 (0.32)	8.09 to 9.54	8.12
MRTP Scenario – female				
2000	% current CC	22.88 (0.53)	21.68 to 24.08	22.50
	% current MRTP	3.18 (0.18)	2.77 to 3.59	3.13
	% current Dual	2.37 (0.14)	2.05 to 2.69	2.05
	% former	19.08 (0.37)	18.24 to 19.92	19.25
2010	% current CC	18.13 (0.51)	16.98 to 19.28	17.10
	% current MRTP	6.32 (0.27)	5.71 to 6.93	6.15
	% current Dual	5.44 (0.25)	4.87 to 6.01	4.85
	% former	8.78 (0.28)	8.15 to 9.41	7.87

Table 7(b) Prevalence (%) of tobacco use in the NULL and MRTP Scenario – comparison of results of simulation and basic analysis – age 50-54

		10 simulations		
		Mean (SE)	95% CI	Basic
NULL Scenario - male				
2000	% current	27.72 (0.37)	26.88 to 28.56	26.19
	% former	34.57 (0.61)	33.18 to 35.96	37.95
2010	% current	26.37 (0.34)	25.60 to 27.14	27.52
	% former	29.57 (0.38)	28.71 to 30.43	29.18
MRTP Scenario - male				
2000	% current CC	24.88 (0.40)	23.98 to 25.78	24.21
	% current MRTP	2.49 (0.24)	1.95 to 3.03	2.44
	% current Dual	0.90 (0.09)	0.70 to 1.10	1.40
	% former	34.02 (0.51)	32.87 to 35.17	26.09
2010	% current CC	21.03 (0.48)	19.94 to 22.12	20.04
	% current MRTP	3.99 (0.16)	3.63 to 4.35	4.43
	% current Dual	1.29 (0.08)	1.11 to 1.47	1.29
	% former	29.40 (0.29)	28.74 to 30.06	30.10
NULL Scenario – female				
2000	% current	23.07 (0.21)	22.59 to 23.55	22.56
	% former	25.32 (0.40)	24.40 to 26.24	25.40
2010	% current	22.92 (0.31)	22.21 to 23.63	23.26
	% former	26.23 (0.47)	25.17 to 27.29	26.92
MRTP Scenario – female				
2000	% current CC	20.61 (0.29)	19.95 to 21.27	18.87
	% current MRTP	1.76 (0.12)	1.49 to 2.03	2.22
	% current Dual	0.62 (0.10)	0.39 to 0.85	0.62
	% former	25.39 (0.35)	24.60 to 26.18	26.26
2010	% current CC	17.88 (0.41)	16.95 to 18.81	17.83
	% current MRTP	3.53 (0.16)	3.17 to 3.89	2.94
	% current Dual	1.09 (0.08)	0.91 to 1.27	1.25
	% former	26.61 (0.45)	25.59 to 27.63	27.99

Table 7(c) Prevalence (%) of tobacco use in the NULL and MRTP Scenario – comparison of results of simulation and basic analysis – age 70-74

		10 simulations		
		Mean (SE)	**95% CI**	**Basic**
NULL Scenario – male				
2000	% current	25.08 (0.52)	23.91 to 26.26	25.20
	% former	52.05 (0.78)	50.30 to 53.81	50.80
2010	% current	23.98 (0.33)	23.25 to 24.72	23.09
	% former	47.80 (0.43)	46.81 to 48.78	47.33
MRTP Scenario – male				
2000	% current CC	20.00 (0.60)	18.64 to 21.36	20.20
	% current MRTP	3.44 (0.29)	2.78 to 4.10	2.80
	% current Dual	1.59 (0.14)	1.27 to 1.91	0.80
	% former	52.10 (0.73)	50.45 to 53.75	52.20
2010	% current CC	17.15 (0.54)	15.93 to 18.37	17.94
	% current MRTP	5.14 (0.36)	4.33 to 5.95	4.58
	% current Dual	1.81 (0.11)	1.56 to 2.06	2.10
	% former	47.68 (0.46)	46.64 to 48.72	45.80
NULL Scenario – female				
2000	% current	18.99 (0.71)	17.38 to 20.60	16.98
	% former	30.62 (0.76)	28.90 to 32.34	34.51
2010	% current	19.40 (0.50)	18.27 to 20.53	21.50
	% former	32.80 (0.51)	31.66 to 33.95	31.40
MRTP Scenario – female				
2000	% current CC	15.05 (0.41)	14.12 to 15.98	15.86
	% current MRTP	2.10 (0.24)	1.56 to 2.64	2.43
	% current Dual	0.94 (0.12)	0.67 to 1.21	0.75
	% former	31.52 (0.57)	30.23 to 32.81	32.46
2010	% current CC	14.35 (0.54)	13.13 to 15.57	14.77
	% current MRTP	3.70 (0.27)	3.09 to 4.31	2.43
	% current Dual	1.29 (0.17)	0.91 to 1.67	1.50
	% former	32.86 (0.62)	31.46 to 34.26	34.21

Source : **Appendices 1, 2 and 22**

Table 8(a) Effect of varying the effective dose for MRTP only users, F, on the reduction in mortality at age 30-79 which is associated with MRTP introduction (effective dose for dual users, G, kept constant at 0.6)

Disease	Sex	Period	F	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	1990-2009	0	9065	0.614	0.781
			0.2 (basic)	7688	0.521	0.663
			0.7	4329	0.293	0.373
	Female	1990-2009	0	5571	0.568	0.783
			0.2 (basic)	4508	0.460	0.633
			0.7	1906	0.194	0.268
IHD	Male	1990-2009	0	23042	0.769	3.610
			0.2 (basic)	19189	0.640	3.006
			0.7	9712	0.324	1.521
	Female	1990-2009	0	8362	0.507	3.597
			0.2 (basic)	6963	0.422	2.995
			0.7	3510	0.213	1.510
Stroke	Male	1990-2009	0	3655	0.582	4.328
			0.2 (basic)	3064	0.488	3.628
			0.7	1603	0.255	1.898
	Female	1990-2009	0	2644	0.424	4.314
			0.2 (basic)	2219	0.356	3.620
			0.7	1165	0.187	1.901
COPD	Male	1990-2009	0	6126	0.859	1.569
			0.2 (basic)	5266	0.739	1.349
			0.7	3149	0.442	0.806
	Female	1990-2009	0	3491	0.541	1.177
			0.2 (basic)	2714	0.420	0.915
			0.7	794	0.123	0.268
Four diseases	Male	1990-2009	0	41888	0.720	1.843
			0.2 (basic)	35206	0.606	1.549
			0.7	18792	0.323	0.827
	Female	1990-2009	0	20068	0.515	1.541
			0.2 (basic)	16403	0.421	1.260
			0.7	7375	0.189	0.566
	Male	2009	0	4560	1.796	4.498
			0.2 (basic)	3759	1.481	3.708
			0.7	1810	0.713	1.786
	Female	2009	0	3284	1.900	4.929
			0.2 (basic)	2862	1.656	4.295
			0.7	1830	1.059	2.746

Source : **Appendices 1 and 3**

Table 8(b) Effect of varying the effective dose for MRTP only users, F, on the reduction in mortality at age 30-79 which is associated with MRTP introduction (effective dose for dual users, G, set at (1+F)/2)

Disease	Sex	Period	F	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	1990-2009	0	9417	0.638	0.812
			0.2 (basic)	7688	0.521	0.663
			0.7	3493	0.237	0.301
	Female	1990-2009	0	5796	0.591	0.814
			0.2 (basic)	4508	0.460	0.633
			0.7	1371	0.140	0.193
IHD	Male	1990-2009	0	23983	0.800	3.757
			0.2 (basic)	19189	0.640	3.006
			0.7	7439	0.248	1.165
	Female	1990-2009	0	8667	0.525	3.728
			0.2 (basic)	6963	0.422	2.995
			0.7	2771	0.168	1.192
Stroke	Male	1990-2009	0	3801	0.605	4.500
			0.2 (basic)	3064	0.488	3.628
			0.7	1247	0.199	1.477
	Female	1990-2009	0	2738	0.439	4.467
			0.2 (basic)	2219	0.356	3.620
			0.7	935	0.150	1.525
COPD	Male	1990-2009	0	6353	0.891	1.627
			0.2 (basic)	5266	0.739	1.349
			0.7	2598	0.364	0.665
	Female	1990-2009	0	3653	0.566	1.231
			0.2 (basic)	2714	0.420	0.915
			0.7	401	0.062	0.135
Four diseases	Male	1990-2009	0	43554	0.749	1.916
			0.2 (basic)	35206	0.606	1.549
			0.7	14776	0.254	0.650
	Female	1990-2009	0	20854	0.535	1.601
			0.2 (basic)	16403	0.421	1.260
			0.7	5477	0.140	0.421
	Male	2009	0	4741	1.867	4.676
			0.2 (basic)	3759	1.481	3.708
			0.7	1385	0.545	1.366
	Female	2009	0	3380	1.956	5.074
			0.2 (basic)	2862	1.656	4.295
			0.7	1602	0.927	2.404

Source : **Appendices 1 and 3**

When G is kept constant at 0.6 (Table 8a), there is a very clear relationship between F and the reduction in mortality, however expressed, for each disease. For the whole 20 year period, and for the four diseases combined, a 30% reduction in effective dose (F = 0.7) would result in 18,792 fewer deaths in males and 7,375 fewer deaths in females, while a 100% reduction (F = 0) would result in 41,888 fewer deaths in males and 20,068 fewer in females. Expressed as a percentage of attributable deaths, the reductions for F = 0 rise to 1.8% for males and 1.5% for females, and are higher for the final year of follow-up, 2009; 4.5% for males and 4.9% for females. The pattern of reductions by disease noted in Table 2 for the basic analysis are similar regardless of F, though percentage reductions in attributable deaths are much higher for the vascular diseases than for lung cancer and COPD.

When G is set at (1+F)/2 (Table 8b), the relationship between F and the reduction in mortality becomes even clearer. Thus, whereas with G = 0.6, the difference in deaths in males associated with MRTP introduction varies from 41,888 for F = 0 to 18,792 for F = 0.7, with G = (1+F)/2 the difference varies from 43,554 for F = 0 to 14,776 for F = 0.7. The greater variation for G = (1+F)/2 is also evident for females, for all four diseases, and for reductions in deaths expressed as a percentage.

Table 9(a) and Table 9(b) concern variation in the effective dose for dual users, G. Table 9a compares results for G = 0.4, 0.6 and 1.2, while Table 9b includes the two values 1.5 and 2.0 intended to assist in the zero benefit analyses. 0.4 corresponds to dual users not increasing consumption, and smoking 25% CCs and 75% MRTPs with an F of 0.2. 1.2 corresponds to a 20-a-day CC smoker becoming a dual user of 20 a day of each product, F still being 0.2. It also corresponds to other possibilities, for example a dual user smoking 15 CCs and 45 MRTPs a day, or smoking 22.5 CCs and 7.5 MRTPs a day.

The pattern of mortality reductions in Table 9a is quite similar to that for F in Table 8a for each disease and overall. Thus, for the whole 20 year period, and for all the four diseases combined, the percentage reductions in attributable deaths for males range from 1.7%

Table 9(a) Effect of varying the effective dose for dual users, G, on the reduction in mortality at age 30-79 which is associated with MRTP introduction

Disease	Sex	Period	G	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	1990-2009	0.4	8384	0.568	0.723
			0.6 (basic)	7688	0.521	0.663
			1.2	5626	0.381	0.485
	Female	1990-2009	0.4	4952	0.505	0.696
			0.6 (basic)	4508	0.460	0.633
			1.2	3189	0.325	0.448
IHD	Male	1990-2009	0.4	21056	0.703	3.299
			0.6 (basic)	19189	0.640	3.006
			1.2	13636	0.455	2.136
	Female	1990-2009	0.4	7569	0.458	3.256
			0.6 (basic)	6963	0.422	2.995
			1.2	5162	0.313	2.220
Stroke	Male	1990-2009	0.4	3354	0.534	3.972
			0.6 (basic)	3064	0.488	3.628
			1.2	2200	0.350	2.604
	Female	1990-2009	0.4	2406	0.386	3.926
			0.6 (basic)	2219	0.356	3.620
			1.2	1660	0.266	2.709
COPD	Male	1990-2009	0.4	5717	0.802	1.464
			0.6 (basic)	5266	0.739	1.349
			1.2	3923	0.550	1.005
	Female	1990-2009	0.4	3035	0.470	1.023
			0.6 (basic)	2714	0.420	0.915
			1.2	1756	0.272	0.592
Four diseases	Male	1990-2009	0.4	38512	0.662	1.694
			0.6 (basic)	35206	0.606	1.549
			1.2	25385	0.437	1.117
	Female	1990-2009	0.4	17962	0.461	1.379
			0.6 (basic)	16403	0.421	1.260
			1.2	11767	0.302	0.904
	Male	2009	0.4	4116	1.621	4.060
			0.6 (basic)	3759	1.481	3.708
			1.2	2706	1.066	2.669
	Female	2009	0.4	3052	1.766	4.581
			0.6 (basic)	2862	1.656	4.295
			1.2	2300	1.331	3.452

Source : **Appendices 1 and 4**
Note that the effective dose for MRTP only users, F, is kept constant at 0.2 in these analyses

Table 9(b) Effect of varying the effective dose for dual users, G, on the reduction in deaths at age 30-79 and for the period 1990-2009 which is associated with MRTP introduction

Sex	G	Four Diseases	Lung Cancer	IHD	Stroke	COPD
Male	0.4	38512	8384	21056	3354	5717
	0.6 (basic)	35206	7688	19189	3064	5266
	0.8	31917	6996	17329	2775	4817
	1.0	28643	6309	15479	2487	4369
	1.2	25385	5626	13636	2200	3923
	1.5	20527	4611	10887	1770	3258
	2.0	12505	2942	6346	1058	2159
Female	0.4	17962	4952	7569	2406	3035
	0.6 (basic)	16403	4508	6963	2219	2714
	0.8	14851	4066	6360	2032	2394
	1.0	13306	3626	5760	1846	2074
	1.2	11767	3189	5162	1660	1756
	1.5	9471	2539	4269	1383	1281
	2.0	5675	1467	2793	923	493

Source : **Appendices 1 and 4**
Note that the effective dose for MRTP only users, F, is kept constant at 0.2 in these analyses

(G = 0.4) to 1.1% (G = 1.2) as compared to 1.8% (F = 0) to 0.8% (F = 0.7). Similarly, for females, they range from 1.4% (G = 0.4) to 0.9% (G = 1.2), as compared to 1.5% (F = 0) to 0.6% (F = 0.7).

Table 9b restricts attention to reductions in numbers of deaths for the whole period studied, but extends the range of the G values studied. For each disease and overall, the reduction in deaths decreases monotonically with increasing G. For the four diseases combined, the reduction for G = 2.0 is 35.5% of that for the basic analysis for males and 34.6% for females. Based on the shape of the relationship of G to the reduction in deaths, it would appear that the zero benefit value of G is approximately 2.8 for each disease and overall. A value of G of 2.8 would, for example, be consistent with dual users smoking 50 CCs and 30 MRTPs a day, which seems implausible.

Tables 10(a), 10(b) and 10(c) concern variation in the relative risk, RR, values.

Table 10(a) shows results using the basic set of RR values and also using those alternative values tested where the excess RRs (RR-1) are 20% less than or 20% more than those for the basic analysis. The effect of varying RR is much smaller in magnitude than the effects of varying F and G. This is related to the smaller relative magnitude of change. From our meta-analyses is seemed unlikely that excess risks could vary more than ±20%. As regards the percentage reduction in attributable deaths the estimate is always higher for excess RRs 80% of basic than for excess RRs 120% of basic, by a factor which is quite consistent by sex, but varies by disease, being about 10% for IHD, and the four diseases combined, somewhat less for stroke, about 20% for COPD and about 35% for lung cancer. For the percentage reduction in total deaths the direction of effect varies, for IHD, stroke and the four diseases combined being greatest for excess RRs 120% of basic, but for lung cancer being greatest for excess RRs 80% of basic, with little effect being seen for COPD.

Table 10(a) Effect of varying the relative risks, RR, on the reduction in mortality at age 30-79 which is associated with MRTP introduction

Disease	Sex	Period	Excess RR (RR-1)[a]	Reduction in Deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	1990-2009	basic x 0.8	8597	0.582	0.781
			basic	7688	0.521	0.663
			basic x 1.2	6925	0.469	0.576
	Female	1990-2009	basic x 0.8	4936	0.503	0.741
			basic	4508	0.460	0.633
			basic x 1.2	4124	0.421	0.553
IHD	Male	1990-2009	basic x 0.8	17054	0.569	3.153
			basic	19189	0.640	3.006
			basic x 1.2	20897	0.697	2.877
	Female	1990-2009	basic x 0.8	6186	0.375	3.185
			basic	6963	0.422	2.995
			basic x 1.2	7578	0.459	2.829
Stroke	Male	1990-2009	basic x 0.8	2643	0.421	3.726
			basic	3064	0.488	3.628
			basic x 1.2	3428	0.546	3.540
	Female	1990-2009	basic x 0.8	1929	0.309	3.774
			basic	2219	0.356	3.620
			basic x 1.2	2461	0.395	3.480
COPD	Male	1990-2009	basic x 0.8	5269	0.739	1.502
			basic	5266	0.739	1.349
			basic x 1.2	5168	0.725	1.224
	Female	1990-2009	basic x 0.8	2638	0.409	1.009
			basic	2714	0.420	0.915
			basic x 1.2	2727	0.422	0.837
Four diseases	Male	1990-2009	basic x 0.8	33562	0.577	1.626
			basic	35206	0.606	1.549
			basic x 1.2	36418	0.626	1.488
	Female	1990-2009	basic x 0.8	15690	0.402	1.337
			basic	16403	0.421	1.260
			basic x 1.2	16890	0.433	1.198
	Male	2009	basic x 0.8	3598	1.417	3.919
			basic	3759	1.481	3.708
			basic x 1.2	3870	1.524	3.539
	Female	2009	basic x 0.8	2752	1.592	4.569
			basic	2862	1.656	4.295
			basic x 1.2	2936	1.699	4.083

Source : **Appendices 1 and 9**

[a] The factors of 0.8 and 1.2 apply to the excess RRs (RR-1) and not to the RRs themselves. Thus if a basic RR was 5, the RR for a factor of 0.8 would be 1+0.8(5-1) = 4.2

Table 10(b) Reduction in deaths at age 30-79 for the period 1990-2009 which is associated with MRTP introduction for the basic analysis compared with that using the current smoker relative risks used by the US Surgeon General (USSURG) as given in Text-table 3

		Reduction in deaths		
Sex	Disease	Basic analysis	USSURG	Ratio[a]
Male	Lung cancer	7688	4833	0.63
	IHD	19189	27414	1.43
	Stroke	3064	5763	1.88
	COPD	5266	2081	0.40
	Four diseases	35206	40091	1.14
Female	Lung cancer	4508	3363	0.75
	IHD	6963	9500	1.36
	Stroke	2219	3065	1.38
	COPD	2714	1024	0.38
	Four diseases	16403	16953	1.03

Source : **Appendices 1 and 9**
[a] Ratio USSURG/Basic analysis

Table 10(c) Comparison of percentage smoking-attributable deaths as reported by the US Surgeon General (USSURG) for 2005-2009 for age 35+ (see Table 5) and as estimated by PHIM for the same period for age 30-79 using the current smoker relative risks given in Text-table 3

		Smoking-attributable deaths as % of deaths from cause		
Sex	Disease[a]	USSURG	PHIM	PHIM/USSURG
Male	Lung cancer	83.7	86.8	1.04
	IHD	28.2	33.4	1.18
	Stroke	15.3	20.9	1.36
	COPD	82.0	89.2	1.09
	Four diseases	46.1	53.9	1.17
Female	Lung cancer	80.7	82.9	1.03
	IHD	19.4	31.6	1.63
	Stroke	8.7	18.9	2.17
	COPD	75.7	87.8	1.16
	Four diseases	36.8	55.6	1.51

Source : USSURG from Table 5, PHIM (NULL Scenario) calculated from **Appendix 9**

[a] The 10th revision ICD codes used by USSURG are lung cancer (C33-C34), IHD (I20-I25), stroke (I60-I69) and COPD (J40-J44). The ICD codes used by PHIM are lung cancer (C33-C34), IHD (I20-I22, I24, I25), stroke (I60-64, I67, I69), and COPD (J40-J47,J67). These codes are the same for lung cancer, and effectively the same for IHD and stroke, as there were no deaths recorded in 2005-2009 under codes I23, I65, I66 or I68. The numbers of deaths recorded for COPD using the PHIM codes are, compared to those recorded using the USSURG codes, 2.5% higher in males and 5.0% higher in females.

Table 10(b) compares reductions in deaths estimated using the alternative RR values reported by USSURG as shown in Text-table 3. For the four diseases combined, the estimates are not that dissimilar, being 14% higher for males and 3% higher for females using the USSURG estimates. However, differences are much greater than this for individual diseases. Thus, for males, estimates based on USSURG are lower by 37% for lung cancer and 60% for COPD, while being higher by 43% for IHD and 88% for stroke. The pattern is similar in females, with estimates based on USSURG being lower by 25% for lung cancer and 62% for COPD, and higher by 36% for IHD and 38% for stroke. The lower estimates for USSURG relate to situations where the RRs they give are substantially higher than those we derived based on meta-analysis of published data.

Table 10(c) compares the percentages of smoking-attributable deaths by cause as reported by USSURG for 2005-2009 and as already given in Table 5, with the corresponding percentages estimated by PHIM for the same period using the USSURG RRs shown in Text-table 3. The percentages for all the diseases are always higher when estimated by PHIM. The PHIM percentages are only slightly higher for lung cancer (by a factor 1.04 in males and 1.03 in females) and COPD (by 1.09 in males and 1.16 in females), but more so for IHD (by 1.18 in males and 1.63 in females) and particularly stroke (by 1.36 in males and 2.17 in females). For all four diseases combined, percentages are higher for PHIM by a factor 1.17 in males and 1.51 in females. It should be noted that only the USSURG estimates include deaths at ages 80 or over. As the vascular disease RRs decline with age (see Text-table 3), and as the proportion of deaths occurring above age 79 is particularly high for stroke, the difference in age range considered by the two analyses may help to explain the observed differences. The differences in the percentages of smoking-attributable deaths would not be explained by differences between PHIM and USSURG in the ICD codes used to define the diseases. As shown in the footnote to Table 10(c) these have only a small effect for COPD, and no effect for the other three diseases.

Table 11 concerns variation in the half-life, H, values. Results are shown for the basic set of values, and for alternatives of 20% less than and 20% more than basic. The effect of varying H is always in the same direction, with half-lives 80% of the basic value always producing larger reductions than those 120% of it. The effect is consistent over sex, and is proportionately slightly larger for percentage reduction in attributable deaths than it is for the percentage reduction in deaths. Thus, for all four diseases combined the ratio of reductions in attributable deaths for the two alternative H values tested is 1.38 for males and 1.32 for females, where the ratio of reductions for deaths is 1.35 for males and 1.29 for females. These ratios are somewhat higher for lung cancer and COPD and lower for IHD and stroke.

We now turn to the other four parameters, which do affect the tobacco use prevalences. Tables 12(a), 12(b) and 12(c) present data on variation in tobacco use prevalences at ages 30-34, 50-54 and 70-74 at the end of follow-up (2010). Results are shown for TTP factor 1 (which multiplies the TTP for switching from MRTP only to CC only, when the subject has previously used CC), TTP factor 2 (which multiplies the TTPs for quitting if the subject has previously quit), and TTP factor 3 (which multiplies the TTPs for re-initiation if the subject is a short-term quitter), and for the definition of short-term quitting. In each case, alternative values of 1 and 3 are compared with the basic value of 2. They are also shown for TTP factor 4 (which multiplies the TTPs for switching from MRTP only to CC only or to dual use, when the subject has used MRTP continuously for more than a short period) and for the definition of short-term use. TTP factor 4 has a basic value of 0, with alternative values tested of 0.5, 1 and ignore. The definition of short-term use has a basic value of 2 years with alternative values tested of 1, 3 and 4 years. Note that if TTP factor 4 is set to a value and an individual uses MRTP continuously for more than the defined period, TTP factor 1 is not applied.

Changes to the distribution of smoking prevalence in the NULL Scenario do not occur in relation to changes in TTP factors 1 and 4 (and the definition of a short-term user), which only affect transitions in the MRTP Scenario. They are also very small in relation to

Table 11 Effect of varying the half-life, H, on the reduction in mortality at age 30-79 which is associated with MRTP introduction

Disease	Sex	Period	H	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Lung cancer	Male	1990-2009	basic x 0.8	9845	0.667	0.859
			basic	7688	0.521	0.663
			basic x 1.2	6292	0.426	0.538
	Female	1990-2009	basic x 0.8	5534	0.564	0.788
			basic	4508	0.460	0.633
			basic x 1.2	3825	0.390	0.533
IHD	Male	1990-2009	basic x 0.8	21672	0.723	3.479
			basic	19189	0.640	3.006
			basic x 1.2	17236	0.575	2.641
	Female	1990-2009	basic x 0.8	7619	0.462	3.358
			basic	6963	0.422	2.995
			basic x 1.2	6419	0.389	2.701
Stroke	Male	1990-2009	basic x 0.8	3456	0.550	4.204
			basic	3064	0.488	3.628
			basic x 1.2	2746	0.437	3.174
	Female	1990-2009	basic x 0.8	2482	0.398	4.150
			basic	2219	0.356	3.620
			basic x 1.2	2003	0.321	3.199
COPD	Male	1990-2009	basic x 0.8	6454	0.906	1.675
			basic	5266	0.739	1.349
			basic x 1.2	4509	0.633	1.152
	Female	1990-2009	basic x 0.8	3232	0.501	1.102
			basic	2714	0.420	0.915
			basic x 1.2	2376	0.368	0.801
Four diseases	Male	1990-2009	basic x 0.8	41427	0.713	1.852
			basic	35206	0.606	1.549
			basic x 1.2	30782	0.529	1.338
	Female	1990-2009	basic x 0.8	18866	0.484	1.471
			basic	16403	0.421	1.260
			basic x 1.2	14623	0.375	1.112
	Male	2009	basic x 0.8	4276	1.684	4.262
			basic	3759	1.481	3.708
			basic x 1.2	3376	1.330	3.307
	Female	2009	basic x 0.8	3285	1.901	4.982
			basic	2862	1.656	4.295
			basic x 1.2	2555	1.479	3.813

Source : **Appendices 1 and 10**

Table 12(a) Effect of varying TTP factors and definitions of short-term quitting and use on tobacco use prevalence (%) at age 30-34 in 2010

			NULL Scenario			MRTP Scenario				
Parameter	Sex	Value of parameter	Never	Current	Former	Never	CC only	MRTP only	Dual use	Former
TTP factor 1[a]	Male	1	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		2 (basic)	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		3	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
	Female	1	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		2 (basic)	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		3	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
TTP factor 2[b]	Male	1	58.82	32.48	8.71	61.05	18.19	6.58	5.36	8.82
		2 (basic)	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		3	58.82	32.37	8.82	61.05	18.08	6.58	5.36	8.93
	Female	1	64.58	27.43	8.00	64.08	17.10	6.15	4.80	7.87
		2 (basic)	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		3	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
TTP factor 3[c]	Male	1	58.82	32.59	8.59	61.05	17.97	6.47	5.36	9.15
		2 (basic)	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		3	58.82	32.70	8.48	61.05	18.19	6.47	5.58	8.71
	Female	1	64.58	27.31	8.12	64.08	17.10	6.15	4.67	8.00
		2 (basic)	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		3	64.58	27.43	8.00	64.08	17.10	6.27	4.80	7.75
Definition of short-term quitter (yrs) for factor 3	Male	1	58.82	32.48	8.71	61.05	18.08	6.47	5.36	9.04
		2 (basic)	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		3	58.82	32.59	8.59	61.05	18.08	6.58	5.36	8.93
	Female	1	64.58	27.31	8.12	64.08	17.00	6.15	4.67	8.00
		2 (basic)	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		3	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
TTP factor 4	Male	0 (basic)	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		1	58.82	32.48	8.71	61.05	18.08	5.80	5.58	9.49
		ignore	58.82	32.48	8.71	61.05	18.19	5.69	5.47	9.60
	Female	0 (basic)	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		1	64.58	27.31	8.12	64.08	17.34	5.90	5.17	7.50
		ignore	64.58	27.31	8.12	64.08	17.34	5.90	5.17	7.50
Definition of short-term user (yrs) for factor 4	Male	1	58.82	32.48	8.71	61.05	17.97	6.81	5.36	8.82
		2 (basic)	58.82	32.48	8.71	61.05	18.08	6.58	5.36	8.93
		4	58.82	32.48	8.71	61.05	18.19	6.58	5.36	8.82
	Female	1	64.58	27.31	8.12	64.08	17.10	6.40	4.80	7.63
		2 (basic)	64.58	27.31	8.12	64.08	17.10	6.15	4.80	7.87
		4	64.58	27.31	8.12	64.08	17.22	6.15	4.80	7.75

Table 12(b) Effect of varying TTP factors and definitions of short-term quitting and use on tobacco use prevalence (%) at age 50-54 in 2010

			NULL Scenario			MRTP Scenario				
Parameter	Sex	Value of parameter	Never	Current	Former	Never	CC only	MRTP only	Dual use	Former
TTP factor 1[a]	Male	1	43.31	27.52	29.18	44.14	20.04	4.52	1.29	30.01
		2 (basic)	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
		3	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
	Female	1	49.82	23.26	26.92	50.00	17.91	2.85	1.25	27.99
		2 (basic)	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
		3	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
TTP factor 2[b]	Male	1	43.31	27.79	28.90	44.14	20.13	4.62	1.29	29.82
		2 (basic)	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
		3	43.31	27.24	29.46	44.14	20.04	4.25	1.02	30.56
	Female	1	49.82	23.71	26.47	50.00	18.09	3.12	1.34	27.45
		2 (basic)	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
		3	49.82	22.55	27.63	50.00	17.56	2.94	0.89	28.61
TTP factor 3[c]	Male	1	43.31	27.15	29.55	44.14	20.04	4.16	1.20	30.47
		2 (basic)	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
		3	43.31	27.61	29.09	44.14	20.31	4.52	1.29	29.73
	Female	1	49.82	22.99	27.18	50.00	17.74	2.94	1.16	28.16
		2 (basic)	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
		3	49.82	23.44	26.74	50.00	17.91	3.48	1.25	27.36
Definition of short-term quitter (yrs) for factor 3	Male	1	43.31	27.33	29.36	44.14	20.04	4.43	1.20	30.19
		2 (basic)	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
		3	43.31	27.70	28.99	44.14	20.13	4.52	1.29	29.92
	Female	1	49.82	23.08	27.09	50.00	17.83	2.94	1.07	28.16
		2 (basic)	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
		3	49.82	23.44	26.74	50.00	17.83	3.03	1.25	27.90
TTP factor 4[c]	Male	0 (basic)	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
		1	43.31	27.52	29.18	44.14	20.31	3.79	1.29	30.47
		ignore	43.31	27.52	29.18	44.14	20.31	3.79	1.48	30.29
	Female	0 (basic)	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
		1	49.82	23.26	26.92	50.00	18.00	2.94	1.43	27.63
		ignore	49.82	23.26	26.92	50.00	18.09	2.85	1.34	27.72
Definition of short-term user (yrs) for factor 4	Male	1	43.31	27.52	29.18	44.14	20.04	4.62	1.39	29.82
		2 (basic)	43.31	27.52	29.18	44.14	20.04	4.43	1.29	30.10
		4	43.31	27.52	29.18	44.14	20.22	4.25	1.39	30.01
	Female	1	49.82	23.26	26.92	50.00	17.91	2.94	1.25	27.90
		2 (basic)	49.82	23.26	26.92	50.00	17.83	2.94	1.25	27.99
		4	49.82	23.26	26.92	50.00	17.91	2.85	1.25	27.99

Table 12(c) Effect of varying TTP factors and definitions of short-term quitting and use on tobacco use prevalence (%) at age 70-74 in 2010

			NULL Scenario			MRTP Scenario				
Parameter	Sex	Value of parameter	Never	Current	Former	Never	CC only	MRTP only	Dual use	Former
TTP factor 1[a]	Male	1	29.58	23.09	47.33	29.58	17.75	4.58	2.29	45.80
		2 (basic)	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
		3	29.58	23.09	47.33	29.58	17.94	4.39	2.10	45.99
	Female	1	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		2 (basic)	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		3	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
TTP factor 2[b]	Male	1	29.58	25.19	45.23	29.58	19.66	4.77	2.48	43.51
		2 (basic)	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
		3	29.58	21.56	48.85	29.58	17.18	4.39	1.34	47.52
	Female	1	47.10	22.06	30.84	47.10	15.14	3.18	1.50	33.08
		2 (basic)	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		3	47.10	20.75	32.15	47.10	14.21	2.24	1.50	34.95
TTP factor 3[c]	Male	1	29.58	22.71	47.71	29.58	17.94	4.01	1.91	46.56
		2 (basic)	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
		3	29.58	23.28	47.14	29.58	18.13	4.77	2.10	45.42
	Female	1	47.10	21.12	31.78	47.10	14.58	2.24	1.68	34.39
		2 (basic)	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		3	47.10	21.68	31.21	47.10	14.95	2.24	1.50	34.21
Definition of short-term quitter (yrs) for factor 3	Male	1	29.58	23.09	47.33	29.58	17.94	4.20	1.91	46.37
		2 (basic)	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
		3	29.58	23.28	47.14	29.58	17.94	4.39	2.10	45.99
	Female	1	47.10	21.12	31.78	47.10	14.77	2.24	1.50	34.39
		2 (basic)	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		3	47.10	21.68	31.21	47.10	14.95	2.24	1.50	34.21
TTP factor 4[d]	Male	0 (basic)	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
		1	29.58	23.09	47.33	29.58	17.94	4.58	1.91	45.99
		Ignore	29.58	23.09	47.33	29.58	17.94	4.39	2.29	45.80
	Female	0 (basic)	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		1	47.10	21.50	31.40	47.10	14.95	2.06	1.68	34.21
		Ignore	47.10	21.50	31.40	47.10	15.14	2.06	1.50	34.21
Definition of short-term user (yrs) for factor 4	Male	1	29.58	23.09	47.33	29.58	17.75	4.58	2.10	45.99
		2 (basic)	29.58	23.09	47.33	29.58	17.94	4.58	2.10	45.80
		4	29.58	23.09	47.33	29.58	17.94	4.39	2.29	45.80
	Female	1	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		2 (basic)	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21
		4	47.10	21.50	31.40	47.10	14.77	2.43	1.50	34.21

Source: **Appendices 1 and 5-8**

[a] The TTP from MRTP to CC is multiplied by TTP factor 1 if previously used CC
[b] The TTPs for quitting are multiplied by TTP factor 2 if previously quit
[c] The TTPs for re-initiation are multiplied by TTP factor 3 if a short-term quitter
[d] The TTPs from MRTP to CCs and from MRTP to dual use are multiplied by TTP factor 4 if a more than short-term user of MRTP

changes in TTP factor 3 and the definition of a short-term quitter as they require a relatively rare event, re-initiation by a short-term quitter. The effects of TTP factor 2 are clearer, increasing the percentage of quitters at the expense of current smokers, but are very small at age 30-34, and even at age 70-74 the percentage of quitters only varies between TTP factors 1 and 3 from 45.2% to 48.9% in males and from 30.8% to 32.2% in females.

The distribution of tobacco use prevalence in the MRTP Scenario also changes little in relation to changes in the parameters studied in Table 12.

Table 13 similarly summarizes data for the same parameters in relation to the estimated reduction in mortality associated with MRTP introduction. Compared with some earlier tables, attention is restricted to overall mortality for the four diseases combined and for the whole follow-up period (1990-2009). As expected from the changes in tobacco use prevalence, the effect of changes in the parameters considered are quite small. The largest effect seems to be in relation to TTP factor 2, where increasing the value from 1 to 3 decreases the estimated reduction in deaths from 36,958 to 32,882 in males and from 17,044 to 16,022 in females.

Table 14 compares the effects on mortality for all the parameters considered in this section (ignoring the zero benefit estimates of G = 1.5 and 2.0 and the alternative USSURG RR values). It is clear that, for the range of alternative values tested, variations in the effective dose, F, has the largest effect on the percentage reduction in mortality associated with MRTP introduction, particularly if the effective dose, G, varies in line with it. Variation in G also has a moderate effect, as does variation in H. Variation in RR only has a smaller effect. Varying the TTP factors (or the associated definitions of short-term quitting or use) has little effect on the estimates. This is particularly true for TTP factor 3, where the change in the estimated percentage reduction in mortality did not always vary monotonically as the value increased. This is due presumably to the underlying effect not being large enough to outweigh the inherent sampling variation.

Table 13 Effect of varying TTP factors 1, 2 and 3 and the definition of short-term quitting on the reduction in mortality from the four diseases combined in 1990-2009 age 30-79 associated with MRTP introduction

Parameter	Sex	Value of parameter	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
TTP factor 1[a]	Male	1	35344	0.608	1.555
		2 (basic)	35206	0.606	1.549
		3	34785	0.598	1.530
	Female	1	16490	0.423	1.266
		2 (basic)	16403	0.421	1.260
		3	16240	0.416	1.279
TTP factor 2[b]	Male	1	36958	0.636	1.622
		2 (basic)	35206	0.606	1.549
		3	32882	0.566	1.450
	Female	1	17044	0.397	1.306
		2 (basic)	16403	0.421	1.260
		3	16022	0.411	1.232
TTP factor 3[c]	Male	1	36328	0.625	1.599
		2 (basic)	35206	0.606	1.549
		3	36087	0.621	1.586
	Female	1	16150	0.414	1.241
		2 (basic)	16403	0.421	1.260
		3	17125	0.439	1.314
Definition of short-term quitter (yrs) for factor 3	Male	1	34883	0.600	1.535
		2 (basic)	35206	0.606	1.549
		3	37084	0.638	1.630
	Female	1	16393	0.420	1.259
		2 (basic)	16403	0.421	1.260
		3	16580	0.425	1.272
TTP factor 4[d]	Male	0 (basic)	35206	0.606	1.549
		1	34938	0.601	1.537
		ignore	34655	0.596	1.524
	Female	0 (basic)	16403	0.421	1.260
		1	16092	0.413	1.236
		ignore	15787	0.405	1.212
Definition of short-term user (yrs) for factor 4	Male	1	35457	0.610	1.560
		2 (basic)	35206	0.606	1.549
		4	34873	0.600	1.534
	Female	1	16577	0.425	1.273
		2 (basic)	16403	0.421	1.260
		4	16143	0.414	1.240

Source : **Appendices 1 and 5-8**

[a] The TTP from MRTP to CC is multiplied by TTP factor 1 if previously used CC
[b] The TTPs for quitting are multiplied by TTP factor 2 if previously quit
[c] The TTPs for re-initiation are multiplied by TTP factor 3 if a short-term quitter
[d] The TTPs from MRTP to CCs and to dual use are multiplied by TTP factor 4 if a more than short-term user of MRTP

Table 14 Comparison of effect of varying different parameters on the estimated % reductions in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction

Parameter varied	Range of values tested (basic value)	Range of % reductions Male	Female
% Reduction in total deaths			
None (basic analysis)	-	0.606	0.421
F (MRTP dose) taking G=0.6	0.7 to 0.0 (0.2)	0.323 to 0.720	0.189 to 0.515
F (MRTP dose) taking G=(1+F)/2	0.7 to 0.0 (0.2)	0.254 to 0.749	0.140 to 0.535
G (Dual use dose)	1.2 to 0.4 (0.6)	0.437 to 0.662	0.302 to 0.461
RR (Relative risks)	−20% to +20% (0)	0.577 to 0.626	0.402 to 0.433
H (Half-life)	+20% to -20% (0)	0.529 to 0.713	0.375 to 0.484
TTP factor 1[a]	3 to 1 (2)	0.598 to 0.608	0.416 to 0.423
TTP factor 2[b]	3 to 1 (2)	0.566 to 0.636	0.411 to 0.397
TTP factor 3[c]	1 to 3 (2)	0.625 to 0.621	0.414 to 0.439
Definition of short-term quitter	1 to 3 (2)	0.600 to 0.638	0.420 to 0.425
TTP factor 4[d]	1 to 0 (0)	0.601 to 0.606	0.413 to 0.421
TTP factor ignored	-	0.596	0.405
Definition of short-term user	4 to 1 (2)	0.600 to 0.610	0.414 to 0.425
% Reduction in attributable deaths			
None (basic analysis)	-	1.549	1.260
F (MRTP dose) taking G=0.6	0.7 to 0.0 (0.2)	0.827 to 1.843	0.566 to 1.541
F (MRTP dose) taking G=(1+F)/2	0.7 to 0.0 (0.2)	0.650 to 1.916	0.421 to 1.601
G (Dual use dose)	1.2 to 0.4 (0.6)	1.117 to 1.694	0.904 to 1.379
RR (Relative risks)	+20% to -20% (0)[e]	1.488 to 1.626	1.198 to 1.337
H (Half-life)	+20% to -20% (0)	1.338 to 1.852	1.112 to 1.471
TTP factor 1[a]	3 to 1 (2)	1.530 to 1.555	1.279 to 1.266
TTP factor 2[b]	3 to 1 (2)	1.450 to 1.622	1.232 to 1.306
TTP factor 3[c]	1 to 3 (2)	1.599 to 1.586	1.241 to 1.314
Definition of short-term quitter	1 to 3 (2)	1.535 to 1.630	1.259 to 1.272
TTP factor 4[d]	1 to 0 (0)	1.537 to 1.549	1.236 to 1.260
TTP factor ignored	-	1.524	1.212
Definition of short-term user	4 to 1 (2)	1.534 to 1.560	1.240 to 1.273

Source : **Appendices 1 and 3-10**

[a] TTP from MRTP to CC increased by TTP factor 1 if previously used CC

[b] TTPs for quitting increased by TTP factor 2 if previously quit

[c] TTPs for re-initiation multiplied by TTP factor 3 if short-term quitter

[d] The TTPs from MRTP to CCs and from MRTP to dual use are multiplied by TTP factor 4 if a more than short-term user of MRTP

[e] Note reversal of direction from total deaths

The effect of varying the parameters on the estimated reductions in mortality from the four diseases combined is illustrated for males in Figures 1 to 10. The interested reader is referred to **Appendix 21** for mortality plots for females and for results for the individual diseases, and also to **Appendix 23** for plots of tobacco use prevalence.

7.4.2 Testing for the effect of variation in the assumption set for the MRTP Scenario

The results of these sensitivity analyses are presented in **Appendices 11** to **14**. Note that in all these analyses, only predictions for the MRTP Scenario vary, so results for the NULL Scenario are not presented.

Varying the relative frequency of initiation and of re-initiation to the three current tobacco use groups

Tables 15 and 16 concern variation in the relative frequency of initiation and of re-initiation to the three current tobacco use groups, and relate to the analyses described in Text-table 3 in section 4.4.2. In these analyses, the overall rates of initiation and re-initiation to current smoking are held constant. Alternative 1 decreases (and Alternative 2 increases) the rates of initiation to MRTP only and dual use, while increasing (or reducing) the rate of initiation to CC only. Alternative 3 decreases (and Alternative 4 increases) the rates of re-initiation to MRTP only and dual use, while increasing (or decreasing) the rate of re-initiation to CC only.

Table 15 presents results for tobacco use prevalence for ages 30-34, 50-54 and 70-74 at the end of follow-up (2010). Results are shown for the four alternative analyses.

Effects of varying the relative frequency of initiation rates (Alternatives 1 and 2) are mainly evident in the 30-34 age group, where the prevalence of CC only smoking varies in both sexes between about 22% under Alternative 1 and about 12% under Alternative 2. However, the effects are much smaller at age 50-54 and are not seen at all at age 70-74, as the TTPs chosen only allow initiation to occur up to age 30-34, so do not affect 70-74 year olds in 2010.

Table 15 Effect of varying the relative frequency of initiation and of re-initiation to the three current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Alternative[a]	Never	CC only	MRTP only	Dual Use	Former
30-34	Male	Basic	61.05	18.08	6.58	5.36	8.93
		Alternative 1	61.05	22.43	4.58	2.68	9.26
		Alternative 2	61.05	12.05	10.71	7.25	8.93
		Alternative 3	61.05	18.30	6.36	5.36	8.93
		Alternative 4	61.05	17.75	6.81	5.47	8.93
	Female	Basic	64.08	17.10	6.15	4.50	7.87
		Alternative 1	64.08	22.02	3.44	2.83	7.63
		Alternative 2	64.08	11.69	9.23	7.26	7.75
		Alternative 3	64.08	17.10	6.15	4.80	7.87
		Alternative 4	64.08	16.97	6.15	4.92	7.87
50-54	Male	Basic	44.14	20.04	4.43	1.29	30.10
		Alternative 1	44.14	20.13	4.25	1.29	30.19
		Alternative 2	44.14	19.94	4.52	1.29	30.10
		Alternative 3	44.14	21.61	3.23	0.92	30.10
		Alternative 4	44.14	19.11	5.17	1.57	30.01
	Female	Basic	50.0	17.83	2.94	1.25	27.99
		Alternative 1	50.0	18.09	2.67	1.25	27.99
		Alternative 2	50.0	17.65	3.03	1.34	27.95
		Alternative 3	50.0	18.72	2.67	0.71	27.90
		Alternative 4	50.0	16.76	3.83	1.43	27.99
70-74	Male	Basic	29.58	17.94	4.58	2.10	45.80
		Alternative 1	29.58	17.94	4.58	2.10	45.80
		Alternative 2	29.58	17.94	4.58	2.10	45.80
		Alternative 3	29.58	19.47	3.63	0.95	46.37
		Alternative 4	29.58	15.65	5.73	3.24	45.80
	Female	Basic	47.10	14.77	2.43	1.50	34.21
		Alternative 1	47.10	14.77	2.43	1.50	34.21
		Alternative 2	47.10	14.77	2.43	1.50	34.21
		Alternative 3	47.10	16.45	1.31	1.12	34.02
		Alternative 4	47.10	13.27	3.18	1.87	34.58

Source : **Appendices 1 and 11**

[a] In all these analyses, the overall rates of initiation and re-initiation are held constant. Alternative 1 decreases (and Alternative 2 increases) the rates of initiation to MRTP only and dual use, while increasing (or decreasing) the rate of initiation to CC only. Alternative 3 decreases (and Alternative 4 increases) the rates of re-initiation to MRTP only and dual use, while increasing (or decreasing) the rates of re-initiation to CC only. See section 4.4.2 for fuller details.

Table 16 Effect of varying the relative frequency of initiation and of re-initiation to the three current tobacco use groups on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction

Sex	Alternative[a]	Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
Male	Basic	35206	0.606	1.549
	Alternative 1	34594	0.595	1.522
	Alternative 2	35673	0.614	1.569
	Alternative 3	29223	0.503	1.286
	Alternative 4	45004	0.774	1.980
Female	Basic	16403	0.421	1.260
	Alternative 1	15982	0.410	1.227
	Alternative 2	16737	0.429	1.285
	Alternative 3	11539	0.296	0.886
	Alternative 4	21250	0.545	1.632

Source : **Appendices 1 and 11**

[a] In all these analyses, the overall rates of initiation and re-initiation are held constant. Alternative 1 decreases (and Alternative 2 increases) the rates of initiation to MRTP only and dual use, while increasing (or decreasing) the rate of initiation to CC only. Alternative 3 decreases (and Alternative 4 increases) the rates of re-initiation to MRTP only and dual use, while increasing (or decreasing) the rates of re-initiation to CC only. See section 4.4.2 for fuller details.

Effects of varying the relative frequency of re-initiation rates (Alternatives 3 and 4) are scarcely evident at all in 30-34 year olds who have little time to both quit and then re-initiate, but are more evident in older age groups, with Alternative 4 increasing the proportion of MRTP only and dual users, as compared to Alternative 3.

Table 16 presents results for the reduction in mortality associated with MRTP introduction for the four diseases combined for 1990-2009. Given effects of varying initiation rates on the distribution of smoking habits is mainly limited to younger ages, effects on mortality are quite small, with the estimated reduction in deaths increased by 3.1% in males and 4.7% in females comparing Alternative 2 with Alternative 1. Effects are greater for variation in the relative frequency of re-initiation rates where the increase is by 54% in males and by 84% in females comparing Alternative 4 with Alternative 3. This is also clearly seen in Figure 11 (Alternatives 1 and 2) and Figure 12 (Alternatives 3 and 4), which show the effects of the alternatives on mortality in males.

Varying initiation and re-initiation rates

While in Tables 15 and 16 the overall frequencies of initiation and of re-initiation to current smoking were held constant, in Tables 17 and 18 the overall rates of initiation and of re-initiation are allowed to increase. These relate to the analyses described in Text-table 5 in section 4.4.2.

Table 17 presents results for tobacco use prevalence laid out similarly to Table 15. Results are shown for 14 alternatives. Alternatives 1, 2 and 3 hold the initiation rate to current CC only smoking constant, but successively increase the initiation rates to current MRTP only and dual use. Alternatives 4-8 successively increase all the initiation rates. Alternatives 9 and 10 hold the re-initiation rates to CC only constant, while successively increasing the re-initiation rate to current MRTP only and dual use, Alternatives 11-14 successively increase all the re-initiation rates. Alternatives 7 to 8 and 13 to 14 were intended to relate to the zero benefit estimation.

Table 17 Effect of varying initiation and re-initiation rates on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Alternative[a]	Never	CC only	MRTP only	Dual use	Former
30-34	Male	Basic	61.05	18.08	6.58	5.36	8.93
		Alternative 1	56.70	17.30	9.38	6.92	9.71
		Alternative 2	51.67	17.08	12.05	8.04	11.16
		Alternative 3	42.19	16.29	15.18	12.95	13.39
		Alternative 4	47.99	25.00	7.59	6.58	12.83
		Alternative 5	39.51	27.79	9.49	7.37	15.85
		Alternative 6	23.33	34.38	13.62	9.82	18.86
		Alternative 7	14.62	40.63	12.17	10.94	21.65
		Alternative 8	2.57	48.44	13.28	8.26	27.46
		Alternative 9	61.05	18.08	6.58	5.58	8.71
		Alternative 10	61.05	18.08	6.70	6.03	8.15
		Alternative 11	61.05	18.19	6.58	5.80	8.37
		Alternative 12	61.05	18.30	6.92	5.58	8.15
		Alternative 13	61.05	18.97	7.70	5.69	6.58
		Alternative 14	61.05	19.87	8.26	6.03	4.80
	Female	Basic	64.08	17.10	6.15	4.80	7.87
		Alternative 1	60.02	16.85	8.36	6.40	8.36
		Alternative 2	54.86	16.24	11.19	8.12	9.59
		Alternative 3	46.00	15.13	13.90	13.53	11.44
		Alternative 4	51.41	21.65	8.73	7.50	10.70
		Alternative 5	39.61	27.43	10.95	9.35	12.67
		Alternative 6	27.43	35.79	10.95	9.10	16.73
		Alternative 7	17.22	40.84	12.92	9.23	19.80
		Alternative 8	2.95	50.18	12.42	9.72	24.72
		Alternative 9	64.08	17.10	6.27	4.80	7.75
		Alternative 10	64.08	17.10	6.27	4.92	7.63
		Alternative 11	64.08	17.10	6.27	4.92	7.63
		Alternative 12	64.08	17.22	6.40	4.67	7.63
		Alternative 13	64.08	17.59	6.77	5.17	6.40
		Alternative 14	64.08	18.20	7.75	5.54	4.43

(table continues)

Table 17 (cont/2) Effect of varying initiation and re-initiation rates on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Alternative[a]	Never	CC only	MRTP only	Dual use	Former
50-54	Male	Basic	44.14	20.04	4.43	1.29	30.10
		Alternative 1	43.77	20.04	4.34	1.66	30.19
		Alternative 2	43.49	20.04	4.34	1.85	30.29
		Alternative 3	42.94	20.04	4.89	1.85	30.29
		Alternative 4	43.67	20.04	4.52	1.66	30.10
		Alternative 5	43.12	20.22	4.71	1.75	30.19
		Alternative 6	42.75	20.41	4.99	1.48	30.38
		Alternative 7	41.83	20.50	4.71	2.03	30.93
		Alternative 8	39.43	21.24	5.72	2.12	31.49
		Alternative 9	44.14	20.04	5.26	1.75	28.81
		Alternative 10	44.14	20.04	6.19	2.22	27.42
		Alternative 11	44.14	21.33	4.99	1.75	27.79
		Alternative 12	44.14	21.98	5.91	2.03	25.95
		Alternative 13	44.14	25.02	9.05	3.79	18.01
		Alternative 14	44.14	26.87	13.11	4.16	11.73
	Female	Basic	50.00	17.83	2.94	1.25	27.99
		Alternative 1	49.73	17.83	2.94	1.43	28.07
		Alternative 2	49.38	17.83	3.03	1.52	28.25
		Alternative 3	48.66	17.83	3.30	1.87	28.34
		Alternative 4	49.47	17.83	3.03	1.52	28.16
		Alternative 5	48.48	17.91	3.48	1.60	28.52
		Alternative 6	47.95	18.63	3.39	1.43	28.61
		Alternative 7	46.97	18.72	3.39	1.96	28.97
		Alternative 8	42.78	19.88	4.01	2.94	30.39
		Alternative 9	50.00	17.83	3.57	1.52	27.09
		Alternative 10	50.00	17.83	4.37	1.60	26.20
		Alternative 11	50.00	18.54	3.74	1.43	26.29
		Alternative 12	50.00	18.89	4.37	2.23	24.51
		Alternative 13	50.00	22.64	7.40	3.30	16.67
		Alternative 14	50.00	25.76	9.80	4.46	9.98

(table continues)

Table 17 (cont/3) Effect of varying initiation and re-initiation rates on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Alternative[a]	Never	CC only	MRTP only	Dual use	Former
70-74	Male	Basic	29.58	17.94	4.58	2.10	45.80
		Alternative 1	29.58	17.94	4.58	2.10	45.80
		Alternative 2	29.58	17.94	4.58	2.10	45.80
		Alternative 3	29.58	17.94	4.58	2.10	45.80
		Alternative 4	29.58	17.94	4.58	2.10	45.80
		Alternative 5	29.58	17.94	4.58	2.10	45.80
		Alternative 6	29.58	17.94	4.58	2.10	45.80
		Alternative 7	29.58	17.94	4.58	2.10	45.80
		Alternative 8	29.58	17.94	4.58	2.10	45.80
		Alternative 9	29.58	17.75	6.49	2.67	43.51
		Alternative 10	29.58	17.56	8.02	2.67	42.18
		Alternative 11	29.58	18.89	6.87	1.72	42.94
		Alternative 12	29.58	20.23	7.82	3.24	39.12
		Alternative 13	29.58	25.38	13.74	6.11	25.19
		Alternative 14	29.58	28.82	18.13	7.63	15.84
	Female	Basic	47.10	14.77	2.43	1.50	34.21
		Alternative 1	47.10	14.77	2.43	1.50	34.21
		Alternative 2	47.10	14.77	2.43	1.50	34.21
		Alternative 3	47.10	14.77	2.43	1.50	34.21
		Alternative 4	47.10	14.77	2.43	1.50	34.21
		Alternative 5	47.10	14.77	2.43	1.50	34.21
		Alternative 6	47.10	14.77	2.43	1.50	34.21
		Alternative 7	47.10	14.77	2.43	1.50	34.21
		Alternative 8	47.10	14.77	2.43	1.50	34.21
		Alternative 9	47.10	14.95	3.36	2.62	31.96
		Alternative 10	47.10	14.95	4.49	1.50	31.96
		Alternative 11	47.10	15.70	3.74	1.31	32.15
		Alternative 12	47.10	16.64	3.93	1.87	30.47
		Alternative 13	47.10	20.56	8.79	5.05	18.50
		Alternative 14	47.10	23.74	14.39	6.36	8.41

Source : **Appendices 1 and 12**

[a] Alternatives 1, 2 and 3 hold the initiation rate to CC only constant, but successively increase the initiation rates to MRTP only and dual use. Alternatives 4-8 successively increase all the initiation rates. Alternatives 9 and 10 hold the re-initiation rates to CC only constant, while successively increase all the re-initiation rate to MRTP only and dual use. Alternatives 11-14 successively increase all the re-initiation rates. Alternatives 7-8 and 13-14 relate to the zero benefit estimation. See section 4.4.2 for fuller details.

Effects of successively increasing the initiation rate on current MRTP only and dual use (Alternatives 1-3 and 4-8) are, as expected, most evident at age 30-34 and not seen at all at age 70-74, with some effect seen at age 50-54. As can be seen in Table 17 at age 30-34, the net effect of the increase is to reduce the percentage of never users, and to increase the percentages in all the other four tobacco use groups. The reduction in never users is most clearly seen in Alternative 8, where increasing all the initiation rates 10-fold compared to the basic analysis meant that there were few never users (2.57% in males, 2.95% in females) by the end of the follow-up period.

In contrast to the effect of increasing the initiation rate, effects of increasing re-initiation rates (Alternatives 9-10 and 11-14) are scarcely evident at all at age 30-34. In contrast, at age 70-74, the proportions of former userss are markedly decreased (males: basic 45.80%, Alternative 13 25.19%, Alternative 14 15.84%; females: basic 34.21%, Alternative 13 18.50%, Alternative 14 8.41%) and the proportion of current users correspondingly increased, the proportion of never users in each case being 29.58% in males and 47.10% in females.

Table 18 presents results for the reduction in mortality associated with MRTP introduction for the four diseases combined for 1990-2009. The effect on mortality of increasing initiation rates (alternatives 1-3 and 4-8) is quite small. Even where all the initiation rates are increased 8-fold (Alternative 8), the estimated reduction in deaths is still not that large. Thus, for males, the reduction in deaths in the basic analysis, 35,206 is decreased to 24,541 (by 30.3%) in Alternative 8. Although the effects on smoking distributions seen in Table 17 were, as noted earlier, large at young age groups, these age groups have low death rates and contribute little to the overall death rate. It is clear that even an extreme effect of MRTP introduction on initiation rates (assuming initiation is restricted to those aged <35 years) cannot eliminate the reduction in deaths associated with its introduction.

Table 18 Effect of varying initiation and re-initiation rates on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction

Sex	Alternative[a]	Reduction in Deaths	% reduction in deaths	% reduction in attributable deaths
Male	Basic	35206	0.606	1.549
	Alternative 1	34692	0.597	1.526
	Alternative 2	34246	0.589	1.507
	Alternative 3	33623	0.578	1.479
	Alternative 4	33946	0.584	1.493
	Alternative 5	32643	0.561	1.436
	Alternative 6	30979	0.533	1.363
	Alternative 7	29013	0.499	1.276
	Alternative 8	24541	0.422	1.080
	Alternative 9	30887	0.531	1.359
	Alternative 10	25301	0.435	1.113
	Alternative 11	21297	0.366	0.937
	Alternative 12	7174	0.123	0.316
	Alternative 13	-70651	-1.125	-3.108
	Alternative 14	-146376	-2.518	-6.439
Female	Basic	16403	0.421	1.260
	Alternative 1	16145	0.414	1.240
	Alternative 2	15983	0.410	1.227
	Alternative 3	15541	0.398	1.193
	Alternative 4	15739	0.404	1.209
	Alternative 5	15136	0.388	1.162
	Alternative 6	13767	0.353	1.057
	Alternative 7	12933	0.332	0.993
	Alternative 8	9537	0.245	0.732
	Alternative 9	12755	0.327	0.979
	Alternative 10	11730	0.301	0.901
	Alternative 11	7221	0.185	0.554
	Alternative 12	-493	-0.013	-0.038
	Alternative 13	-44782	-1.148	-3.439
	Alternative 14	-85005	-2.179	-6.527

Source : **Appendices 1 and 12**

[a] Alternatives 1, 2 and 3 hold the initiation rate to CC only constant, but successively increase the initiation rates to MRTP only and dual use. Alternatives 4-8 successively increase all the initiation rates. Alternatives 9 and 10 hold the re-initiation rates to CC only constant, while successively increase all the re-initiation rate to MRTP only and dual use. Alternatives 11-14 successively increase all the re-initiation rates. Alternatives 7-8 and 13-14 relate to the zero benefit estimation. See section 4.4.2 for fuller details.

The effect on mortality of increasing re-initiation rates (Alternatives 9-10 and 11-14) is larger than the effect of increasing initiation rates, particularly where all the re-initiation rates are increased. Where re-initiation rates are increased by a large enough factor, the reduction in deaths associated with MRTP introduction is eliminated. Given that Alternative 12 involves multiplying re-initiation rates by 2, and Alternative 13 involving multiplying them by 5, the results in Table 18 suggest that the appropriate multiplication factor for zero benefit is about 2.2 to 2.3 for males, and about 2.0 for females. The effects on mortality for males are also illustrated in Figure 13 (Alternatives 1-3), Figure 14 (Alternatives 4-8), Figure 15 (Alternatives 9-10), and Figure 16 (Alternatives 11-14).

Varying quitting rates

Tables 19(a) and 20(a) concern variation in the quitting rates for MRTP only users and dual users, while keeping the quitting rates for CC only smokers constant. The analyses compare the basic analysis with alternatives in which the quitting rates of MRTP only users and dual users are multiplied by 0.5, 0.75, 1.5 or 2. Tables 19(b) and 20(b) similarly concern variation in the quitting rates for CC only smokers, while keeping the quitting rates for MRTP only users and dual users constant. Here, the basic analysis quitting rates are multiplied by 0, 0.25 and 0.5. Tables 19(c) and 20(c) concern variation in all the quitting rates. The quitting rate in the MRTP Scenario for CC only smokers is decreased 10, 20 or 30%, while the other quitting rates are increased 50, 100 or 150%. These factors were chosen with the intention of keeping the overall quit rate approximately constant.

Tables 19(a), (b) and (c) present data on tobacco use prevalences. As expected, an increasing trend in the percentage of former users is seen with increasing rates of quitting. This is evident in all age groups and both sexes. In Table 19(a), doubling the basic quit rate compared to halving it increases the percentage of former users by a factor of about 50% at age 30-34, with a much smaller proportional increase seen at higher ages. In Table 19(b), reducing the quit rate of CC only smokers to zero reduces the percentage of former users in each sex from that in the basic analysis, by about 12% at age 70-74, 11%

Table 19(a) Effect of varying quitting rates of MRTP only users and dual users on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative quit rates[a]	Never	CC only	MRTP only	Dual Use	Former
30-34	Male	Basic rates x 0.5	61.05	18.19	7.48	5.80	7.48
		Basic rates x 0.75	61.05	18.19	7.03	5.58	8.15
		Basic rates	61.05	18.08	6.58	5.36	8.93
		Basic rates x 1.5	61.05	18.08	5.58	5.13	10.16
		Basic rates x 2	61.05	18.08	5.02	4.69	11.16
	Female	Basic rates x 0.5	64.08	17.10	7.01	5.54	6.27
		Basic rates x 0.75	64.08	17.10	6.64	5.41	6.77
		Basic rates	64.08	17.10	6.15	4.80	7.87
		Basic rates x 1.5	64.08	17.10	5.90	4.55	8.36
		Basic rates x 2	64.08	17.10	4.80	4.06	9.96
50-54	Male	Basic rates x 0.5	44.14	20.04	4.89	1.29	29.64
		Basic rates x 0.75	44.14	20.04	4.52	1.29	30.01
		Basic rates	44.14	20.04	4.43	1.29	30.10
		Basic rates x 1.5	44.14	20.13	3.69	1.02	31.02
		Basic rates x 2	44.14	20.13	3.32	0.83	31.58
	Female	Basic rates x 0.5	50.00	17.74	3.39	1.60	27.27
		Basic rates x 0.75	50.00	17.74	3.39	1.34	27.54
		Basic rates	50.00	17.83	2.94	1.25	27.99
		Basic rates x 1.5	50.00	17.83	2.85	0.71	28.61
		Basic rates x 2	50.00	17.83	2.32	0.62	29.23
70-74	Male	Basic rates x 0.5	29.58	17.94	4.96	2.67	44.85
		Basic rates x 0.75	29.58	17.94	4.58	2.29	45.61
		Basic rates	29.58	17.94	4.58	2.10	45.80
		Basic rates x 1.5	29.58	18.13	3.82	1.34	47.14
		Basic rates x 2	29.58	17.94	3.44	0.76	48.28
	Female	Basic rates x 0.5	47.10	14.77	3.55	1.68	32.90
		Basic rates x 0.75	47.10	14.77	2.99	1.50	33.64
		Basic rates	47.10	14.77	2.43	1.50	34.21
		Basic rates x 1.5	47.10	14.77	2.06	1.50	34.58
		Basic rates x 2	47.10	14.77	1.68	1.50	34.95

Source : **Appendices 1 and 13**

[a] Note that quitting rates for CC only smokers are held constant

Table 19(b) Effect of varying quitting rates of CC only smokers on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative quit rates[a]	Never	CC only	MRTP only	Dual Use	Former
30-34	Male	Basic rates x 0.0	61.05	24.33	6.47	5.36	2.79
		Basic rates x 0.25	61.05	22.77	6.47	5.36	4.35
		Basic rates x 0.5	61.05	21.09	6.47	5.36	6.03
		Basic rates	61.05	18.08	6.58	5.36	8.93
	Female	Basic rates x 0.0	64.08	21.28	6.27	4.92	3.44
		Basic rates x 0.25	64.08	20.05	6.40	4.92	4.55
		Basic rates x 0.5	64.08	18.57	6.40	4.92	6.03
		Basic rates	64.08	17.10	6.15	4.80	7.87
50-54	Male	Basic rates x 0.0	44.14	31.12	4.99	1.29	18.47
		Basic rates x 0.25	44.14	27.89	4.80	1.20	21.98
		Basic rates x 0.5	44.14	24.56	4.71	1.20	25.39
		Basic rates	44.14	20.04	4.43	1.29	30.10
	Female	Basic rates x 0.0	50.00	28.97	2.85	0.89	17.29
		Basic rates x 0.25	50.00	25.31	2.85	1.16	20.68
		Basic rates x 0.5	50.00	22.55	2.94	1.25	23.26
		Basic rates	50.00	17.83	2.94	1.25	27.99
70-74	Male	Basic rates x 0.0	29.58	32.82	4.01	1.34	32.25
		Basic rates x 0.25	29.58	27.48	4.20	1.34	37.40
		Basic rates x 0.5	29.58	24.43	4.39	1.53	40.08
		Basic rates	29.58	17.94	4.58	2.10	45.80
	Female	Basic rates x 0.0	47.10	25.61	3.18	1.31	22.80
		Basic rates x 0.25	47.10	22.62	3.36	1.50	25.42
		Basic rates x 0.5	47.10	20.37	2.62	1.50	28.41
		Basic rates	47.10	14.77	2.43	1.50	34.21

Source : **Appendices 1 and 13**

[a] Note that quitting rates for MRTP only users and dual users are held constant

Table 19(c) Effect of varying all quit rates on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative quit rates[a]	Never	CC only	MRTP only	Dual Use	Former
30-34	Male	Basic rates	61.05	18.08	6.58	5.36	8.93
		Basic rates x 0.9, 1.5	61.05	18.53	5.58	5.13	9.71
		Basic rates x 0.8, 2.0	61.05	19.08	5.02	4.69	10.16
		Basic rates x 0.7, 2.5	61.05	19.98	4.46	4.02	10.49
	Female	Basic rates	64.08	17.10	6.15	4.80	7.87
		Basic rates x 0.9, 1.5	64.08	17.34	5.90	4.55	8.12
		Basic rates x 0.8, 2.0	64.08	17.59	4.80	4.06	9.47
		Basic rates x 0.7, 2.5	64.08	18.08	3.94	3.69	10.21
50-54	Male	Basic rates	44.14	20.04	4.43	1.29	30.10
		Basic rates x 0.9, 1.5	44.14	20.87	3.79	1.02	30.19
		Basic rates x 0.8, 2.0	44.14	21.70	3.42	0.83	29.92
		Basic rates x 0.7, 2.5	44.14	22.62	3.14	0.74	29.36
	Female	Basic rates	50.00	17.83	2.94	1.25	27.99
		Basic rates x 0.9, 1.5	50.00	18.18	2.94	0.71	28.16
		Basic rates x 0.8, 2.0	50.00	19.43	2.32	0.62	27.63
		Basic rates x 0.7, 2.5	50.00	20.86	1.69	0.53	26.92
70-74	Male	Basic rates	29.58	17.94	4.58	2.10	45.80
		Basic rates x 0.9, 1.5	29.58	19.27	4.01	1.34	45.80
		Basic rates x 0.8, 2.0	29.58	20.61	3.63	0.76	45.42
		Basic rates x 0.7, 2.5	29.58	20.99	3.05	0.76	45.61
	Female	Basic rates	47.10	14.77	2.43	1.50	34.21
		Basic rates x 0.9, 1.5	47.10	15.89	2.24	1.31	33.46
		Basic rates x 0.8, 2.0	47.10	17.10	1.87	1.31	32.71
		Basic rates x 0.7, 2.5	47.10	18.32	1.12	1.50	31.96

Source : **Appendices 1 and 13**

[a] The first multiplicative factor is for CC only smokers, the second for MRTP only and dual users.

Table 20(a) Effect of varying quitting rates of MRTP only users and dual users on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction

		Reduction in deaths	% Reduction in deaths	% Reduction in attributable deaths				
Sex	Relative quit rates[a]	Four diseases	Four diseases	Lung cancer	IHD	Stroke	COPD	Four Diseases
Male	Basic rates x 0.5	33671	0.579	0.633	2.877	3.471	1.288	1.481
	Basic rates x 0.75	34463	0.593	0.650	2.939	3.550	1.324	1.516
	Basic rates	35206	0.606	0.663	3.006	3.628	1.349	1.549
	Basic rates x 1.5	36800	0.633	0.694	3.139	3.793	1.412	1.619
	Basic rates x 2	37769	0.650	0.712	3.221	3.891	1.450	1.661
Female	Basic rates x 0.5	15654	0.401	0.602	2.885	3.481	0.853	1.202
	Basic rates x 0.75	16059	0.412	0.619	2.942	3.554	0.888	1.233
	Basic rates	16403	0.421	0.633	2.995	3.620	0.915	1.260
	Basic rates x 1.5	17110	0.439	0.662	3.105	3.751	0.970	1.314
	Basic rates x 2	17588	0.451	0.681	3.190	3.845	1.000	1.351

Source : **Appendices 1 and 13**

[a] Note that quitting rates for CC only smokers are held constant

Table 20(b) Effect of varying quitting rates of CC only smokers on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction

		Reduction in deaths	% Reduction in deaths	% Reduction in attributable deaths				
Sex	Relative quit rates[a]	Four diseases	Four diseases	Lung cancer	IHD	Stroke	COPD	Four Diseases
Male	Basic rates x 0.0	-49319	-0.848	-0.803	-4.673	-5.361	-1.445	-2.170
	Basic rates x 0.25	-27380	-0.471	-0.445	-2.613	-2.955	-0.778	-1.204
	Basic rates x 0.5	-5277	-0.091	-0.054	-0.650	-0.632	0.009	-0.232
	Basic rates	35206	0.606	0.663	3.006	3.628	1.349	1.549
Female	Basic rates x 0.0	-36006	-0.923	-1.436	-5.846	-6.654	-2.735	-2.765
	Basic rates x 0.25	-23413	-0.600	-0.950	-3.739	-4.189	-1.818	-1.798
	Basic rates x 0.5	-11939	-0.306	-0.502	-1.796	-1.899	-1.020	-0.917
	Basic rates	16403	0.421	0.633	2.995	3.620	0.915	1.260

Source : **Appendices 1 and 13**

[a] Note that quitting rates for MRTP only users and dual users are held constant

Table 20(c) Effect of varying quitting rates of CC only smokers on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction

		Reduction in deaths	% Reduction in deaths	% Reduction in attributable deaths				
Sex	Relative quit rates[a]	Four diseases	Four diseases	Lung cancer	IHD	Stroke	COPD	Four Diseases
Male	Basic rates	35206	0.606	0.663	3.006	3.628	1.349	1.549
	Basic rates x 0.9, 1.5	29576	0.509	0.574	2.454	3.034	1.201	1.301
	Basic rates x 0.8, 2.0	20995	0.361	0.404	1.740	2.164	0.864	0.924
	Basic rates x 0.7, 2.5	14636	0.252	0.297	1.145	1.506	0.670	0.644
Female	Basic rates	16403	0.421	0.633	2.995	3.620	0.915	1.260
	Basic rates x 0.9, 1.5	11488	0.295	0.432	2.166	2.690	0.582	0.882
	Basic rates x 0.8, 2.0	6796	0.174	0.244	1.375	1.770	0.261	0.522
	Basic rates x 0.7, 2.5	1375	0.035	0.023	1.474	0.747	−0.117	0.106

Source : **Appendices 1 and 13**

[a] The first multiplicative factor is for CC only smokers, the second for MRTP only and dual users.

at age 50-54, and 5% at age 30-34. In Table 19(c) there is no consistent trend in the overall quit rate, with a slight increase in the percentage of former smokers at younger ages and a slight decrease at older ages. There is, however, as expected, a consistent increase in the percentage of CC only smokers and a consistent decrease in the percentage of MRTP only and dual users.

Tables 20(a), (b) and (c) present data on the reduction in mortality associated with MRTP introduction. Here, results are shown for individual diseases as the half-life varies dependent on the disease. As expected, the increase in the percentage of quitters and reduction in the percentage of current smokers leads to some increase in the reduction in mortality associated with MRTP introduction. This is evident for both sexes and all diseases. In Table 20(a), doubling the basic quit rate compared to halving it increases the percentage reduction in attributable deaths for the four diseases combined from 1.48% to 1.66% in males and from 1.20% to 1.35% in females. In Table 20(b), reducing the quit rate of CC only smokers to zero reverses the estimated reduction in deaths for the four diseases combined for males associated with MRTP introduction, from 35,206 for the basic analysis to −49,319. For females, the corresponding estimates are 16,403 and −36,006. In Table 20(c), reducing the quit rate of CC only smokers, while increasing the quit rate of the other current tobacco use groups, results in a clear decrease in the reduction in deaths associated with MRTP introduction. The trend is evident in all diseases and both sexes. For the four diseases combined in males, the reduction falls from 35,206 for the basic analysis to 14,636, while the corresponding reductions in females are 16,403 and 1,375. The effect of varying the quitting rate on mortality for males is also illustrated in Figure 17 (varying quit rates for MRTP only users and dual users), and Figure 18 (varying quit rates for CC only smokers), and Figure 19 (varying all quit rates).

Varying switching rates between current tobacco users

Tables 21 and 22 vary switching rates between current tobacco users and relate to analyses described in section 4.4.2. In Alternatives 1-18, some switching rates in Text-table 4 are either halved, or multiplied by five or ten in each set of three. There are six sets, three for to switching to and three for switching from each of the current tobacco use groups. Alternatives 19-22 are comparable to Alternatives 7-9 in that switching rates from MRTP only or dual use to CC only are varied, with the basic rates multiplied by 20, 50, 100 or 150. Here, to avoid TTPs exceeding 1, TTP factor 1 is set at 1 rather than 2.

Table 21 presents data on tobacco use prevalences. Within sex and age, there is no effect of varying switch rates on the percentage of never users, and relatively little on the percentage of quitters. The major changes are in the relative distribution of the other three groups. These generally follow the direction expected by the change in switch rates. For example, in set 1, increasing the switch rate from CC or dual use to MRTP only 20-fold (basic x 10 vs. basic x 0.5) increases the percentage of MRTP only users in 30-34 year old males from 5.69% to 15.40%, and decreases the percentage of CC only smokers from 18.86% to 10.60% and that of dual users from 5.58% to 3.57%. The same pattern is seen at other ages and in females, while in other sets prevalences for the current tobacco use groups similarly increase for groups switched to and decrease for groups switched from. However, note that when considering switching to CC only (Alternatives 7-9 and 18-22), although percentages of MRTP only or dual users decrease steadily as rates are multiplied, they never reach zero as some new cases arise from re-initiation.

Table 22 presents data on the mortality reduction from MRTP introduction. For each set, except set 6 (switching from dual use), clear similar trends are seen for each disease and sex. As expected, increasing the rate of switching to CC only (sets 3 and 7) substantially decreases the reduction in mortality associated with MRTP introduction, with a 150-fold increase (from basic to basic × 150) reducing the reduction by 62.3% in males and 71.1% in females. Also as expected, increasing the rate of switching to MRTP only (set 1)

Table 21 Effect of varying switching rates between current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative switch rates	Never	CC only	MRTP only	Dual Use	Former
1. Switching from CC only or dual use to MRTP only							
30-34	Male	Basic x 0.5	61.05	18.86	5.69	5.58	8.82
		Basic	61.05	18.08	6.58	5.36	8.93
		Basic x 5	61.05	14.40	10.71	4.69	9.15
		Basic x 10	61.05	10.60	15.40	3.57	9.38
	Female	Basic x 0.5	64.08	17.47	5.54	5.17	7.75
		Basic	64.08	17.10	6.15	4.80	7.87
		Basic x 5	64.08	14.02	10.09	4.18	7.63
		Basic x 10	64.08	10.95	13.53	3.08	8.36
50-54	Male	Basic x 0.5	44.14	21.24	3.14	1.02	30.47
		Basic	44.14	20.04	4.43	1.29	30.10
		Basic x 5	44.14	13.20	12.47	1.02	29.18
		Basic x 10	44.14	7.94	17.91	0.55	29.46
	Female	Basic x 0.5	50.00	18.45	2.41	1.16	27.99
		Basic	50.00	17.83	2.94	1.25	27.99
		Basic x 5	50.00	12.21	9.71	0.80	27.27
		Basic x 10	50.00	7.31	13.90	0.45	28.34
70-74	Male	Basic x 0.5	29.58	19.08	3.63	1.72	45.99
		Basic	29.58	17.94	4.58	2.10	45.80
		Basic x 5	29.58	12.02	9.35	1.72	47.33
		Basic x 10	29.58	6.87	14.89	1.53	47.14
	Female	Basic x 0.5	47.10	15.89	2.24	0.93	33.83
		Basic	47.10	14.77	2.43	1.50	34.21
		Basic x 5	47.10	8.41	9.16	0.93	34.39
		Basic x 10	47.10	5.61	12.71	0.75	33.83
2. Switching from CC only or MRTP only to dual use							
30-34	Male	Basic x 0.5	61.05	18.19	6.70	5.25	8.82
		Basic x 5	61.05	17.41	6.25	5.80	9.49
		Basic x 10	61.05	16.52	5.92	7.37	9.15
	Female	Basic x 0.5	64.08	17.22	6.15	4.67	7.87
		Basic x 5	64.08	16.36	5.78	5.41	8.36
		Basic x 10	64.08	15.87	5.54	6.64	7.87
50-54	Male	Basic x 0.5	44.14	20.31	4.43	0.92	30.19
		Basic x 5	44.14	18.65	4.43	3.23	29.55
		Basic x 10	44.14	17.45	4.16	5.54	28.72
	Female	Basic x 0.5	50.00	18.00	3.03	1.07	27.90
		Basic x 5	50.00	15.78	2.76	2.76	28.70
		Basic x 10	50.00	14.44	2.76	4.10	28.70
70-74	Male	Basic x 0.5	29.58	17.94	4.58	2.10	45.80
		Basic x 5	29.58	16.60	4.39	3.44	45.99
		Basic x 10	29.58	15.08	4.01	5.53	45.80
	Female	Basic x 0.5	47.10	14.95	2.43	1.12	34.39
		Basic x 5	47.10	13.27	2.80	2.43	34.39
		Basic x 10	47.10	11.96	2.24	4.30	34.39

(table continues)

Table 21 (cont) Effect of varying switching rates between current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative switch rates	Never	CC only	MRTP only	Dual Use	Former
3. Switching from MRTP only or dual use to CC only							
30-34	Male	Basic x 0.5	61.05	17.97	6.70	5.47	8.82
		Basic x 5	61.05	18.75	6.25	5.02	8.93
		Basic x 10	61.05	19.98	6.14	3.46	9.38
	Female	Basic x 0.5	64.08	17.10	6.15	5.17	7.50
		Basic x 5	64.08	18.57	5.90	4.31	7.13
		Basic x 10	64.08	19.68	5.66	3.32	7.26
50-54	Male	Basic x 0.5	44.14	19.94	4.43	1.29	30.19
		Basic x 5	44.14	20.22	4.16	1.11	30.38
		Basic x 10	44.14	20.59	3.51	0.92	30.84
	Female	Basic x 0.5	50.00	17.83	2.94	1.34	27.90
		Basic x 5	50.00	18.27	3.03	0.71	27.99
		Basic x 10	50.00	18.89	1.96	0.71	28.43
70-74	Male	Basic x 0.5	29.58	17.37	4.96	2.48	45.61
		Basic x 5	29.58	18.51	4.01	1.53	46.37
		Basic x 10	29.58	19.08	4.01	1.34	45.99
	Female	Basic x 0.5	47.10	14.77	2.43	1.50	34.21
		Basic x 5	47.10	15.14	2.62	1.50	33.64
		Basic x 10	47.10	15.51	1.87	1.50	34.02
4. Switching from CC only to MRTP only or dual use							
30-34	Male	Basic x 0.5	61.05	18.75	5.80	5.36	9.04
		Basic x 5	61.05	13.84	9.82	6.36	8.93
		Basic x 10	61.05	9.82	13.50	7.14	8.48
	Female	Basic x 0.5	64.08	17.59	5.54	4.80	8.00
		Basic x 5	64.08	13.28	8.73	5.17	8.73
		Basic x 10	64.08	10.46	11.19	5.78	8.49
50-54	Male	Basic x 0.5	44.14	21.51	3.23	0.83	30.29
		Basic x 5	44.14	12.47	12.10	2.95	28.35
		Basic x 10	44.14	6.46	16.34	3.23	29.82
	Female	Basic x 0.5	50.00	18.72	2.41	0.98	27.90
		Basic x 5	50.00	11.32	9.27	2.05	27.36
		Basic x 10	50.00	6.51	13.37	2.67	27.45
70-74	Male	Basic x 0.5	29.58	19.27	3.63	1.72	45.80
		Basic x 5	29.58	10.50	8.97	3.63	47.33
		Basic x 10	29.58	5.73	13.36	4.77	46.56
	Female	Basic x 0.5	47.10	16.07	2.24	0.93	33.64
		Basic x 5	47.10	7.66	8.60	1.68	34.95
		Basic x 10	47.10	5.05	11.59	2.62	33.64

(table continues)

Table 21(cont/2) Effect of varying switching rates between current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative switch rates	Never	CC only	MRTP only	Dual Use	Former
5. Switching from MRTP only to CC only or dual use							
30-34	Male	Basic x 0.5	61.05	18.08	6.81	5.36	8.71
		Basic x 5	61.05	18.19	5.92	5.80	9.04
		Basic x 10	61.05	18.75	5.25	5.80	9.15
	Female	Basic x 0.5	64.08	17.10	6.27	4.67	7.87
		Basic x 5	64.08	17.47	5.66	4.92	7.87
		Basic x 10	64.08	17.71	5.17	5.17	7.87
50-54	Male	Basic x 0.5	44.14	20.04	4.43	1.39	30.01
		Basic x 5	44.14	20.31	3.88	1.48	30.19
		Basic x 10	44.14	20.50	3.42	1.85	30.10
	Female	Basic x 0.5	50.00	17.91	2.94	1.25	27.90
		Basic x 5	50.00	18.00	2.50	1.43	28.07
		Basic x 10	50.00	18.18	1.78	2.23	27.81
70-74	Male	Basic x 0.5	29.58	17.75	4.58	2.10	45.99
		Basic x 5	29.58	18.32	4.20	2.48	45.42
		Basic x 10	29.58	18.70	3.63	2.10	45.99
	Female	Basic x 0.5	47.10	14.77	2.62	1.50	34.02
		Basic x 5	47.10	15.14	2.24	1.50	34.02
		Basic x 10	47.10	15.14	1.68	1.87	34.21
6. Switching from dual use to CC only or MRTP only							
30-34	Male	Basic x 0.5	61.05	17.97	6.58	5.58	8.82
		Basic x 5	61.05	18.64	7.25	3.57	9.49
		Basic x 10	61.05	19.42	8.82	1.90	8.82
	Female	Basic x 0.5	64.08	17.10	6.03	5.41	7.38
		Basic x 5	64.08	18.20	6.89	3.69	7.13
		Basic x 10	64.08	18.33	8.49	2.09	7.01
50-54	Male	Basic x 0.5	44.14	19.94	4.34	1.29	30.29
		Basic x 5	44.14	20.04	4.34	0.83	30.66
		Basic x 10	44.14	20.13	4.80	0.46	30.47
	Female	Basic x 0.5	50.00	17.83	2.85	1.34	27.99
		Basic x 5	50.00	18.00	3.48	0.71	27.81
		Basic x 10	50.00	18.45	3.30	0.53	27.72
70-74	Male	Basic x 0.5	29.58	17.56	4.77	2.29	45.80
		Basic x 5	29.58	17.94	4.77	1.34	46.37
		Basic x 10	29.58	18.32	4.96	0.95	46.18
	Female	Basic x 0.5	47.10	14.77	2.43	1.50	34.21
		Basic x 5	47.10	14.77	2.62	1.50	34.02
		Basic x 10	47.10	14.95	2.43	1.50	34.02

(table continues)

Table 21(cont/3) Effect of varying switching rates between current tobacco use groups on tobacco use prevalence (%) for the MRTP Scenario in 2010

Age	Sex	Relative switch rates	Never	CC only	MRTP only	Dual Use	Former
7. Switching from MRTP only or dual use to CC only (TTP factor 1 = 1)							
30-34	Male	Basic x 20	61.05	22.88	5.25	1.90	8.93
		Basic x 50	61.05	25.78	3.68	0.78	8.71
		Basic x 100	61.05	26.90	3.01	0.22	8.82
		Basic x 150	61.05	27.79	1.79	0.22	9.15
	Female	Basic x 20	64.08	21.77	5.17	1.97	7.01
		Basic x 50	64.08	23.99	4.18	0.98	6.77
		Basic x 100	64.08	25.46	2.83	0.74	6.89
		Basic x 150	64.08	26.69	1.97	0.37	6.89
50-54	Male	Basic x 20	44.14	21.42	3.51	0.55	30.38
		Basic x 50	44.14	22.25	2.86	0.37	30.38
		Basic x 100	44.14	23.36	1.85	0.09	30.56
		Basic x 150	44.14	24.28	1.39	0.00	30.19
	Female	Basic x 20	50.00	19.34	1.87	0.53	28.25
		Basic x 50	50.00	21.21	1.25	0.36	27.18
		Basic x 100	50.00	21.57	0.89	0.36	27.18
		Basic x 150	50.00	21.84	0.80	0.27	27.09
70-74	Male	Basic x 20	29.58	19.66	4.20	0.95	45.61
		Basic x 50	29.58	20.99	3.24	0.76	45.42
		Basic x 100	29.58	21.95	2.29	0.19	45.99
		Basic x 150	29.58	23.09	1.53	0.19	45.61
	Female	Basic x 20	47.10	15.33	1.87	1.68	34.02
		Basic x 50	47.10	16.07	1.68	1.31	33.83
		Basic x 100	47.10	16.45	1.12	0.75	34.58
		Basic x 150	47.10	17.38	1.12	0.37	34.02

Source : **Appendices 1 and 14**

Table 22 Effect of varying switching rates between current tobacco use groups on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction

Sex	Relative switch rates	Reduction in deaths	% Reduction in deaths	% Reduction in attributable deaths				
		Four diseases	Four diseases	Lung cancer	IHD	Stroke	COPD	Four Diseases
1. Switching from CC or dual use to MRTP only								
Male	Basic x 0.5	29535	0.508	0.571	2.459	3.021	1.194	1.299
	Basic	35206	0.606	0.663	3.006	3.628	1.349	1.549
	Basic x 5	83882	1.443	1.484	7.667	8.642	2.672	3.690
	Basic x 10	134620	2.315	2.358	12.539	13.770	3.993	5.922
Female	Basic x 0.5	11735	0.301	0.445	2.195	2.724	0.605	0.901
	Basic	16403	0.421	0.633	2.995	3.620	0.915	1.260
	Basic x 5	41476	1.063	1.660	7.281	8.535	2.529	3.185
	Basic x 10	72973	1.871	3.022	12.400	14.187	4.699	5.603
2. Switching from CC or MRTP only to dual use								
Male	Basic x 0.5	34784	0.598	0.653	2.979	3.597	1.320	1.530
	Basic x 5	41043	0.706	0.776	3.506	4.209	1.564	1.805
	Basic x 10	46878	0.806	0.874	4.070	4.815	1.715	2.062
Female	Basic x 0.5	16390	0.420	0.630	3.010	3.639	0.902	1.259
	Basic x 5	18592	0.477	0.711	3.473	4.196	0.972	1.428
	Basic x 10	21883	0.561	0.845	4.058	4.832	1.171	1.680
3. Switching from MRTP only or dual use to CC only								
Male	Basic x 0.5	35574	0.612	0.669	3.040	3.667	1.360	1.565
	Basic x 5	32919	0.566	0.621	2.806	3.380	1.268	1.448
	Basic x 10	30574	0.526	0.580	2.594	3.131	1.190	1.345
Female	Basic x 0.5	16599	0.426	0.641	3.025	3.658	0.930	1.275
	Basic x 5	15187	0.389	0.587	2.782	3.379	0.834	1.166
	Basic x 10	13905	0.356	0.534	2.585	3.127	0.733	1.068

(table continues)

Table 22 (cont) **Effect of varying switching rates between current tobacco use groups on the reduction in mortality in 1990-2009 at age 30-79 which is associated with MRTP introduction**

Sex	Relative switch rates	Reduction in deaths	% Reduction in deaths	% Reduction in attributable deaths				
		Four diseases	Four diseases	Lung cancer	IHD	Stroke	COPD	Four Diseases
4. Switching from CC only to MRTP only or dual use								
Male	Basic x 0.5	29495	0.507	0.573	2.447	3.016	1.200	1.298
	Basic x 5	84491	1.453	1.486	7.756	8.708	2.658	3.717
	Basic x 10	136878	2.354	2.400	12.742	13.948	4.078	6.021
Female	Basic x 0.5	10785	0.277	0.407	2.026	2.528	0.548	0.828
	Basic x 5	43444	1.114	1.754	7.521	8.770	2.728	3.336
	Basic x 10	75001	1.923	3.101	12.854	14.625	4.746	5.759
5. Switching from MRTP only to CC only or dual use								
Male	Basic x 0.5	35520	0.611	0.667	3.039	3.660	1.355	1.563
	Basic x 5	32983	0.567	0.620	2.820	3.395	1.262	1.451
	Basic x 10	30778	0.529	0.583	2.611	3.161	1.197	1.354
Female	Basic x 0.5	16516	0.423	0.638	3.012	3.642	0.925	1.268
	Basic x 5	15078	0.387	0.583	2.765	3.353	0.825	1.158
	Basic x 10	13693	0.351	0.527	2.544	3.097	0.719	1.051
6. Switching from dual use to CC only or MRTP only								
Male	Basic x 0.5	35385	0.609	0.667	3.018	3.646	1.358	1.557
	Basic x 5	35440	0.610	0.666	3.033	3.647	1.351	1.559
	Basic x 10	35889	0.617	0.678	3.051	3.696	1.377	1.579
Female	Basic x 0.5	16433	0.421	0.635	2.997	3.622	0.919	1.262
	Basic x 5	16505	0.423	0.637	3.011	3.641	0.923	1.267
	Basic x 10	16386	0.420	0.633	2.984	3.602	0.922	1.258
7. Switching from MRTP only or dual use to CC only (TTP factor 1 = 1)								
Male	Basic x 20	29755	0.512	0.570	2.506	3.048	1.171	1.309
	Basic x 50	25245	0.434	0.490	2.101	2.550	1.025	1.111
	Basic x 100	17381	0.299	0.356	1.365	1.723	0.790	0.765
	Basic x 150	13264	0.228	0.282	1.001	1.295	0.642	0.583
Female	Basic x 20	13243	0.340	0.510	2.468	2.979	0.692	1.017
	Basic x 50	10476	0.269	0.404	1.973	2.420	0.516	0.804
	Basic x 100	6823	0.175	0.252	1.420	1.740	0.222	0.524
	Basic x 150	4727	0.121	0.166	1.076	1.357	0.071	0.363

Source : **Appendices 1 and 14**

substantially increases the reduction in mortality associated with MRTP introduction, with a 3.8-fold increase in males and a 4.4-fold increase in females associated with a 10-fold increase in the switching rate. Switching to dual use (set 2) also increases the reductions, but the effect is much smaller, a 1.3-fold increase in each sex for a 10-fold increase in the switching rate. In contrast, a 10-fold increase in the rate of switching from CC only (set 4) increases the reductions (3.9-fold in males and 4.6-fold in females), while similarly increasing rates of switching from MRTP only (set 5) decreases them (by 12.6% in males and 16.5% in females). Increasing 10-fold the rate of switching from dual use (set 6) has little discernible effect. The reductions in mortality for males for the seven sets are shown in Figures 20-26.

These effects on mortality are all readily understandable in terms of the F values for CC only (1), dual use (0.6) and MRTP only (0.2). Switching to or from a group with an extreme F value will clearly have more effect than switching to or from the group with an intermediate F value.

7.5 Adjusting for population size

The results of this sensitivity analysis are presented in **Appendix 15** and show the effect of adjustment for the reduced mortality in the MRTP Scenario increasing the population at risk relative to that in the NULL Scenario. This adjustment only affects the estimations of risk, the results of which are summarized in Table 23. As can be seen, the effect of the adjustment is quite modest, very small indeed for IHD and stroke, and still not very large for lung cancer and COPD. For these two diseases, the effect of adjustment is greater for males than females, and greater with increasing follow-up period. Even for 2009, the percentage reduction never exceeds 7% (males, lung cancer).

Table 23 Effect of adjustment for population size on estimates of the reduction in mortality at age 30-79 which is associated with MRTP introduction

			% reduction in deaths			% reduction in attributable deaths		
Disease	**Sex**	**Year**	**Unadjusted**	**Adjusted**	**Ratio**	**Unadjusted**	**Adjusted**	**Ratio**
Lung cancer	Male	2000	0.605	0.581	0.96	0.773	0.743	0.96
		2009	1.250	1.159	0.93	1.628	1.512	0.93
		1990-2009	0.521	0.491	0.94	0.663	0.625	0.94
	Female	2000	0.206	0.206	1.00	0.283	0.283	1.00
		2009	1.739	1.719	0.99	2.394	2.367	0.99
		1990-2009	0.460	0.456	0.99	0.639	0.629	0.99
IHD	Male	2000	0.676	0.671	0.99	3.257	3.234	0.99
		2009	1.653	1.636	0.99	7.678	7.609	0.99
		1990-2009	0.640	0.635	0.99	3.006	2.983	0.99
	Female	2000	0.307	0.307	1.00	2.195	2.195	1.00
		2009	1.678	1.674	1.00	10.573	10.549	1.00
		1990-2009	0.422	0.421	1.00	2.995	2.991	1.00
Stroke	Male	2000	0.521	0.518	0.99	4.043	4.023	1.00
		2009	1.170	1.160	0.99	8.272	8.212	0.99
		1990-2009	0.488	0.485	0.99	3.628	3.607	0.99
	Female	2000	0.256	0.256	1.00	2.675	2.673	1.00
		2009	1.309	1.306	1.00	12.032	12.010	1.00
		1990-2009	0.356	0.355	1.00	3.620	3.615	1.00
COPD	Male	2000	0.901	0.883	0.98	1.661	1.628	0.98
		2009	1.558	1.486	0.95	2.968	2.834	0.95
		1990-2009	0.739	0.714	0.97	1.349	1.303	0.97
	Female	2000	0.132	0.133	1.01	0.287	0.288	1.00
		2009	1.740	1.728	0.99	3.723	3.698	0.99
		1990-2009	0.420	0.419	1.00	0.915	0.911	1.00
Four diseases	Male	2000	0.668	0.658	0.99	1.766	1.738	0.98
		2009	1.481	1.437	0.97	3.708	3.603	0.97
		1990-2009	0.606	0.592	0.98	1.549	1.514	0.98
	Female	2000	0.246	0.246	1.00	0.751	0.751	1.00
		2009	1.656	1.646	0.99	4.295	4.270	0.99
		1990-2009	0.421	0.419	1.00	1.260	1.255	1.00

Source : **Appendices 1 and 15**

7.6 Extreme situations

Appendix 16 presents the full results for four extreme situations. In the first extreme situation, it is assumed that in the MRTP Scenario all smokers quit immediately, and that there is no further initiation or re-initiation. It is equivalent to the situation where the whole population switches to MRTP only, and MRTP has an effective dose of F = 0. As expected, inspection of these results showed that, in the MRTP Scenario, the whole population consists of never and former smokers, and that within a birth cohort (e.g. males age 50-54 at 5 years follow-up, 55-59 at 10 years follow-up, 60-64 at 15 years follow-up and 65-69 at 20 years follow-up) the percentage of never smokers and former smokers stays fixed (in the example being 30.48% and 69.52% respectively). Note also that the percentage of former smokers at 5 years follow-up is equal to the sum of the percentages of current and former smokers at the start of follow-up. Thus in the males considered above there are at age 45-49 at the start of follow-up, 33.49% current and 36.03% former smokers, which sum to 69.52%.

Of more interest are the estimated percentage drops in deaths and in attributable deaths shown in Table 24(a). These estimates are, as expected, greater than seen for any of the sensitivity analyses. Thus for the four diseases combined, the % drops in attributable deaths (26.6% in males, 25.5% in females) can be compared with 1.5% in males and 1.3% in females for the basic analysis, and no more than about 6% for any of the sensitivity analyses (see Table 22 set 4). It is notable that the % drops in attributable deaths are much lower for lung cancer and COPD than for IHD and stroke. This reflects the higher half-life estimates for lung cancer and COPD than for the vascular diseases, the excess risk from smoking being virtually eliminated for the vascular diseases by the end of the 20 year follow-up, but not for lung cancer and COPD.

In the second extreme situation, CC smoking is totally replaced by MRTP use. Initiation rates for CC only and for dual use are added to those for MRTP only use and then reset to zero. The same applies to the re-initiation rates. Switching within current tobacco users is all to MRTP only. As expected, in the MRTP Scenario, there are no current CC only

Table 24(a) Effect on the reduction in mortality in 1990-2009 at age 30-79 in the first extreme situation where all smokers quit immediately and no initiation or re-initiation occurs

Disease	Sex	Reduction in deaths	% drop in deaths	% drop in attributable deaths
Lung cancer	Male	143456	9.719	12.353
	Female	113985	11.624	15.996
IHD	Male	350437	11.693	54.652
	Female	123016	7.452	52.705
Stroke	Male	46291	7.368	54.500
	Female	34481	5.530	55.991
COPD	Male	65137	9.139	16.641
	Female	61545	9.533	20.712
Four diseases	Male	605321	10.412	26.563
	Female	333027	8.538	25.525

Source : **Appendix 16**

Table 24(b) Effect on the reduction in mortality in 1990-2009 at age 30-79 in the second extreme situation where CC smoking is totally replaced by MRTP use

Disease	Sex	Reduction in deaths	% drop in deaths	% drop in attributable deaths
Lung cancer	Male	99890	6.767	8.602
	Female	79471	8.105	11.153
IHD	Male	259044	8.644	40.399
	Female	92533	5.606	39.645
Stroke	Male	35418	5.638	41.699
	Female	26458	4.243	42.963
COPD	Male	49275	6.913	12.589
	Female	46152	7.149	15.532
Four diseases	Male	443627	7.630	19.467
	Female	244615	6.272	18.748

Source : **Appendix 16**

Table 24(c) Effect on the reduction in mortality in 1990-2009 at age 30-79 in the third extreme situation where the whole population becomes current MRTP only users

Disease	Sex	Reduction in deaths	% drop in deaths	% drop in attributable deaths
Lung cancer	Male	23388	1.584	2.017
	Female	2090	0.213	0.294
IHD	Male	75601	2.523	11.864
	Female	7059	0.428	3.041
Stroke	Male	10684	1.701	12.675
	Female	2515	0.403	4.111
COPD	Male	11585	1.625	2.969
	Female	−1164	−0.180	−0.393
Four diseases	Male	121258	2.086	5.338
	Female	10500	0.269	0.807

Source : **Appendix 16**

Table 24(d) Comparison of reductions in mortality in 1990-2009 at age 30-79 in the basic analysis, and in the fourth extreme situation, where current CC only smokers who would otherwise have switched to MRTP only or to dual use quit instead

Disease	Sex	Basic model	Extreme Situation 4	Ratio extreme/ basic
Lung cancer	Male	7688	84021	10.93
	Female	4508	68128	15.11
IHD	Male	19189	230610	12.02
	Female	6963	81691	11.73
Stroke	Male	3064	31033	10.13
	Female	2219	23409	10.55
COPD	Male	5266	41251	7.83
	Female	2714	39321	14.49
Four diseases	Male	35206	386915	10.99
	Female	16403	212548	12.96

Source : **Appendices 1 and 16**

smokers or dual users except at baseline. The percentages of never users, current MRTP only and former users at the end of the follow-up period in males are, respectively, 61.05%, 30.25% and 8.71% at age 30-34, 44.14%, 26.41% and 29.46% at age 50-54, and 29.58%, 26.34% and 44.08% at age 70-74. In females, they are 64.08%, 28.04% and 7.87% at age 30-34, 50.00%, 24.33% and 25.67% at age 50-54, and 47.10%, 21.68% and 31.21% at age 70-74.

As shown in Table 24(b), the estimated drops in deaths are smaller than those in the first extreme situation, where everyone quits, but are still substantial. Thus, for the four diseases combined, the reduction in deaths for males in the second extreme situation, 443,627, is 73.3% of the reduction in the first extreme situation, 605,321. For females, the reduction in the second situation, 244,615, is 73.5% of the reduction in the first situation, 333,027. Similar relative reductions for the two situations are also evident for each of the four diseases individually.

In the third extreme situation, the whole population takes up MRTP only use at the start of the follow-up, with no further CC only smoking, dual use or quitting. As expected, the whole population becomes current MRTP only users in the MRTP Scenario immediately after baseline. As shown in Table 24(c), this situation shows a differing effect by sex. In males, there is an overall reduction in deaths for the four diseases combined of 121,258, 20.0% of that in extreme situation 1. This reduction is mainly seen for IHD, though reductions are evident for each of the other diseases. In females, the reduction in deaths is much smaller, 10,500, and is only 3.2% of that in extreme situation 1. While the reduction is again mainly evident for IHD, and some reduction is also evident for lung cancer and stroke, there is a small increase in deaths for COPD. Note that the third extreme situation balances advantages of reductions in the effective dose for current smokers at baseline, as against increasing effective doses for those who would otherwise have stayed as never smokers or as former smokers.

In all the first three extreme situations, the % drops in deaths and attributable deaths increase with increasing length of follow-up. For example, for males for extreme situation 1, the % drop in attributable deaths, 26.563% over the whole 20-year period as shown in Table 24(a), rises steadily to 50.916% for 2009. While, in extreme situations 1 and 2, for both sexes and for extreme situation 3 in males, this is not always so for extreme situation 3 in females. Here the drops are initially (in 1991) negative and become positive later. For IHD they become positive from 1992, for stroke from 1994, and for lung cancer and COPD from 2001.

In the fourth extreme situation, current CC only smokers who would otherwise have switched to MRTP only or to dual use quit instead. Thus, the two TTPs for current CC only smokers switching are added to the quitting rate and then reset to zero. Here, the comparison is with the basic analysis. As regards prevalence, the percentages of former smokers are increased and those of current smokers, correspondingly decreased, the percentage of never smokers remaining unchanged. For males, the percentage of former smokers in 2010, 8.93% at age 30-34, 30.10% at age 50-54, and 45.80% at age 70-74 in the basic analysis becomes, respectively, 28.24%, 51.80% and 65.08% in the fourth extreme situation. For females, the percentages of former smokers, 7.87% at age 30-34, 27.99% at age 50-54, and 34.21% at age 70-74 in the basic analysis, are similarly increased in the fourth extreme situation, to, respectively, 25.34%, 46.43% and 48.97%.

As shown in Table 24(d), the reductions in deaths in the fourth extreme situation for all four diseases combined are greater than those for the basic analysis by a factor of 10.99 for males and 12.96 for females. Ratios vary somewhat by disease and sex, but all are in the range 7.83 to 15.11. The reductions in deaths in the fourth extreme situation are a substantial proportion of those shown in Table 24(a) for the first extreme situation, where all smokers quit and no initiation or re-initiation occurs. For the four diseases combined, the ratios are 386,915/605,321 = 0.639 for males, and 212,548/333,027 = 0.638 for females.

7.7 Varying combinations of parameters – first analysis

The results of these analyses are presented in **Appendix 17**. Attention is restricted to variation in the following four parameters (each using two alternatives):

(a) effective dose, with F taking the value 0.1 or 0.5, and G, concomitantly, taking the values (1+0.1)/2 = 0.55 and (1+0.5)/2 = 0.75;

(b) rates of switching to MRTP only (from CC only or dual use), with the alternatives being a half or 10 times the basic values;

(c) rates of switching to CC only (from MRTP only or dual use), with the alternatives being a half or 10 times the basic values; and

(d) quitting rates from MRTP or dual use, with the alternatives being a half or twice the basic values.

Each of the possible 16 combinations of the alternatives were tested, with combination 1 choosing those alternatives expected to produce the largest (L) reductions in mortality (F = 0.1, rates of switching to MRTP only increase 10 times, rates of switching to CC only halved, and quitting rates from MRTP doubled), while combination 16 chooses those alternatives expected to produce the smallest (S) reductions. In Tables 25 and 26 describing the results, the various alternatives chosen are marked L and S.

Table 25 presents results for tobacco use prevalence. Note that the percentage of never smokers does not vary between the 16 alternatives and that varying F has no effect on the distribution of smoking. For both sexes and all age groups, Alternative 1 is characterized by a relatively high percentage of MRTP only users and quitters, and a relatively low percentage of CC only smokers, while Alternative 16 is characterized by a relatively high percentage of CC only smokers and a low percentage of MRTP only users.

Table 26 presents results for mortality reduction. Compared to Alternative 16, Alternative 1 is associated with reductions in deaths and attributable deaths that are about 13 times higher for males and about 42 times higher for females.

Table 25(a) Effect of varying four parameters simultaneously (first analysis) on smoking prevalence (%) at age 30-34 in the MRTP Scenario in 2010

Sex	Alternative	Parameters varied[a]				Smoking prevalence				
		F[b]	Switch to[c] MRTP only	Switch to[d] CC only	Quit from[e] MRTP	Never	CC only	MRTP only	Dual use	Former
Male	1	L	L	L	L	64.17	11.05	12.72	2.34	9.71
	2	L	L	L	S	64.17	10.94	16.29	3.13	5.47
	3	L	L	S	L	64.17	13.50	11.05	1.79	9.49
	4	L	L	S	S	64.17	13.62	14.17	2.34	5.69
	5	L	S	L	L	64.17	19.53	4.58	3.35	8.37
	6	L	S	L	S	64.17	19.42	5.92	4.46	6.03
	7	L	S	S	L	64.17	21.21	4.35	2.23	8.04
	8	L	S	S	S	64.17	21.21	5.69	3.01	5.92
	9	S	L	L	L	64.17	11.05	12.72	2.34	9.71
	10	S	L	L	S	64.17	10.94	16.29	3.13	5.47
	11	S	L	S	L	64.17	13.50	11.05	1.79	9.49
	12	S	L	S	S	64.17	13.62	14.17	2.34	5.69
	13	S	S	L	L	64.17	19.53	4.58	3.35	8.37
	14	S	S	L	S	64.17	19.42	5.92	4.46	6.03
	15	S	S	S	L	64.17	21.21	4.35	2.23	8.04
	16	S	S	S	S	64.17	21.21	5.69	3.01	5.92
Female	1	L	L	L	L	65.93	11.07	11.32	2.21	9.47
	2	L	L	L	S	65.93	11.07	14.39	2.71	5.90
	3	L	L	S	L	65.93	13.53	10.58	1.85	8.12
	4	L	L	S	S	65.93	13.65	12.92	2.21	5.29
	5	L	S	L	L	65.93	17.84	4.80	3.20	8.24
	6	L	S	L	S	65.93	17.84	6.64	4.43	5.17
	7	L	S	S	L	65.93	19.80	4.18	2.46	7.63
	8	L	S	S	S	65.93	19.93	5.78	2.95	5.41
	9	S	L	L	L	65.93	11.07	11.32	2.21	9.47
	10	S	L	L	S	65.93	11.07	14.39	2.71	5.90
	11	S	L	S	L	65.93	13.53	10.58	1.85	8.12
	12	S	L	S	S	65.93	13.65	12.92	2.21	5.29
	13	S	S	L	L	65.93	17.84	4.80	3.20	8.24
	14	S	S	L	S	65.93	17.84	6.64	4.43	5.17
	15	S	S	S	L	65.93	19.80	4.18	2.46	7.63
	16	S	S	S	S	65.93	19.93	5.78	2.95	5.41

Table 25(b) Effect of varying four parameters simultaneously (first analysis) on smoking prevalence (%) at age 50-54 in the MRTP Scenario in 2010

Sex	Alternative	Parameters varied[a]				Smoking prevalence				
		F[b]	Switch to[c] MRTP only	Switch to[d] CC only	Quit from[e] MRTP	Never	CC only	MRTP only	Dual use	Former
Male	1	L	L	L	L	43.40	8.13	15.05	0.28	33.15
	2	L	L	L	S	43.40	7.85	20.31	0.74	27.70
	3	L	L	S	L	43.40	10.06	13.30	0.09	33.15
	4	L	L	S	S	43.40	9.97	18.28	0.37	27.98
	5	L	S	L	L	43.40	21.05	2.86	0.74	31.95
	6	L	S	L	S	43.40	20.96	3.79	1.75	30.10
	7	L	S	S	L	43.40	21.70	2.40	0.18	32.32
	8	L	S	S	S	43.40	21.79	3.14	0.74	30.93
	9	S	L	L	L	43.40	8.13	15.05	0.28	33.15
	10	S	L	L	S	43.40	7.85	20.31	0.74	27.70
	11	S	L	S	L	43.40	10.06	13.30	0.09	33.15
	12	S	L	S	S	43.40	9.97	18.28	0.37	27.98
	13	S	S	L	L	43.40	21.05	2.86	0.74	31.95
	14	S	S	L	S	43.40	20.96	3.79	1.75	30.10
	15	S	S	S	L	43.40	21.70	2.40	0.18	32.32
	16	S	S	S	S	43.40	21.79	3.14	0.74	30.93
Female	1	L	L	L	L	48.13	7.13	10.52	0.80	33.42
	2	L	L	L	S	48.13	7.04	18.18	1.16	25.49
	3	L	L	S	L	48.13	9.36	9.36	0.62	32.53
	4	L	L	S	S	48.13	9.36	15.42	0.62	26.47
	5	L	S	L	L	48.13	18.18	2.50	1.16	30.04
	6	L	S	L	S	48.13	18.09	3.92	2.23	27.63
	7	L	S	S	L	48.13	19.34	1.87	0.71	29.95
	8	L	S	S	S	48.13	19.61	2.76	1.25	28.25
	9	S	L	L	L	48.13	7.13	10.52	0.80	33.42
	10	S	L	L	S	48.13	7.04	18.18	1.16	25.49
	11	S	L	S	L	48.13	9.36	9.36	0.62	32.53
	12	S	L	S	S	48.13	9.36	15.42	0.62	26.47
	13	S	S	L	L	48.13	18.18	2.50	1.16	30.04
	14	S	S	L	S	48.13	18.09	3.92	2.23	27.63
	15	S	S	S	L	48.13	19.34	1.87	0.71	29.95
	16	S	S	S	S	48.13	19.61	2.76	1.25	28.25

Table 25(c) Effect of varying four parameters simultaneously (first analysis) on smoking prevalence (%) at age 70-74 in the MRTP Scenario in 2010

Sex	Alternative	Parameters varied[a]				Smoking prevalence				
		F[b]	Switch to[c] MRTP only	Switch to[d] CC only	Quit from[e] MRTP /dual	Never	CC only	MRTP only	Dual use	Former
Male	1	L	L	L	L	29.58	7.25	9.92	1.34	51.91
	2	L	L	L	S	29.58	6.07	17.18	1.34	45.04
	3	L	L	S	L	29.58	9.54	9.35	0.57	50.95
	4	L	L	S	S	29.58	9.16	14.69	1.34	45.23
	5	L	S	L	L	29.58	20.04	1.91	1.72	46.76
	6	L	S	L	S	29.58	19.85	2.86	2.48	45.23
	7	L	S	S	L	29.58	20.80	1.72	1.34	46.56
	8	L	S	S	S	29.58	20.99	2.29	1.91	45.23
	9	S	L	L	L	29.58	7.25	9.92	1.34	51.91
	10	S	L	L	S	29.58	6.07	17.18	1.34	45.04
	11	S	L	S	L	29.58	9.54	9.35	0.57	50.95
	12	S	L	S	S	29.58	9.16	14.69	1.34	45.23
	13	S	S	L	L	29.58	20.04	1.91	1.72	46.76
	14	S	S	L	S	29.58	19.85	2.86	2.48	45.23
	15	S	S	S	L	29.58	20.80	1.72	1.34	46.56
	16	S	S	S	S	29.58	20.99	2.29	1.91	45.23
Female	1	L	L	L	L	47.10	6.17	9.16	0.75	36.82
	2	L	L	L	S	47.10	6.17	13.27	1.31	32.15
	3	L	L	S	L	47.10	7.29	8.60	0.93	36.07
	4	L	L	S	S	47.10	7.66	12.52	1.50	31.21
	5	L	S	L	L	47.10	16.64	1.50	0.56	34.21
	6	L	S	L	S	47.10	16.64	2.43	0.93	32.90
	7	L	S	S	L	47.10	17.01	1.31	0.56	34.02
	8	L	S	S	S	47.10	17.20	1.87	0.75	33.08
	9	S	L	L	L	47.10	6.17	9.16	0.75	36.82
	10	S	L	L	S	47.10	6.17	13.27	1.31	32.15
	11	S	L	S	L	47.10	7.29	8.60	0.93	36.07
	12	S	L	S	S	47.10	7.66	12.52	1.50	31.21
	13	S	S	L	L	47.10	16.64	1.50	0.56	34.21
	14	S	S	L	S	47.10	16.64	2.43	0.93	32.90
	15	S	S	S	L	47.10	17.01	1.31	0.56	34.02
	16	S	S	S	S	47.10	17.20	1.87	0.75	33.08

Source : **Appendix 17**

[a] For each parameter, L means that the alternative producing the largest reduction in risk has been selected, while S means the smallest

[b] L is F = 0.1 S is F = 0.5

[c] L is 10 times the basic rate S is half of it

[d] L is half of the basic rate S is10 times it

[e] L is twice the basic rate S is half of it

Table 26 Effect of varying four parameters simultaneously (first analysis) on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction

Sex	Alternative	Parameters varied[a]				Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
		F[b]	Switch to[c] MRTP only	Switch to[d] CC only	Quit from[e] MRTP			
Male	1	L	L	L	L	158456	2.725	6.970
	2	L	L	L	S	153706	2.644	6.762
	3	L	L	S	L	137710	2.369	6.058
	4	L	L	S	S	132055	2.271	5.809
	5	L	S	L	L	31680	0.545	1.394
	6	L	S	L	S	29078	0.500	1.279
	7	L	S	S	L	27868	0.479	1.226
	8	L	S	S	S	24779	0.426	1.090
	9	S	L	L	L	96392	1.658	4.240
	10	S	L	L	S	78106	1.343	3.436
	11	S	L	S	L	83705	1.440	3.682
	12	S	L	S	S	66760	1.148	2.937
	13	S	S	L	L	20147	0.347	0.886
	14	S	S	L	S	14510	0.250	0.638
	15	S	S	S	L	17751	0.305	0.781
	16	S	S	S	S	12038	0.207	0.530
Female	1	L	L	L	L	83071	2.130	6.379
	2	L	L	L	S	79888	2.048	6.134
	3	L	L	S	L	73678	1.889	5.657
	4	L	L	S	S	70839	1.816	5.439
	5	L	S	L	L	13100	0.336	1.006
	6	L	S	L	S	11296	0.290	0.867
	7	L	S	S	L	10705	0.274	0.822
	8	L	S	S	S	9070	0.233	0.696
	9	S	L	L	L	47881	1.228	3.677
	10	S	L	L	S	37556	0.963	2.884
	11	S	L	S	L	43278	1.110	3.323
	12	S	L	S	S	33836	0.867	2.598
	13	S	S	L	L	6548	0.168	0.503
	14	S	S	L	S	2929	0.075	0.225
	15	S	S	S	L	5073	0.130	0.390
	16	S	S	S	S	1983	0.051	0.152

Source : **Appendix 17**

[a] For each parameter, L means that the alternative producing the largest reduction in risk has been selected, while S means the smallest

[b] L is F = 0.1 S is F = 0.5

[c] L is 10 times the basic rate S is half of it

[d] L is half of the basic rate S is 10 times it

[e] L is twice the basic rate S is half of it

One can assess the relative importance of the different parameters by considering pairs of alternatives in which only the parameter of interest varies. Thus, for judging the effect of F, one can calculate the ratio of reductions for alternatives 1 and 9, 2 and 10, 3 and 11 and so on up to alternatives 8 and 16, and take the mean of the ratios. Similarly, for judging the effect of switching to MRTP only, one can calculate the ratio of reductions for 1 and 5, 2 and 6, 3 and 7 and so on up to alternatives 12 and 16. These ratios proved to be essentially invariant of the index of reduction. In general, for both sexes, they were largest for variation in switching to MRTP only, where the geometric mean of the eight ratios is 5.12 in males and 8.70 in females, and next highest for variation in F, where the geometric mean is 1.79 in males and 2.36 in females. The geometric mean is substantially lower for variation in quitting from MRTP (1.20 in males and 1.39 in females) and for variation in switching to CC only (1.16 in males and 1.21 in females).

These analyses suggest a high rate of switching to MRTP only and a low F value have the greatest effect in reducing mortality. However, the comparison between the variables is not straightforward due to the different factors by which the parameters varied.

7.8 Varying combinations of parameters – second analysis

The results of these analyses are presented in **Appendix 18**. Attention is restricted to variations in the same four parameters as considered in the first analysis, the only difference being that, for each parameter, fixed ratios of twice the basic value and half the basic value were considered, in order to allow more direct comparison of their effects.

Table 27 presents results for mortality reduction, laid out similarly to Table 26. Based on these results, it could be seen that for both sexes, the largest variations are again for variation in F (geometric mean of eight ratios 1.49 in males and 1.77 in females) and for variation in the rate of switching to MRTP only (1.71 in males and 2.27 in females). Again, the geometric means are substantially lower for variation in quitting from MRTP (1.17 in males and 1.28 in females) and for variation in switching to CC only (1.03 in males and 1.04 in females).

Table 27 Effect of varying four parameters simultaneously (second analysis) in the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction

Sex	Alternative	Parameters varied[a]				Reduction in deaths	% reduction in deaths	% reduction in attributable deaths
		F[b]	Switch to[c] MRTP only	Switch to[d] CC only	Quit from[e] MRTP			
Male	1	L	L	L	L	53802	0.925	2.367
	2	L	L	L	S	50299	0.865	2.213
	3	L	L	S	L	52668	0.906	2.317
	4	L	L	S	S	48936	0.842	2.153
	5	L	S	L	L	31680	0.545	1.394
	6	L	S	L	S	29078	0.500	1.279
	7	L	S	S	L	31153	0.536	1.370
	8	L	S	S	S	28292	0.487	1.245
	9	S	L	L	L	38550	0.663	1.696
	10	S	L	L	S	31489	0.542	1.385
	11	S	L	S	L	37722	0.649	1.659
	12	S	L	S	S	30347	0.522	1.335
	13	S	S	L	L	23010	0.396	1.012
	14	S	S	L	S	18120	0.312	0.797
	15	S	S	S	L	22666	0.390	0.997
	16	S	S	S	S	17439	0.300	0.767
Female	1	L	L	L	L	26445	0.678	2.031
	2	L	L	L	S	24678	0.633	1.895
	3	L	L	S	L	25554	0.655	1.962
	4	L	L	S	S	23751	0.609	1.824
	5	L	S	L	L	13100	0.336	1.006
	6	L	S	L	S	11296	0.290	0.867
	7	L	S	S	L	12641	0.324	0.971
	8	L	S	S	S	10835	0.278	0.832
	9	S	L	L	L	17707	0.454	1.360
	10	S	L	L	S	13885	0.356	1.066
	11	S	L	S	L	16987	0.436	1.304
	12	S	L	S	S	13135	0.337	1.009
	13	S	S	L	L	8176	0.210	0.628
	14	S	S	L	S	5003	0.128	0.384
	15	S	S	S	L	7906	0.203	0.607
	16	S	S	S	S	4685	0.120	0.360

Source : **Appendix 18**

[a] For each parameter, L means that the alternative producing the largest reduction in risk has been selected, while S means the smallest

[b] L is F = 0.1 S is F = 0.4

[c] L is twice the basic rate S is half of it

[d] L is half the basic rate S is twice it

[e] L is twice the basic rate S is half of it

These results highlight a high rate of switching to MRTP only and a low F value as the most important parameters in predicting a large reduction in deaths associated with MRTP introduction.

7.9 Zero benefit analysis

Five parameters were considered which might individually, or in combination, eliminate the effect of MRTP introduction. Before describing the additional analyses to be conducted, the results of relevant previous analyses are summarized.

Dual users increasing consumption This relates to the parameter G, where the results shown in Table 9(b) suggest that a value of about G = 2.8 would eliminate the effect of MRTP introduction.

Increasing initiation rates Here the results shown in Table 18 for Alternative 8 make it clear that even increasing initiation rates 8-fold only has quite a minor effect on the reduction in deaths, reducing it 30.3% in males and 41.9% in females. It is clear that even this large increase does not come close to eliminating the reduction in deaths associated with MRTP introduction. This can be explained by initiation only occurring up to age 30-34 years, so not affecting mortality rates in those aged 55+ years during follow-up, where the great majority of deaths occur.

Increasing re-initiation rates Here the results in Table 18 for Alternative 12 show that increasing all the re-initiation rates 2-fold does approximately eliminate the reduction in deaths associated with MRTP introduction, decreasing it by 79.6% in males and 103.0% in females.

Decreasing quit rates of CC only smokers Here the results shown in Table 20(b) show that halving the quit rate of CC only smokers more than eliminates the reduction in deaths associated with MRTP, and suggests that multiplying the quit rate by about 0.57 in

males and 0.71 in females would approximately eliminate it, or by about 0.64 for the sexes combined.

Increasing switching rates to CC only smoking As shown in Table 22 set 3, increasing 10-fold rates of switching from MRTP only or dual use to CC only compared to the basic analysis only reduced the reduction in deaths associated with MRTP introduction from 35,206 to 30,574 in males, and from 16,403 to 13,905 in females. These represent, respectively, reductions of 13.2% and 15.2%. Further very large increases, shown in set 7, did give some limited additional reductions, but these calculations required setting TTP factor 1 to 1 to avoid transition probabilities exceeding 1 and cannot be compared directly with the basic analysis. Increasing switching rates to CC only smoking only affects those who have earlier initiated with or switched to MRTP, so requiring at least two transitions to occur during follow-up, which is relatively unlikely.

Based on these results (see **Appendix 19**), additional analyses were conducted to give insight into the joint effect of these parameters. Increasing initiation rates and increasing switching rates to CC only smoking were not studied as the effect was so small, but for the other parameters a sequence of five alternative values (V_1, V_2…V_5) was chosen which successively reduced the expected reduction in deaths associated with MRTP introduction. The first alternative set of analyses used all the V_1 values, the second all the V_2 values and so on. The values selected were as follows:

Effective dose for dual users, G	0.82, 1.04, 1.26, 1.48, 1.70
Re-initiation rates to CC only smoking	Basic rates x 1.1, 1.2, 1.3, 1.4, 1.5
Quit rate of CC only smokers	Basic rate x 0.964, 0.928, 0.892, 0.856, 0.820

For these parameters, where the effect of MRTP introduction could be eliminated, the values chosen are equal to the basic value plus 10%, 20%, 30%, 40% or 50% of the difference between the elimination value and the basic value. Thus, for G where the basic

value is 0.6, and the elimination value is 2.8, $V_1 = 0.6 + 0.1\ (2.8-0.6) = 0.82$, $V_2 = 0.6 + 0.2\ (2.8-0.6) = 1.04$ and so on.

It can be seen from the results in Table 28 that the estimated reduction in deaths associated with MRTP introduction reduces successively for the five alternatives, becoming clearly negative for alternatives 4 and 5 in both sexes. Interpolation suggests that for males the zero benefit estimate is about 60% of the way between Alternatives 3 and 4, while for females it is about 40% of the way between Alternatives 2 and 3. For the sexes combined, Alternative 3 is clearly closest to the zero benefit point.

While it is clear that in theory the effects of MRTP introduction might be eliminated in some situations, it seems somewhat unlikely that they would occur in practice. Thus Alternative 3, which approximately eliminates the effect, involves all of the following occurring:

1. Increasing G from 0.6 to 1.26. This would be consistent with a 20 a day CC smoker becoming a dual user of 21 CCs and 21 MRTPs a day, as compared to the 10 CCs and 10 MRTPs a day assumed in the basic analysis.
2. Increasing all the re-initiation rates by 30% from those for the basic analysis.
3. Decreasing the quit rate of CC only smokers 10.8%.

Whether such a possibility is likely to occur is open to question.

7.10 Changes in relative and absolute risk by time

Figures 27 to 34 give plots for eight individuals. For each Figure there are two plots, one showing results for relative and one for absolute risk. The first four figures (one for each disease) compare individuals each of which start to smoke CCs at age 16, and then switch to MRTPs at age 25, 40, 55 or not at all. The second four figures (again one for each disease) compare individuals again starting to smoke CCs at age 16, who then quit at age 25, 40, 55 or not at all. In all the figures, the RRs for continuing CC smokers increase

Table 28 Zero benefit analyses. Effect of varying three parameters on the reduction in mortality from the four diseases combined in 1990-2009 at age 30-79 which is associated with MRTP introduction

		Parameters varied					% reduction in attributable deaths
Sex	Alternative	G	Re-initiation rates	Quitting of CC only	Reduction in deaths	% reduction in deaths	
Male	Basic	0.60	Basic	Basic	35206	0.606	1.549
	1	0.82	x 1.1	x 0.964	27486	0.473	1.209
	2	1.04	x 1.2	x 0.928	18402	0.317	0.810
	3	1.26	x 1.3	x 0.892	7984	0.137	0.351
	4	1.48	x 1.4	x 0.856	-5838	-0.100	-0.257
	5	1.70	x 1.5	x 0.820	-14022	-0.241	-0.617
Female	Basic	0.60	Basic	Basic	16403	0.421	1.260
	1	0.82	x 1.1	x 0.964	8303	0.213	0.638
	2	1.04	x 1.2	x 0.928	2123	0.054	0.163
	3	1.26	x 1.3	x 0.892	-3433	-0.088	-0.264
	4	1.48	x 1.4	x 0.856	-8284	-0.212	-0.636
	5	1.70	x 1.5	x 0.820	-13139	-0.337	-1.009

Source : **Appendix 19**
Note that, for the smoking parameters, parameter values are expressed as a multiple of the basic value

steadily from a value of 1 at age 15 towards the basic values given in Text-table 3. For lung cancer and COPD, where the basic values are independent of age, and the half-life values are relatively long, the curves are continuous, and it takes until age 50 or so before the plotted values approximate to the basic values of 11.68 for lung cancer and 4.56 for COPD. For heart disease and stroke, where the half-life values are relatively short, and the RRs vary by age, the plotted values quite rapidly reach the basic values for age <55 years of 3.38 for IHD and 2.48 for stroke, subsequent changes being due to the reductions in basic values with age for these diseases. On quitting, the RRs decline, again more rapidly for IHD and stroke than for lung cancer and COPD, and tend asymptotically towards 1. On switching to MRTP, a similar pattern is seen but the decline is asymptotically towards 1+0.2 (RR-1) where RR is the basic value.

The individuals in the plots are all assumed to be born in 1940, so that as absolute risks were only estimated for 1980 to 2009, they are only shown in the figures for ages 40 to 69. Whereas the RRs for quitters and switchers decline with increasing age, the absolute risks increase. However, they are clearly reduced as the time of quit or switch increases. Note that the absolute risk data are available only by 5 year age group, so that the estimates in the figures rise in steps. The estimates within a step are not quite constant as they relate to different years.

8 DISCUSSION AND CONCLUSIONS

8.1 General conclusions

The PHIM system starts by assigning a group of individuals to an initial smoking group, and then generates individual tobacco use histories in the NULL and MRTP Scenarios based on assumed sets of TTPs. Given estimates of the exposure of MRTP and dual users relative to CC smokers, and disease-specific estimates of H and of current continuing CC smoker RRs derived from published evidence, an extension of the negative exponential model then allows estimation of RRs at intervals during follow-up**.** These RRs, coupled with national data on population size and disease incidence, then allow estimation of attributable deaths due to tobacco use in each Scenario, with the difference representing the reduction in deaths associated with MRTP introduction.

The model used to estimate RRs for each individual is an extension of the simple negative exponential model shown to adequately describe data on quitting and on reduction in amount smoked. As illustrated in Figures 27 to 34, the model allows the user to track relative and absolute risks over time for individuals with a variety of smoking histories.

One conclusion from the results presented in section 7 is that the predictions from the NULL Scenario seem quite consistent with what has been observed in the USA, as regards both estimated smoking prevalences over the period from 1990 to 2010, and the estimated percentage of deaths attributable to smoking. While there are differences from estimates for other published sources (ISS for smoking prevalences, USSURG for attributable deaths), these may in part be due to weaknesses in these data and to lack of representativeness in a simulated population followed for 20 years and assumed not to die. While no doubt the NULL Scenario TTPs used could be modified slightly to predict smoking prevalences better (e.g. by varying estimates by follow-up period), and the RRs used may be somewhat inaccurate (though based on extensive meta-analyses), it seems unlikely that this would materially have affected the further conclusions listed below.

Another conclusion is that carrying out the sensitivity analyses using a larger sample than the 10,000 used for each sex would have had only a relatively small effect on the conclusions from these analyses or the accuracy of the predictions for the basic analysis.

The results of the sensitivity analyses allow a number of conclusions. First, effects on tobacco use prevalences in the MRTP Scenario were very much as one would have expected *a priori*. Thus, increasing initiation rates had the most effect at younger age groups, while increasing re-initiation rates tended to have more effect at older age groups. Also varying the TTP factors tended to have quite a modest effect on the distribution of tobacco use habits as these all involved multiple changes of smoking status, so occurred less frequently. Varying quitting rates and rates of switching between products had a larger effect on tobacco use distributions in the MRTP Scenario.

As regards the effect of varying parameters on the predicted reductions in mortality in the MRTP Scenario, it was clear that varying any of the four TTP factors or the definitions of short-term quitting or short-term use had quite a small effect. Indeed, for TTP factor 3, the effect of a 3-fold variation in the factor value caused variations that were small and non-monotonic, with the underlying "signal", such as it was, not clearly outweighing the "noise" from the Monte Carlo nature of the process. For the range of alternative values tested, the largest variations in reductions in deaths resulted from varying the effective dose F, particularly if the effective dose for dual use, G, varied in line with it. Variation in G also had a moderate effect. Switching to MRTP only (from the other current tobacco use groups), switching to CC only (again from the other current tobacco use groups), re-initiation and quitting also had large effects. Effects of other switches between current tobacco use groups were less, though clearly seen, except for switching from dual use. Effects of varying RR and H to within a range of ±20% of the basic values (which seemed reasonable from the confidence limits of the meta-analysis derived estimates) were also clearly evident. Increasing the RRs to values consistent with the USSURG estimates produced quite similar estimated reductions in mortality to those given by the

basic analysis for the four diseases combined, but clear differences were seen for individual diseases.

Generally, effects of varying parameters on reductions in deaths were in the same direction for each of the four diseases studied separately and combined. An exception was for varying RR values, where increasing them always decreased the percentage reduction in attributable deaths, but increased the reduction in deaths (total and percent) for IHD, stroke and all four diseases combined.

"Zero benefit" analyses were also conducted to see what changes in parameter values might eliminate the estimated reduction in deaths associated with MRTP introduction. While clearly no reduction would be seen if the MRTP did not reduce the effective dose (F = 1) or if there was no uptake of MRTP, there were some situations where even where MRTP was introduced and reduced the effective dose, the estimated reduction in deaths might be reduced or eliminated. Elimination of the effect could in theory occur in three situations – firstly if dual users increased consumption, secondly if re-initiation rates were increased, and thirdly if quitting rates of CC only smokers were decreased. However, the increases required seem large. Thus elimination of the effect by increasing consumption would require an effective dose for dual users (G) of about 2.8 (consistent with smokers of 20 cigs/day of CCs before MRTP introduction consuming about 47 CCs and 47 MRTPs a day after introduction), while elimination of the effect by increasing all the re-initiation rates would require as much as a 2-fold increase in the rate, and elimination by decreasing quitting rates of CC only smokers would require about a 35% reduction in the rates. Some reduction of the effect could occur if MRTP introduction resulted in increased rates of initiation of smoking but, as initiation is assumed only to occur in those aged up to 34 years, this would only have a minor effect. Increasing rates of switching to CC only smoking could also reduce the effect, but as this only affects those making multiple transitions during follow-up could not eliminate it.

In the basic analysis, MRTP introduction was associated with a reduction in deaths from the four diseases combined over the 20 year follow-up period of 35,206 in males and 16,403 in females in the basic analysis considered. The reduction in deaths can be compared with those of 605,321 in males and 333,027 in females in an extreme situation where all smokers quit immediately and no initiation or re-initiation occurs, and with 443,627 in males and 244,615 in females in a second extreme situation where CC smoking is totally replaced by MRTP use following the introduction of MRTP. While the reductions in these extreme situations are larger, the situations themselves are clearly less plausible. The same is true for another extreme situation where current CC smokers who would otherwise have switched to MRTP only or to dual use quit instead, the estimated reductions in deaths then being 386,915 in males and 212,548 in females.

That MRTP introduction is unlikely to be associated with an adverse effect on risk is demonstrated by results for a situation where the whole population become MRTP only users immediately on MRTP introduction. Here, the overall effect on mortality is to reduce deaths by 121,258 in males and by 10,500 in females.

8.2 Conclusions as regards the FDA Segments

As noted in section 6, the results only provide information for five of the seven FDA segments. Conclusions to be drawn for these are described below.

8.2.1 Segment 1 **"Tobacco users who switch from other commercially marketed tobacco products to the proposed product"**

The results relating most to Segment 1 are those described in set 4 of Tables 21 and 22. These analyses relate to variation in switching from CC only smoking to MRTP only use or dual use. As shown there, increasing the rates from half of the basic rate to 10 times the basic rate, at all ages and in both sexes, substantially increases the prevalence of MRTP only use and dual use and decreases the prevalence of CC only smoking. Associated with this is a large increase in the reduction in mortality associated with

MRTP introduction. A clear effect is also seen in the analyses described in set 1 of Tables 21 and 22, which relate to the reverse switch, and also in the analyses described in Tables 25 and 26 varying four parameters simultaneously.

The reductions in mortality are all clearly associated with an increase in the proportion of the population in segment 1.

8.2.2 Segment 2 **"Tobacco users and smokers who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk"**

As noted in section 6.2, the MRTP Scenario does not consider switching to or switching back to products other than CCs. The results relating most to segment 2 are those described in set 3 of Tables 21 and 22. These analyses relate to variation in switching from MRTP only use or dual use to CC only smoking. Increasing the rates from half of the basic rate to 10 times the basic rate, at all ages and in both sexes, somewhat increases the prevalence of CC only smoking, while reducing the prevalence of the other two current tobacco use groups. Associated with this, the reduction in mortality associated with MRTP introduction is also somewhat reduced. The reduction in mortality is also decreased slightly as TTP factor 1 (the probability of switching from MRTP to CC only for those who previously used CCs) increases. Some effect of increasing the switch rate back to CC only is also evident in set 5 of Tables 21 and 22, where the switch is from MRTP only to CC only or dual use, and in the analyses described in Tables 25 and 26 varying four parameters simultaneously.

The increases in mortality are all clearly associated with an increase in the proportion of the population in segment 2.

8.2.3 Segment 3 **"Tobacco users who opt to use the proposed product rather than cease tobacco use altogether"**

Here, the relevant analyses are those summarized in Table 24(d) where reductions in mortality are compared for the basic analysis and for the fourth extreme situation, where current CC only smokers who would otherwise have switched to MRTP only or to dual user quit instead. Reductions in deaths for the 20 year follow-up period are somewhat over 10 times higher in the fourth extreme situation. However, it should be realized that it is unlikely that all current CC only smokers who choose to switch would have quit had the MRTP not been available. While it is clear that some current CC smokers may opt to use MRTPs rather than quit, with a consequent adverse effect on their risk of death, most who opt to use MRTPs would not have quit.

8.2.4 Segment 5 **"Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users"**

The analyses relevant to initiation of the MRTP by never smokers and youth are those summarized in alternatives 1 and 2 of Tables 15 and 16 and alternatives 1, 2 and 3 of Tables 17 and 18. The first set of analyses involves the situation where the overall rate of initiation remains constant, the alternatives varying the relative initiation rates to CC only smoking and to MRTP only use or dual use. The second set of analyses holds the initiation rates to CC only smoking constant but increases the rates to MRTP only use or dual use. In both sets of analyses, varying the initiation rates mainly affects the distribution of smoking group for younger age groups and does not affect the distribution at older ages. This is because allowance is only made for initiation to any smoking group to occur up to age 30-34, so variations in rates cannot possibly affect the distribution of those aged 55 or more by the end of the follow-up period. Because of this, and the fact that death rates increase substantially with age, the effects on the reductions in mortality associated with changes in initiation rates seen in Tables 16 and 18 are generally very small, and are still moderate even in Alternative 8 of Table 18, where initiation rates to

CC only, MRTP only or dual use are increased to 8 times that of the basic analysis. Clearly the effect might have been greater had a longer follow-up period been used.

While former users cannot, by definition, initiate tobacco use with MRTPs, former smokers of CCs can re-initiate tobacco use with MRTPs. Here the relevant analyses are those summarized in Alternatives 3 and 4 of Tables 15 and 16 and Alternatives 9 and 10 of Tables 17 and 18. The first set of analyses involves the situation where the overall rate of re-initiation remains constant, the alternatives varying the relative re-initiation rates to CC only smoking and to MRTP use or dual use. The second set of analyses holds the re-initiation rates to CC only smoking constant but increases the rates to MRTP use or to dual use. In both sets of analyses, varying the re-initiation rates has little or no effect for younger age groups and even for older age groups is still quite small. The effects on mortality are correspondingly moderate. Thus, for example, in Alternative 4 in Table 16, reductions in deaths caused by increasing the re-initiation rate to MRTP only and dual use while keeping the overall re-initiation rate constant (and correspondingly decreasing the re-initiation rate to CC only) increased in males from 35,206 (basic analysis) to 45,004 deaths, and in females from 16,403 to 21,250 deaths, increases of, respectively, 27.8% and 29.5%. Also, in Alternative 10 in Table 18, reductions in deaths caused by increasing the re-initiation rate to MRTP only and dual use, while keeping the re-initiation rate to CC only constant, decreased in males from 35,206 to 25,301 deaths and in females from 16,403 to 11,730 deaths, reductions of, respectively, 28.1% and 28.5%.

Also relevant to segment 5 is the third extreme situation where the whole population becomes current MRTP only users. Here, the effect of the large reduction in effective dose for current smokers of CC is balanced against the effects of the smaller increases in effective dose for non-smokers. For males and females combined, there is a predicted reduction in deaths over the 20 year period of 131,378 deaths, as compared to the reduction of 51,609 in the basic analysis.

It must be concluded that, when considering a 20 year follow-up period, effects of increased numbers of never smokers taking up MRTP will be very small. If MRTP

introduction were to encourage large numbers of former smokers to re-initiate with MRTPs, some of the reduction in deaths associated with MRTP introduction would be lost, but probably only a small part of it.

8.2.5 Segment 6 **"Tobacco users who use the product in conjunction with other tobacco products"**

Dual CC and MRTP users may or may not keep their overall cigarette consumption constant. Given the effective dose for MRTP only users, F, is 0.2 (and given linearity in dose), dual users who keep their overall consumption constant would have an effective dose, G, of 0.4 if they smoked 25% CCs, 0.6 if they smoked 50% CCs, or 0.8 if they smoked 75% CCs. Dual users who increased their overall cigarette consumption may have a higher G, for example 1.2 if they kept their original CC consumption unchanged and used the same number of MRTPs. The effect of varying G on the reduction in mortality associated with MRTP introduction is presented in Table 9. For all four diseases and overall, reductions are about 3 times less for G = 2.0 than for G = 0.4. Even in the G = 2.0 situation, there is a reduction because of the reduced mortality in MRTP only users. Increasing G further could eliminate the mortality reduction, but this assumes a considerable increase in daily consumption. For example, a value of G = 3.0 would be consistent with dual use of 50 CCs and 50 MRTPs a day.

The analyses summarized in Tables 15 to 18 (initiation and re-initiation) and in Tables 21 and 22 (switching between current tobacco use groups) are also relevant to dual use. Effects on initiation and re-initiation on the reduction in mortality associated with MRTP introduction are generally modest, but effects of switching between current tobacco use groups are larger. These analyses all concern switching from one group to the other two, or to one group from the other two, and all concern effective doses of F = 0.2 for MRTP only, F = 0.6 for dual use and F = 1.0 for CC only. Generally, switches which substantially increase the average dose of current users (e.g. from MRTP only or dual use to CC only) cause a clear reduction in the estimated mortality benefit of MRTP introduction, while switches which substantially reduce the average dose increase it.

Switches which have a smaller effect on average dose (e.g. from dual use to CC only or MRTP only) have a less clear effect.

Overall, it is clear that current smokers who continue to use tobacco following MRTP introduction will have a reduced average effective dose, and hence a reduced risk of disease unless the risk of dual users is greater than that of current CC only smokers. The lower the effective dose of MRTP only users, the greater will the effective dose of dual users need to be to cancel the benefit of MRTP introduction. An increased risk of dual users compared to CC only smokers is only likely to be achieved in practice if dual users smoke substantially more CCs that they did initially (or if there is some unforeseen interaction between the effects of CCs and MRTPs).

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Figures

Figure 1(a) **Effect of varying the effective dose for MRTP only, F, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). G is taken as the basic value of 0.6. Source: Appendix 3. Basic analysis value = 0.2**

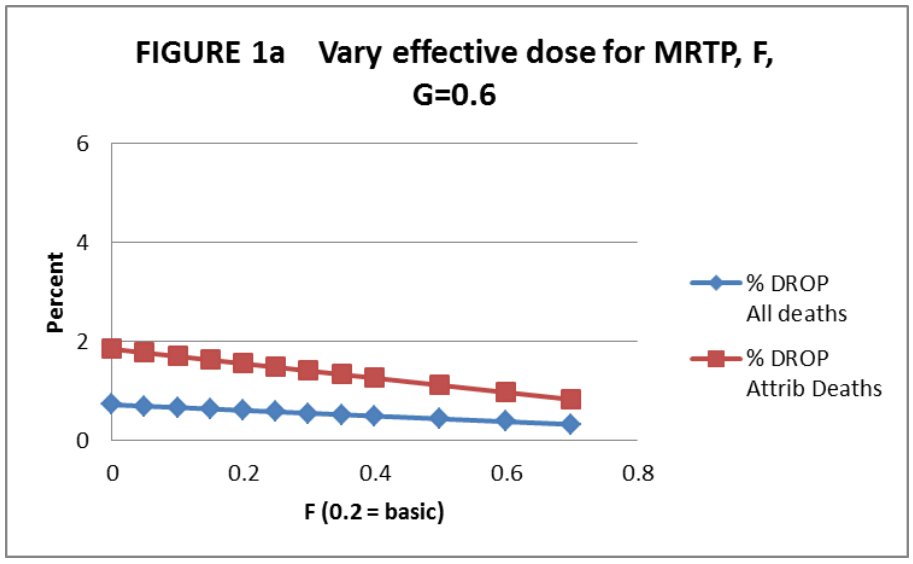


Figure 1(b) Effect of varying the effective dose for MRTP only, F, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). G is taken as (1+F)/2. Source: Appendix 3. Basic analysis value = 0.2

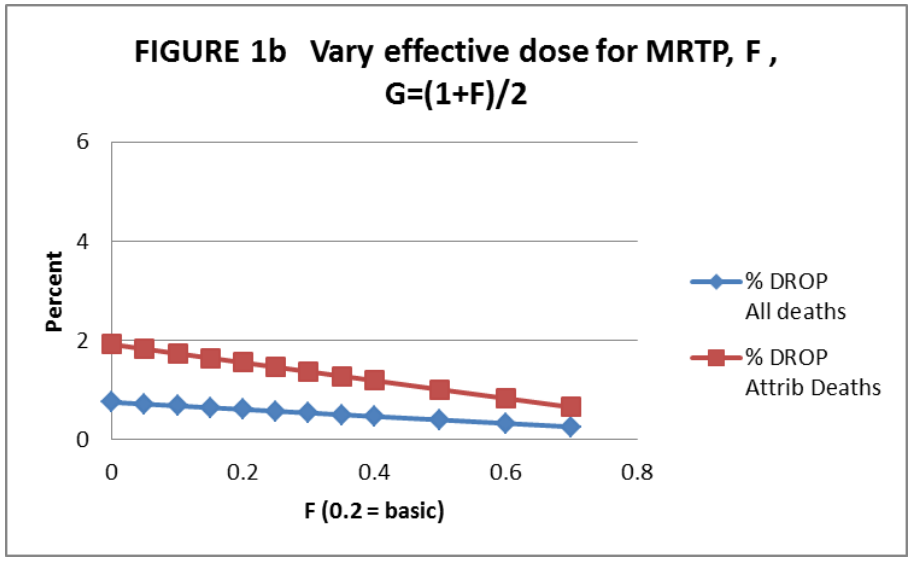


Figure 2 **Effect of varying the effective dose for dual use, G, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 4. Basic analysis value = 0.6**

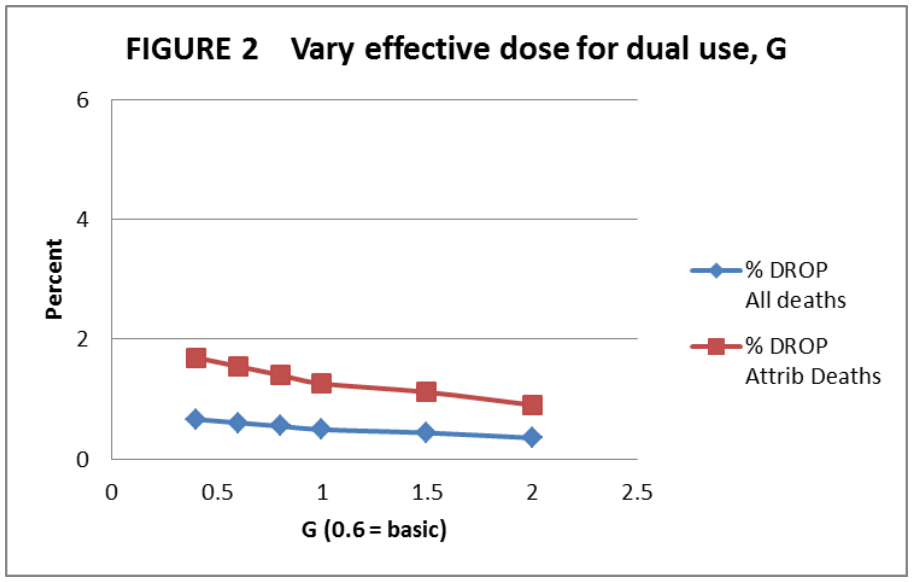


Figure 3 **Effect of varying TTP Factor 1 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 5. Basic analysis value = 2. The TTP from MRTP to CC is multiplied by TTP Factor 1 if previously used CC.**

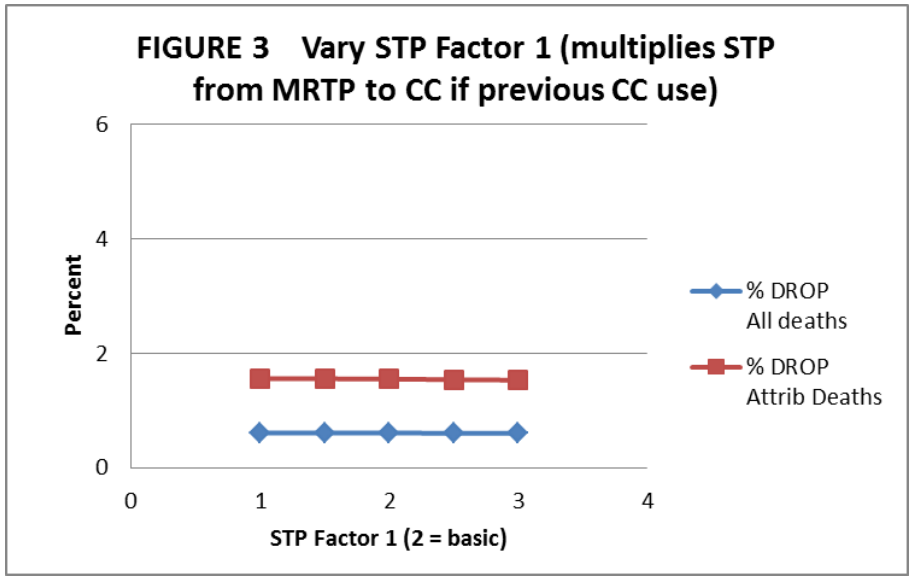


Figure 4 **Effect of varying TTP Factor 2 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 6. Basic analysis value = 2. The TTPs for quitting are multiplied by TTP Factor 2 if previously quit.**

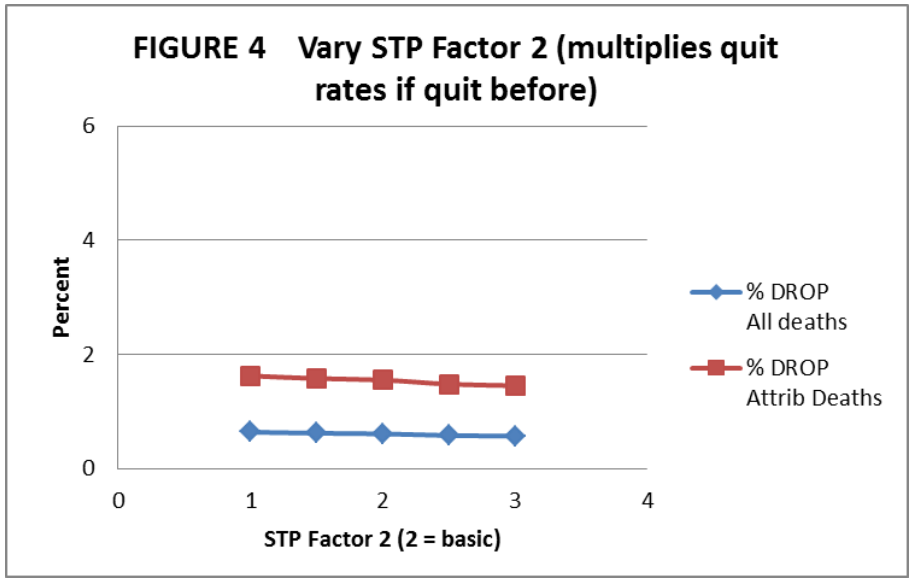


Figure 5 **Effect of varying TTP Factor 3 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 7. Basic analysis value = 2. The TTPs for re-initiation are multiplied by TTP Factor 3 if a short-term quitter.**

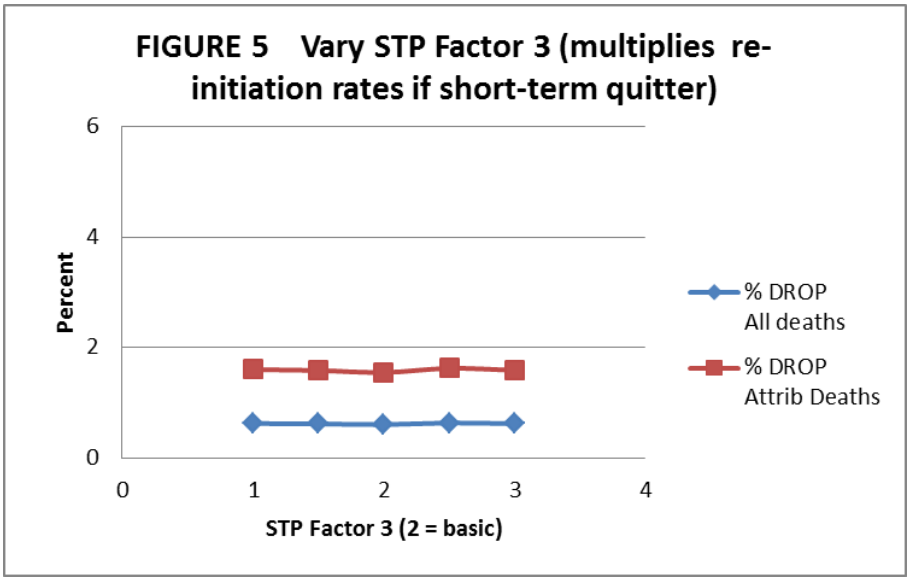


Figure 6 **Effect of varying the definition of short-term quitting (years) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 8. Basic analysis value = 2**

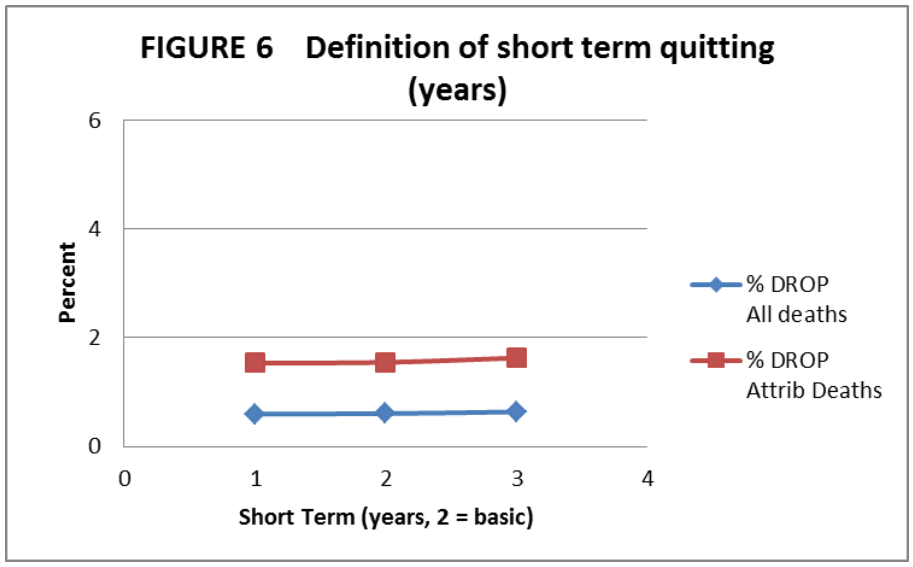


Figure 7 **Effect of varying TTP factor 4 on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 5. Basic analysis value = 0. The TTPs from MRTP to CCs and to dual use were multiplied by TTP factor 4 if a more than short-term user of MRTP.**

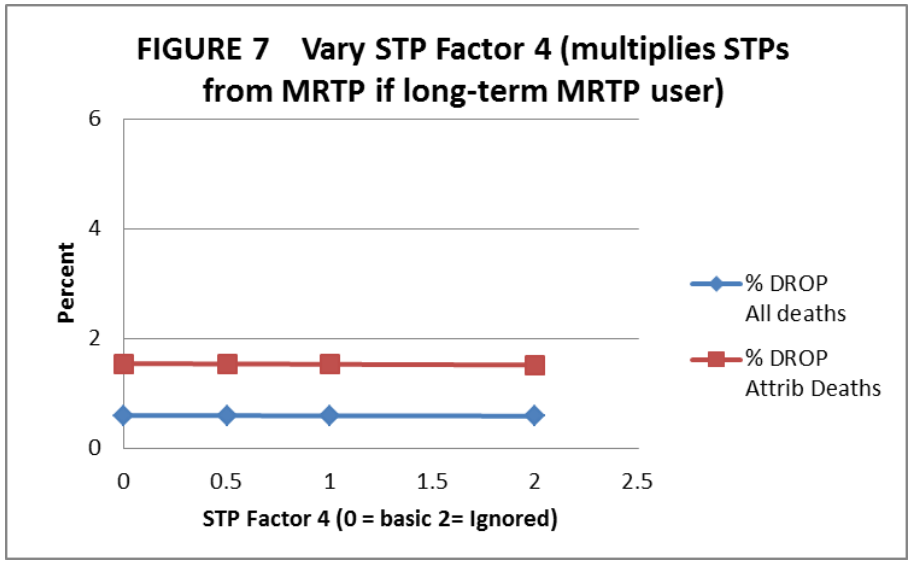


Figure 8 **Effect of varying the definition of short-term use (years) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 5. Basic analysis value = 2**

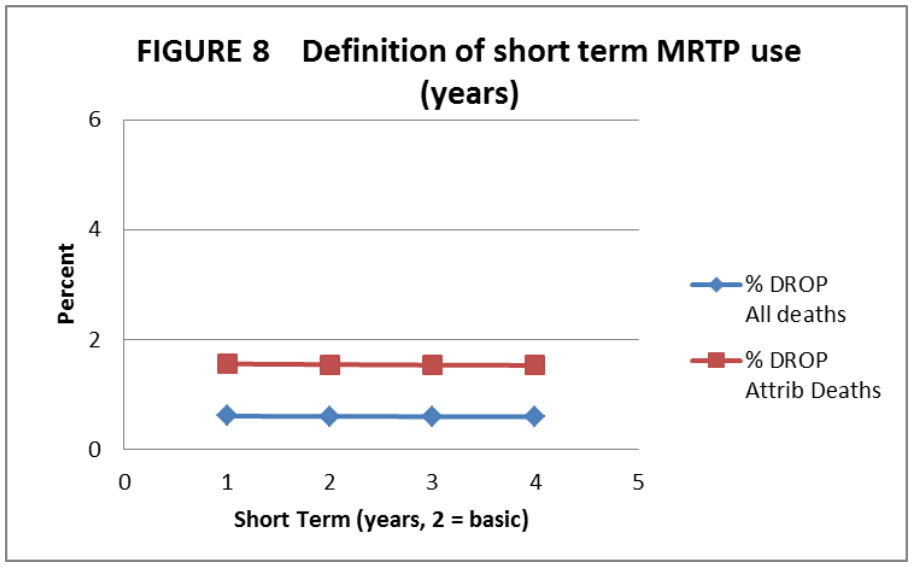


Figure 9 **Effect of varying the relative risk, RR, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 9. The excess relative risks (RR-1) from the basic analysis are multiplied by 0.8 or 1.2 in the alternative analyses.**

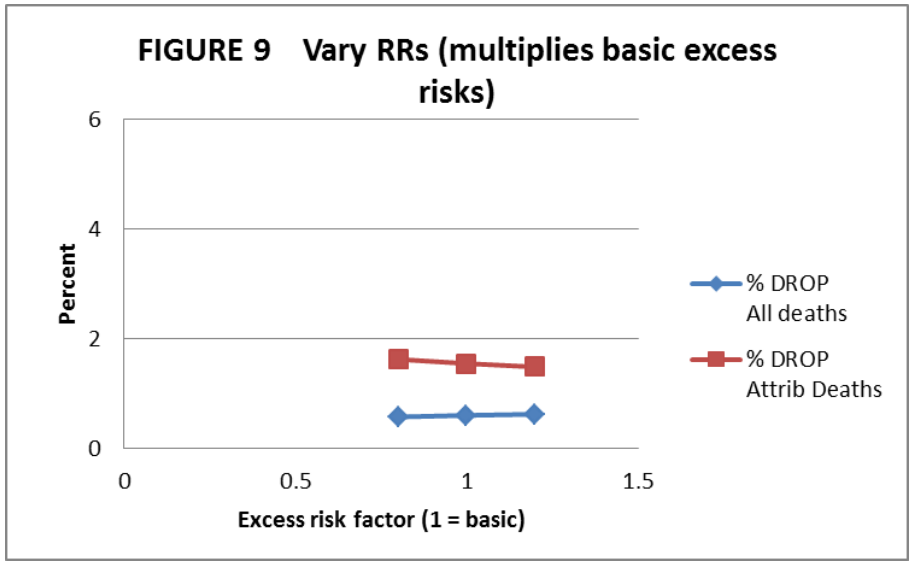


Figure 10 **Effect of varying the half-life, H, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 10. The half-lives from the basic analysis are multiplied by 0.8 or 1.2 in the alternative analyses.**

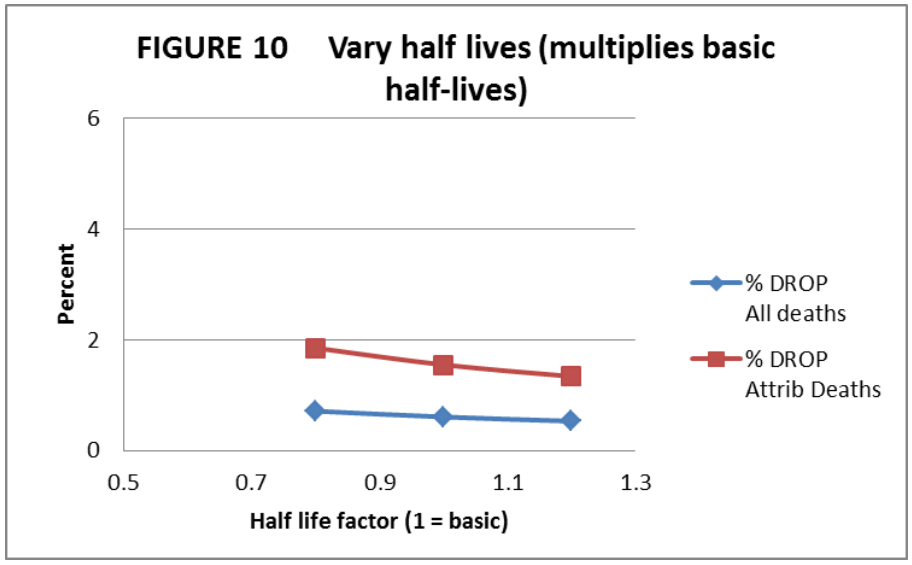


Figure 11 **Effect of varying the relative frequency of initiation to MRTP only and dual use (with the total initiation rate held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 11. Alternative 1 decreases (and Alternative 2 increases) the frequencies relative to the basic analysis. In the Figure, the results for Alternative 1, basic, and Alternative 2 are given against values of 1, 2 and 3 on the x-axis).**

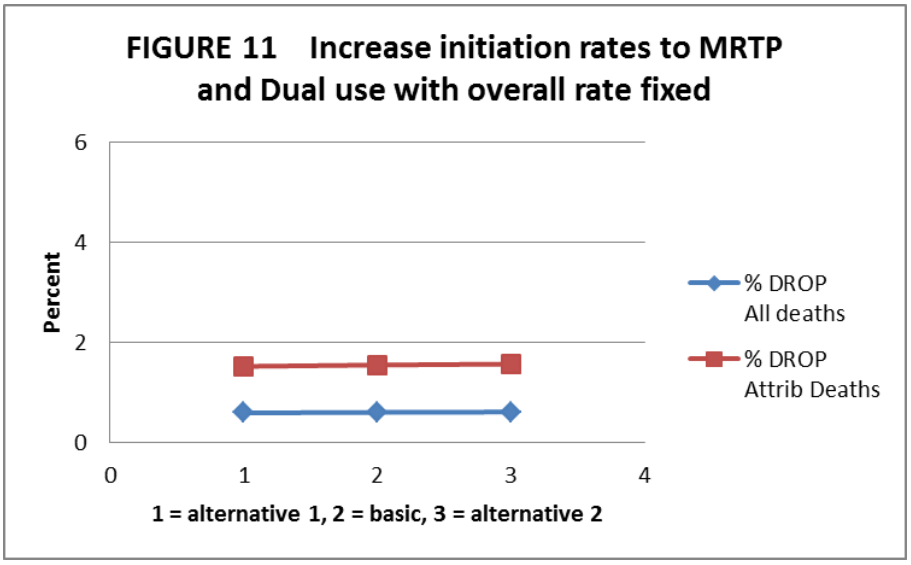


Figure 12 **Effect of varying the relative frequency of re-initiation to MRTP only and dual use (with the total initiation rate held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 11. Alternative 3 decreases (and Alternative 4 increases) the frequencies relative to the basic analysis. In the Figure, the results for Alternative 3, basic, and Alternative 4 are given against values of 1, 2 and 3 on the x-axis).**

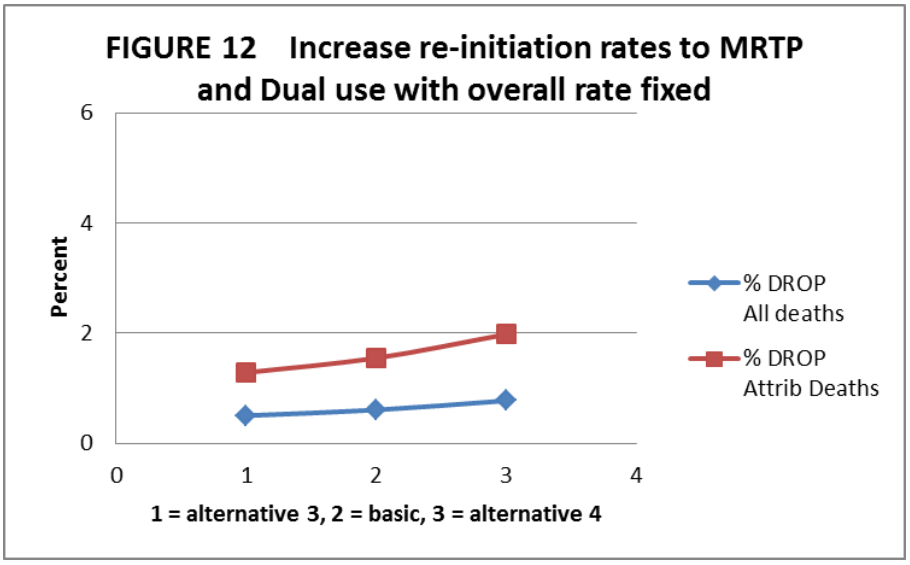


Figure 13 **Effect of varying initiation rates to MRTP only and dual use (with the initiation rate to CC only held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, alternatives 1, 2 and 3 successively increase the initiation rates to MRTP only and dual use. In the Figure, the results for basic, Alternative 1, Alternative 2 and Alternative 3 are given against values of 1, 2, 3 and 4 on the x-axis.**

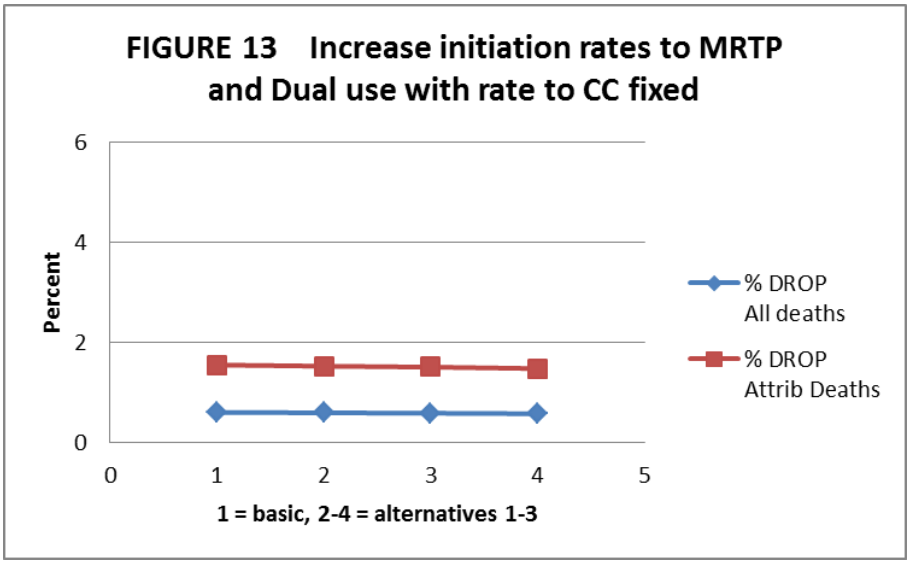


Figure 14 **Effect of varying initiation rates on the percentage reduction in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, Alternatives 4-8 successively increase all the initiation rates. In the Figure, the results for basic, Alternative 4, Alternative 5, Alternative 6, Alternative 7 and Alternative 8 are given against values of 1, 2, 3, 4, 5 and 6 on the x-axis.**

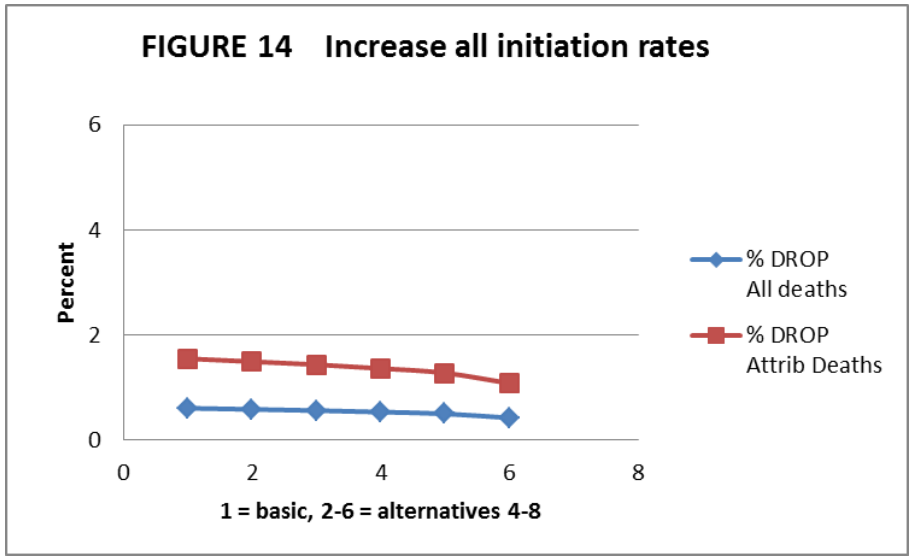


Figure 15 **Effect of varying re-initiation rates to MRTP only and dual use (with the re-initiation rate to CC only held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, Alternatives 9-10 successively increase the re-initiation rate to MRTP only and dual use. In the Figure, the results for basic, Alternative 9 and Alternative 10 are given against values of 1, 2 and 3, on the x-axis.**

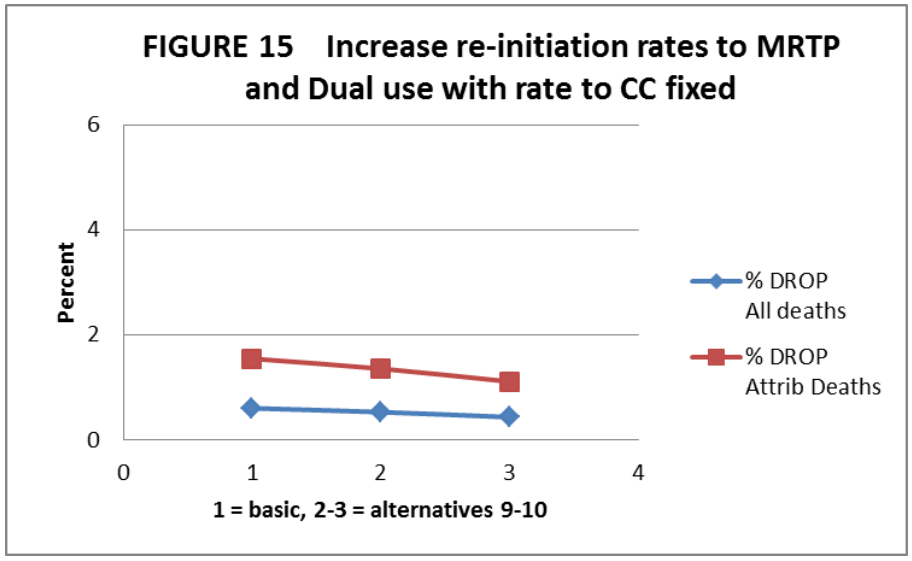


Figure 16 **Effect of varying re-initiation rates on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 12. Compared to the basic rate, Alternatives 11 to 14 successively increase all the re-initiation rates In the Figure, the results for basic, Alternative 11, Alternative 12, Alternative 13 and Alternative 14 are given against values of 1, 2, 3, 4 and 5 on the x-axis.**

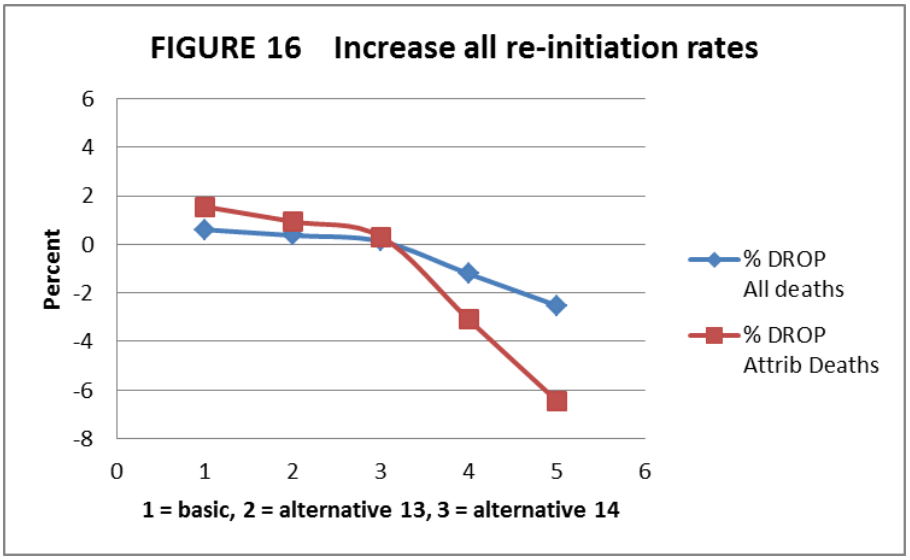


Figure 17 **Effect of varying quitting rates for MRTP only and dual use (with quitting rates for CC only held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 13. The quitting rates from the basic analysis are multiplied by 0.5, 0.75, 1.5 or 2 in the alternative analyses.**

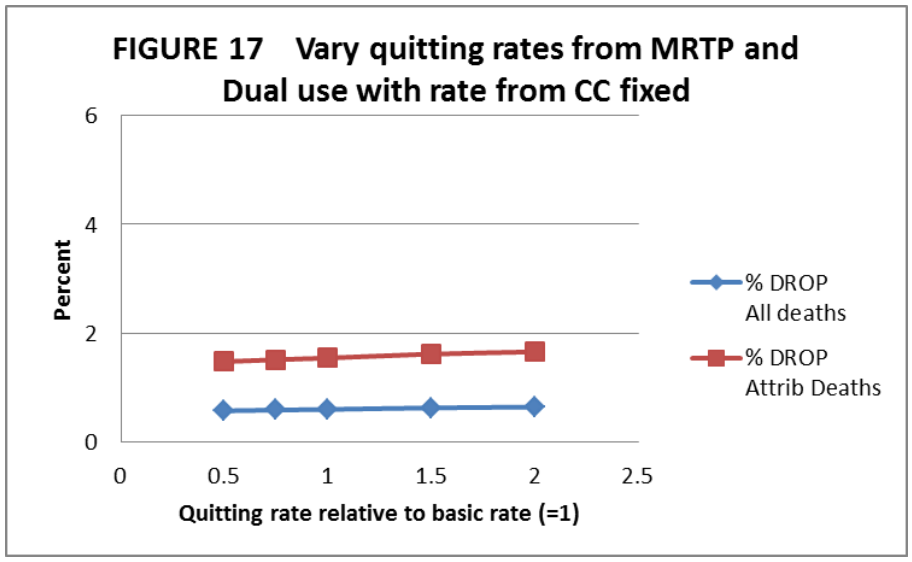


Figure 18 **Effect of varying quitting rates for CC only (with quitting rates for MRTP only and dual use held constant) on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 13. The quitting rates from the basic analysis are multiplied by 0.0, 0.25 or 0.50 in the alternative analyses.**

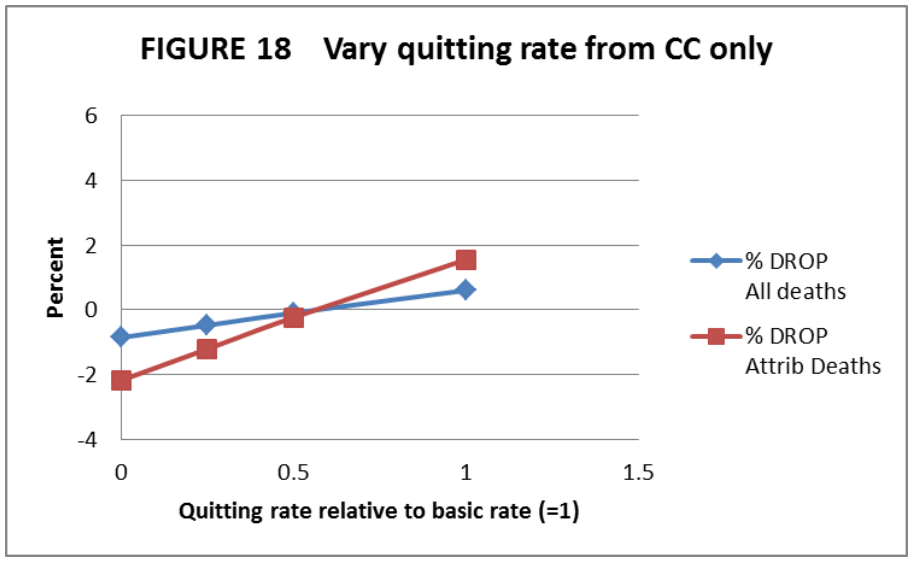


Figure 19 **Effect of decreasing quitting rates for CC only, and simultaneously increasing quitting rates for MRTP only and dual use so as to keep overall quit rates approximately constant, on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 13. In the Figure, the results for basic, Alternative 1 (CC x 0.9, Other x 1.5), Alternative 2 (CC x 0.8, Other x 2.0) and Alternative 3 (CC x 0.7, Other x 2.5) are shown against values of 1, 2, 3 and 4 on the x-axis.**

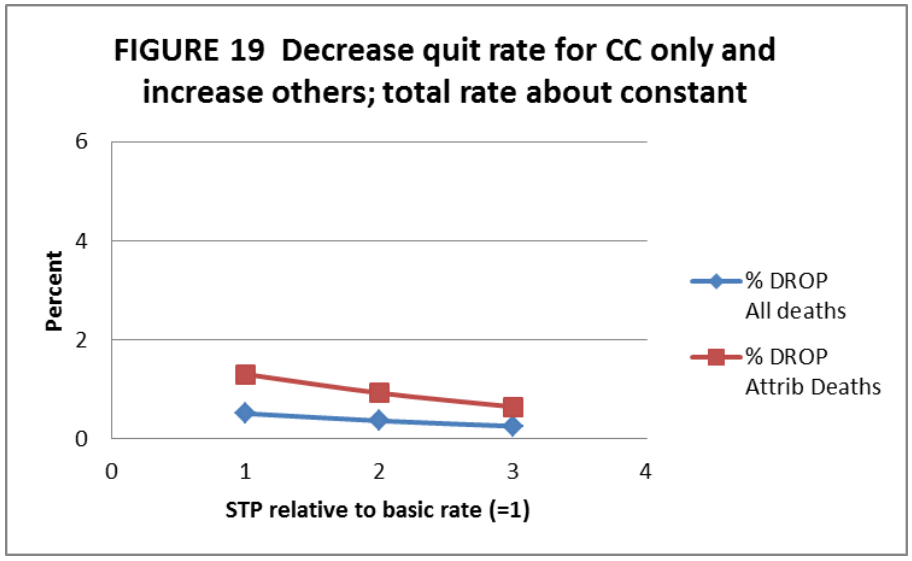


Figure 20 **Effect of varying switching rates from CC only or dual use to MRTP only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses.**

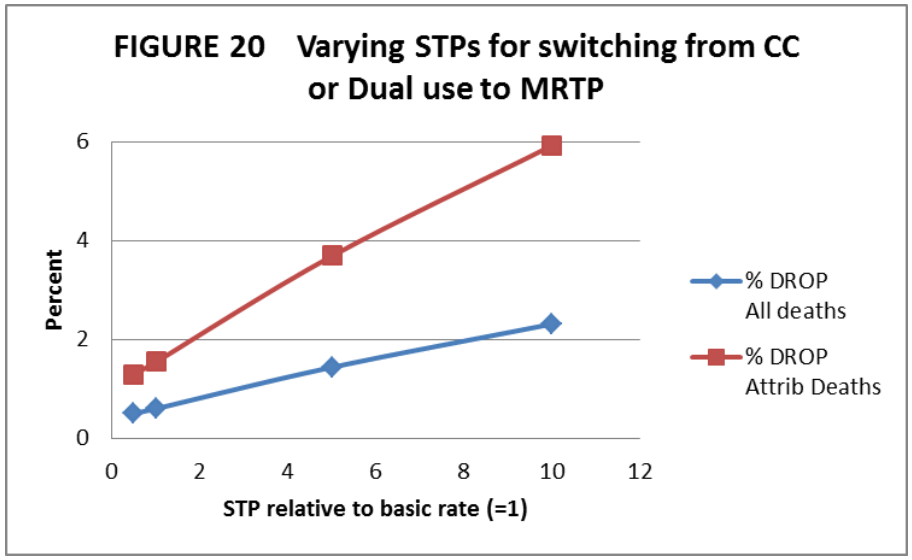


Figure 21 **Effect of varying switching rates from CC only or MRTP only to dual use on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses.**

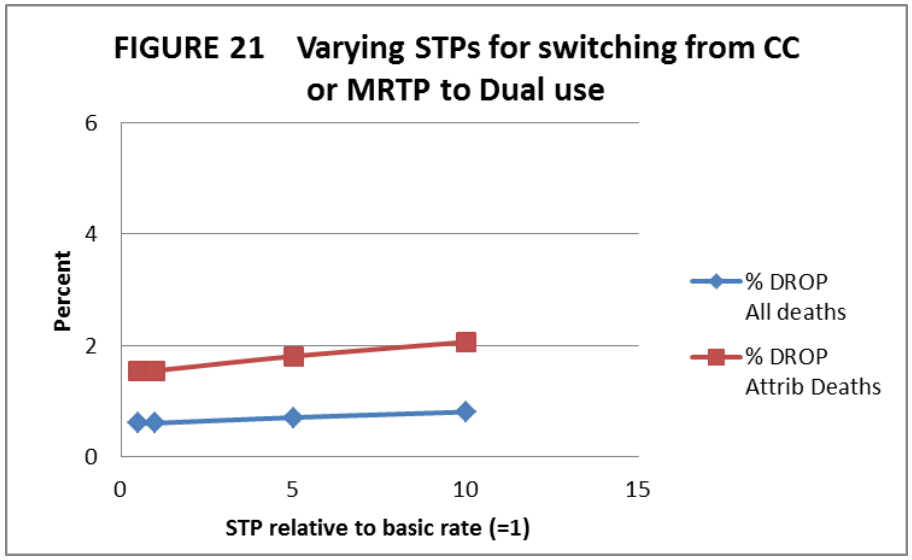


Figure 22 **Effect of varying switching rates from MRTP only or dual use to CC only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses.**

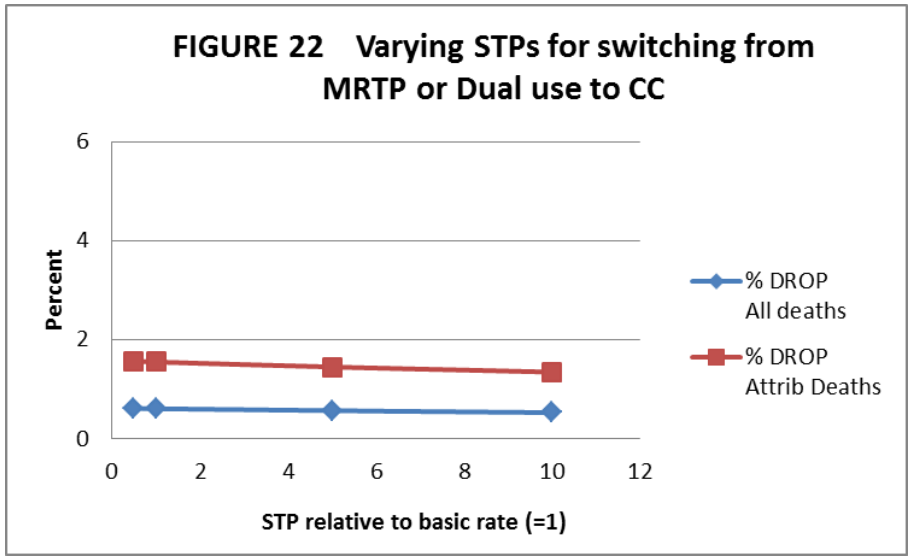


Figure 23 **Effect of varying switching rates from CC only to MRTP only or dual use on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses.**

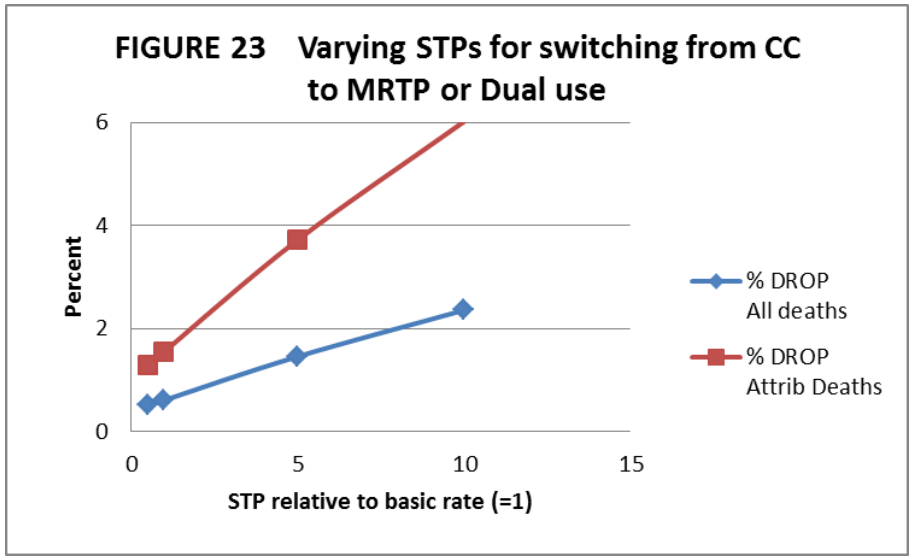


Figure 24 **Effect of varying switching rates from MRTP only to CC only or dual use on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses.**

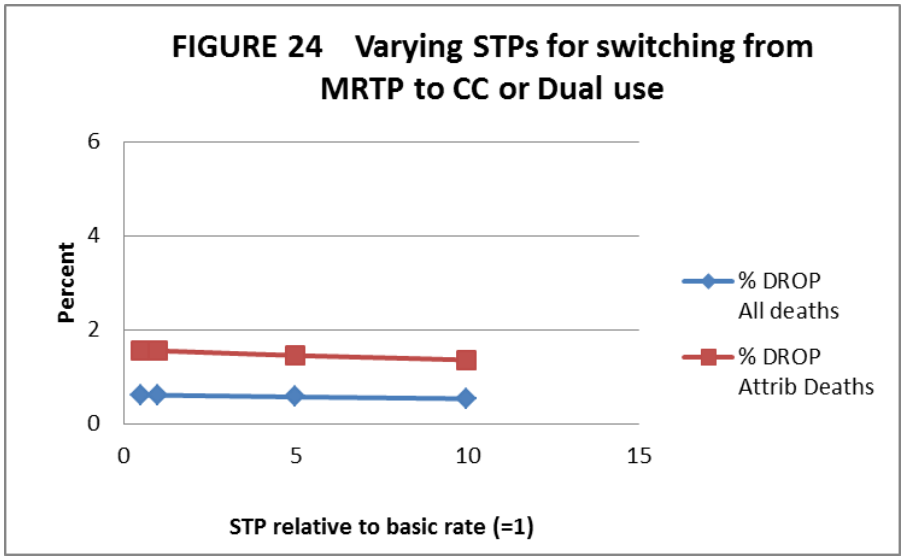


Figure 25 **Effect of varying switching rates from dual use to CC only or MRTP only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 0.5, 5 or 10 in the alternative analyses.**

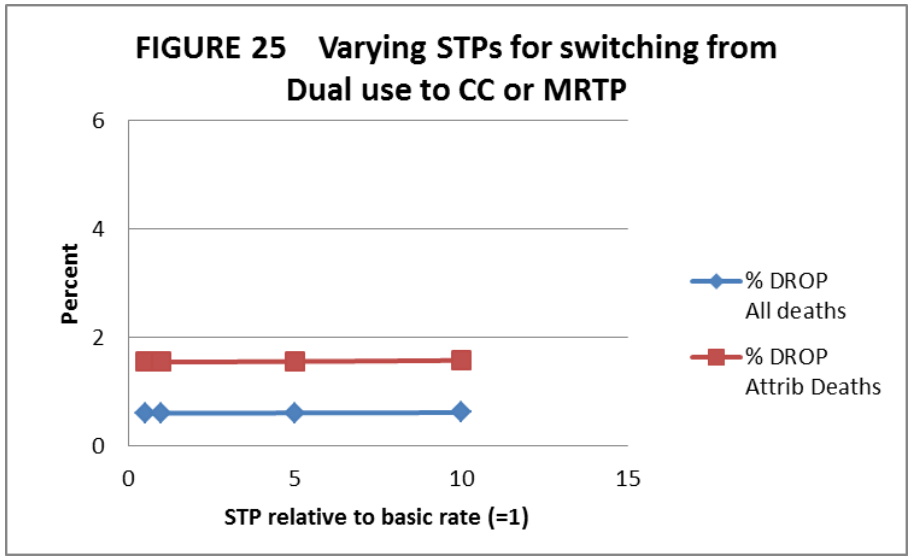


Figure 26 **Effect of varying switching rates from MRTP only or dual use to CC only on the percentage reductions in mortality associated with MRTP introduction (Males, 1990-2009, age 30-79, four diseases combined). Source: Appendix 14. The switching rates from the basic analysis are multiplied by 20, 50, 100 or 150 in the alternative analyses with the TTP Factor 1 set to 1.**

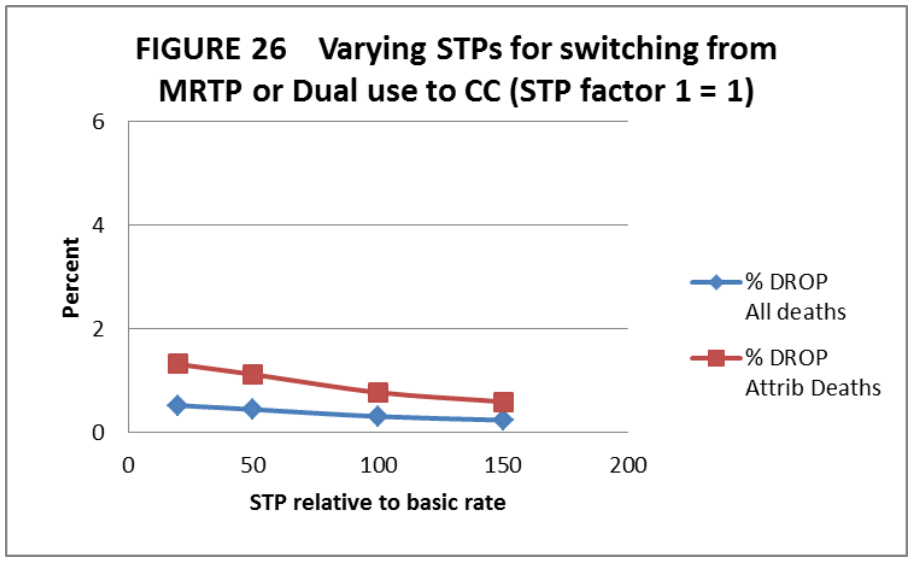
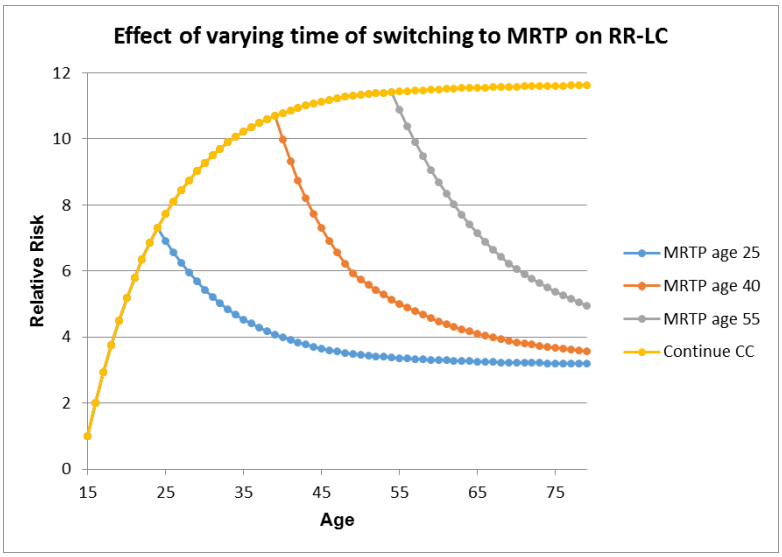


Figure 27 **Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of lung cancer for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.**



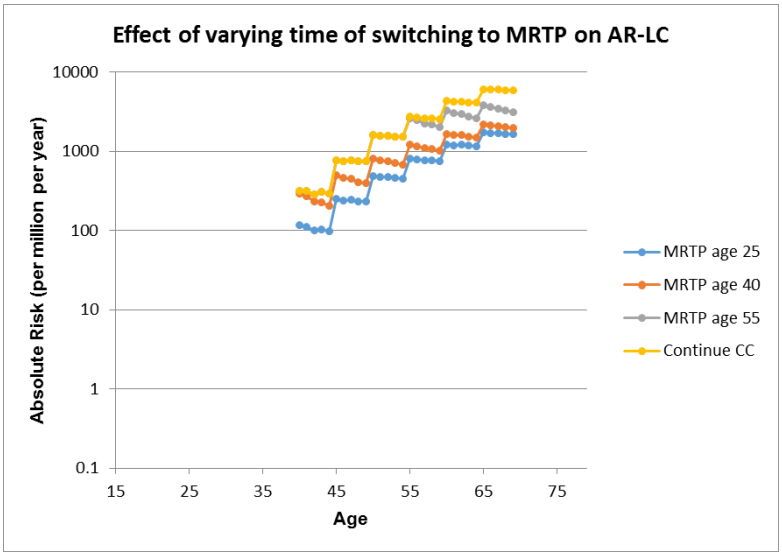


Figure 28 **Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of IHD for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.**

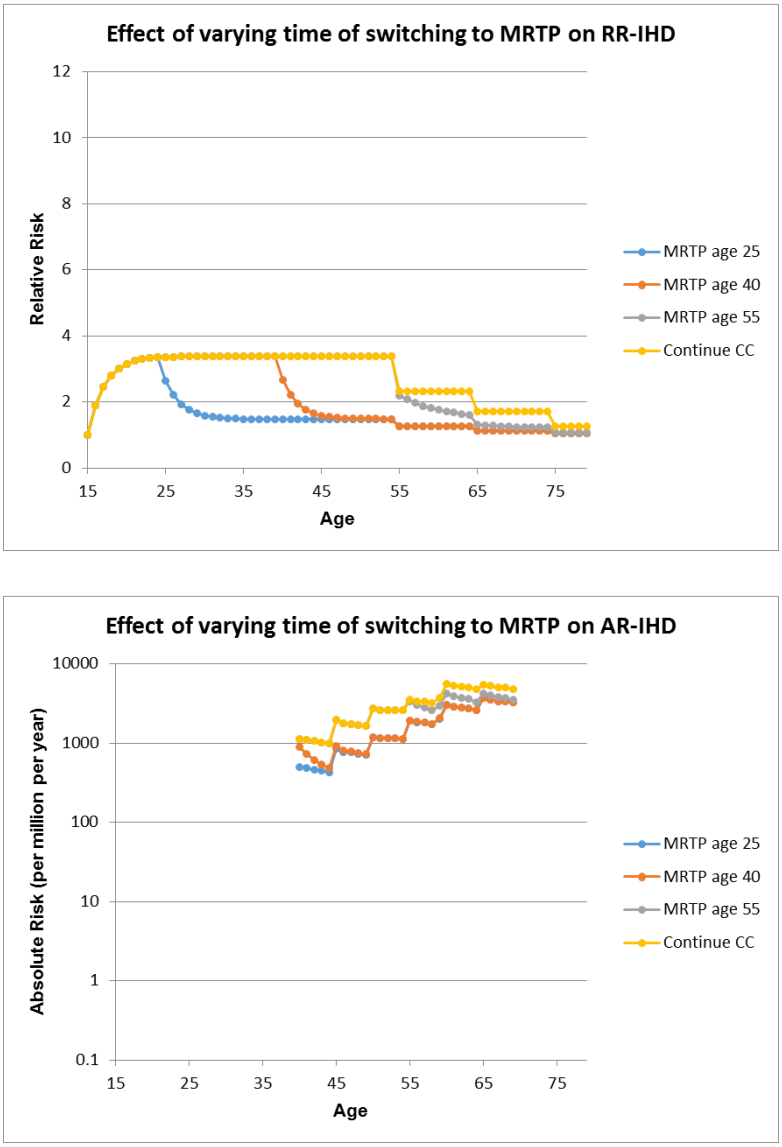
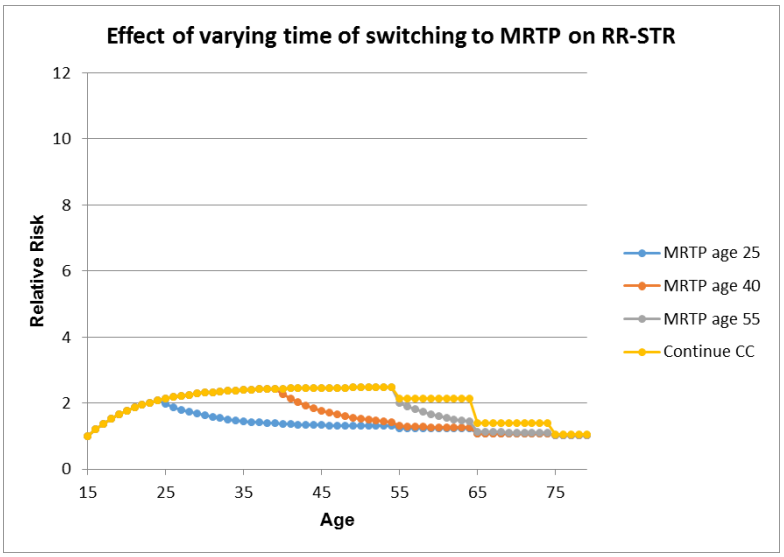


Figure 29 **Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of stroke for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.**



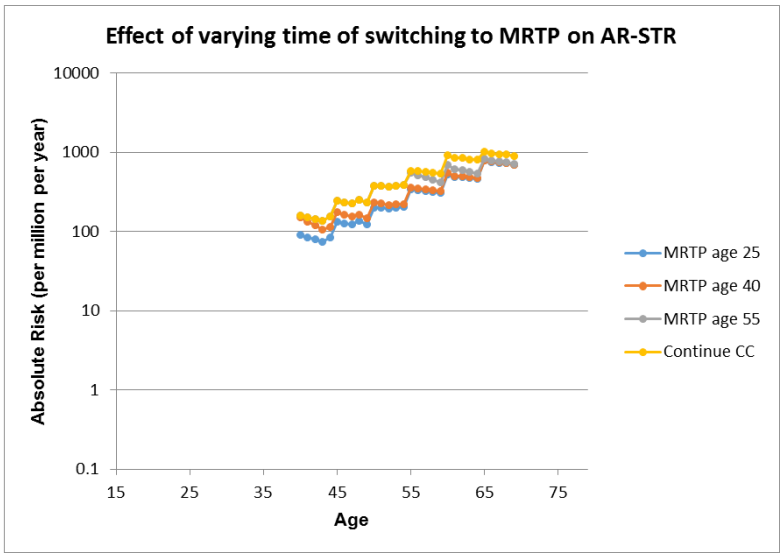
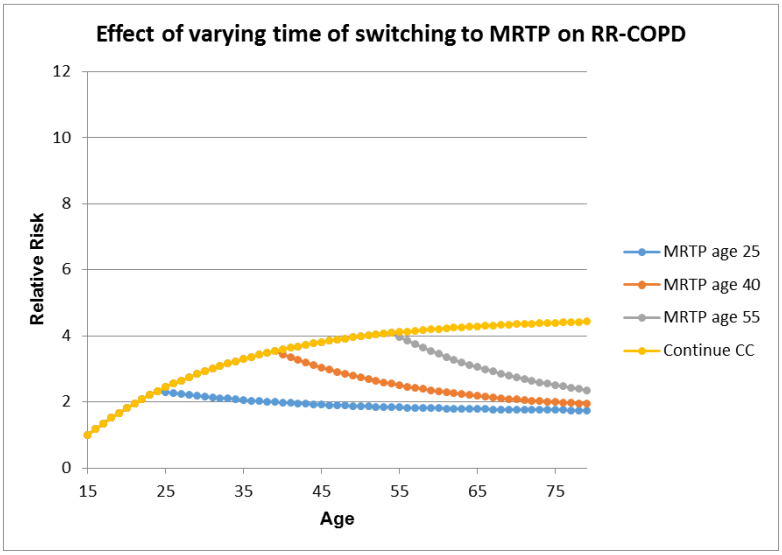


Figure 30 **Effect of varying time of switching to MRTPs on relative risk (top half) and absolute risk (bottom half) of COPD for an individual starting to smoke CCs at age 16. Ages of switch are 25, 40, 55 or not at all.**



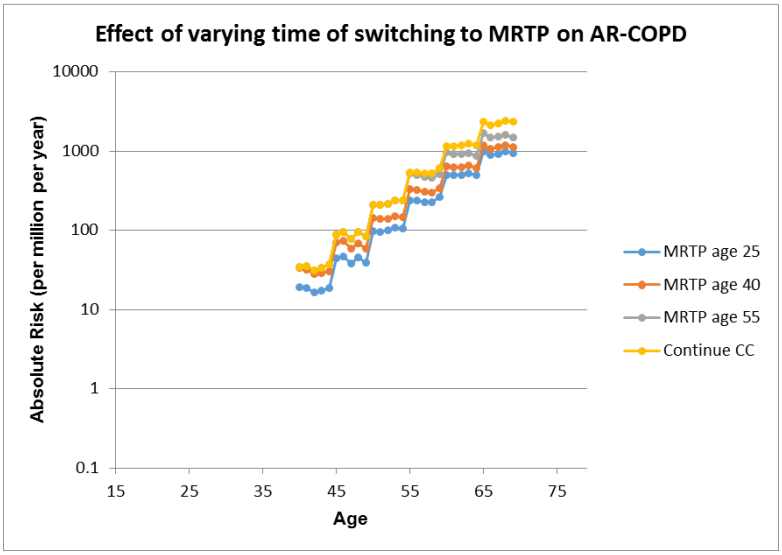


Figure 31 **Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of lung cancer for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.**

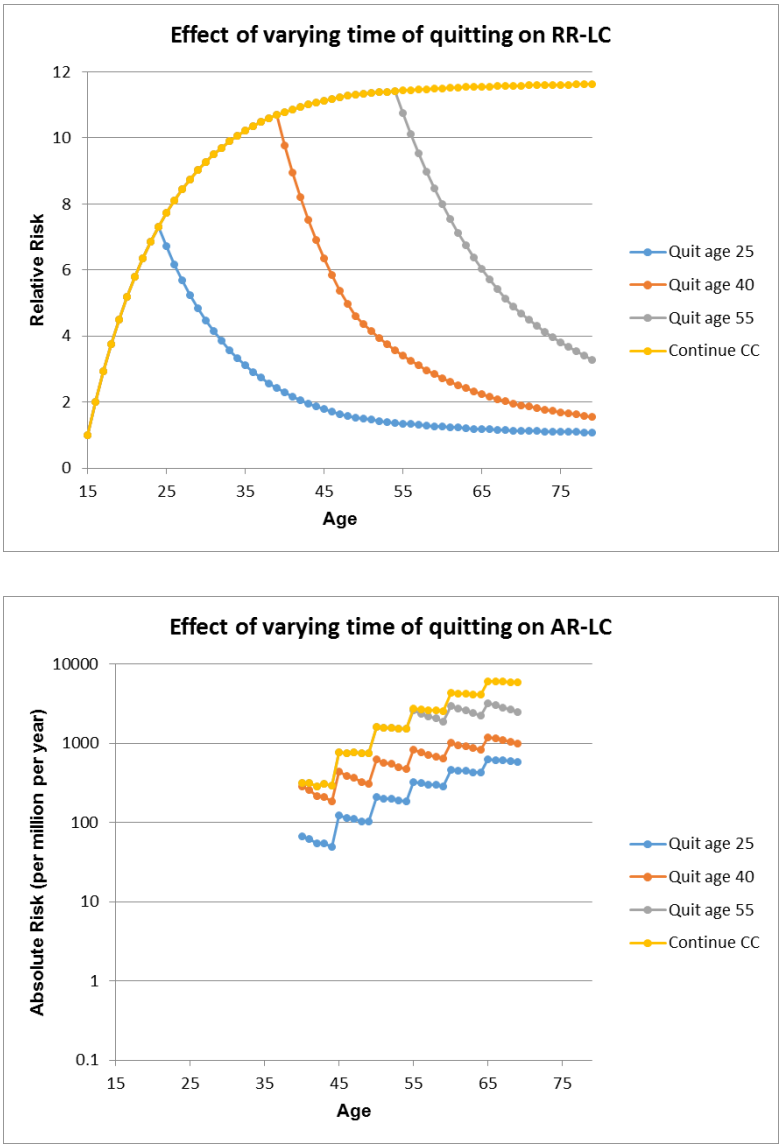


Figure 32 **Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of IHD for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.**

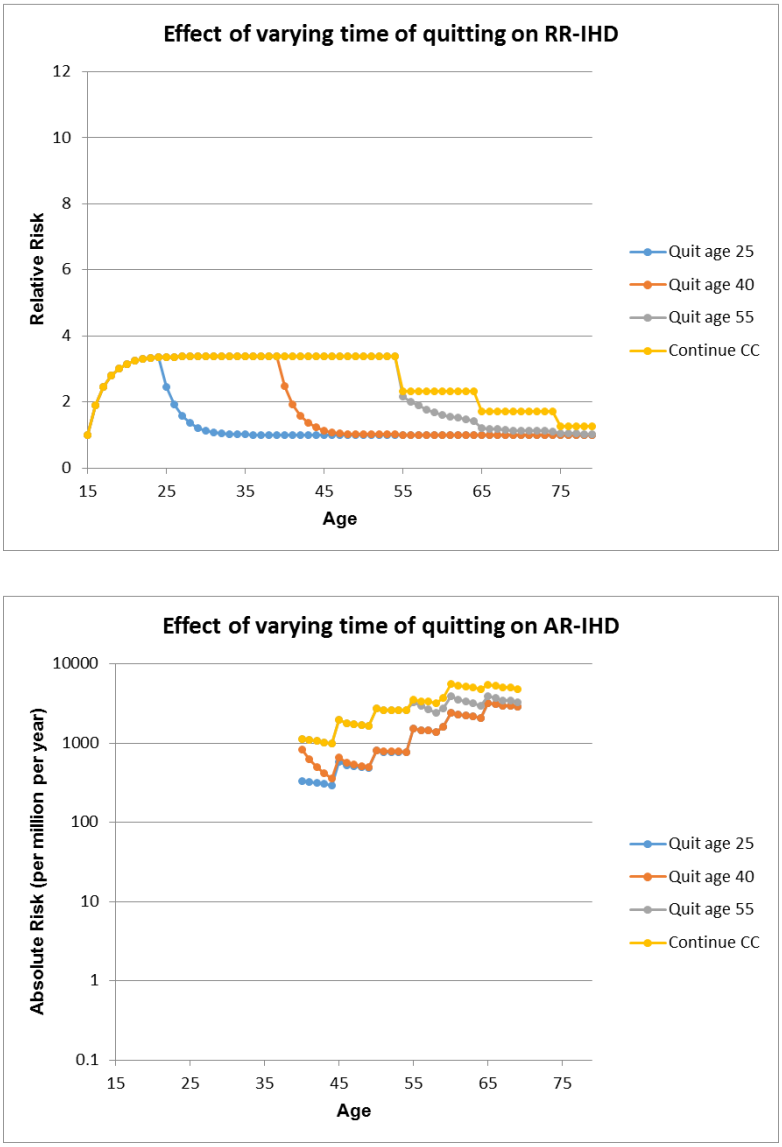


Figure 33 Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of stroke for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.

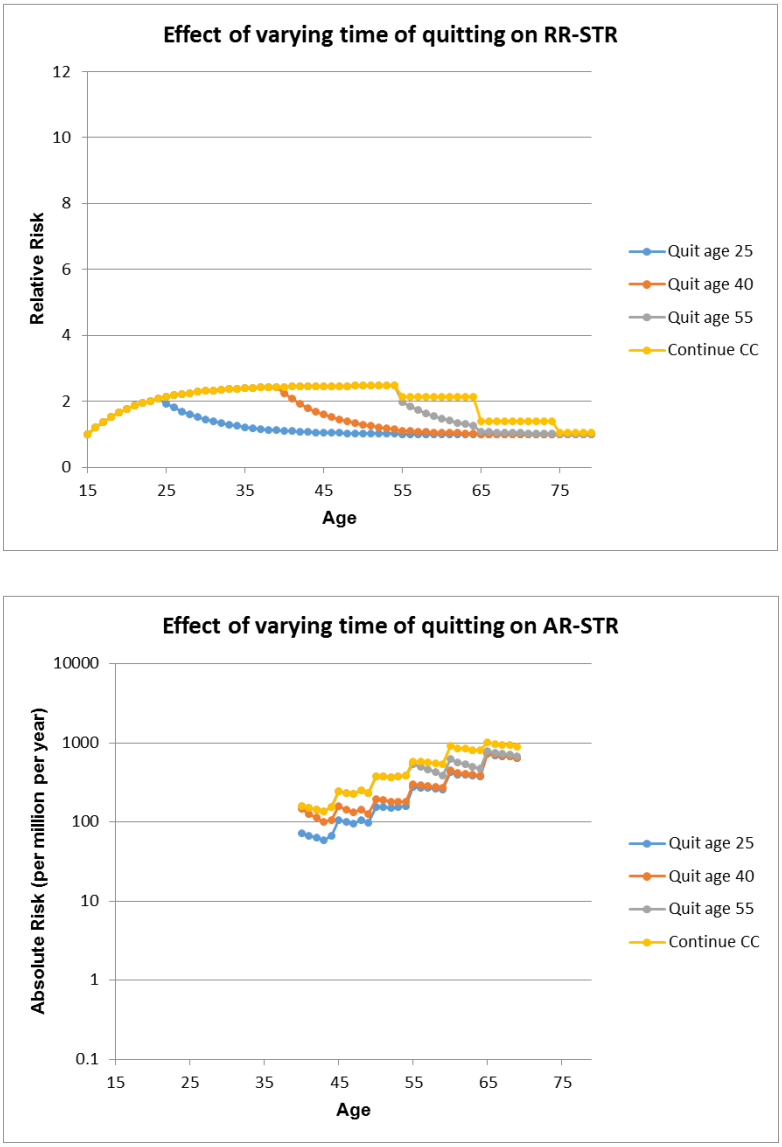
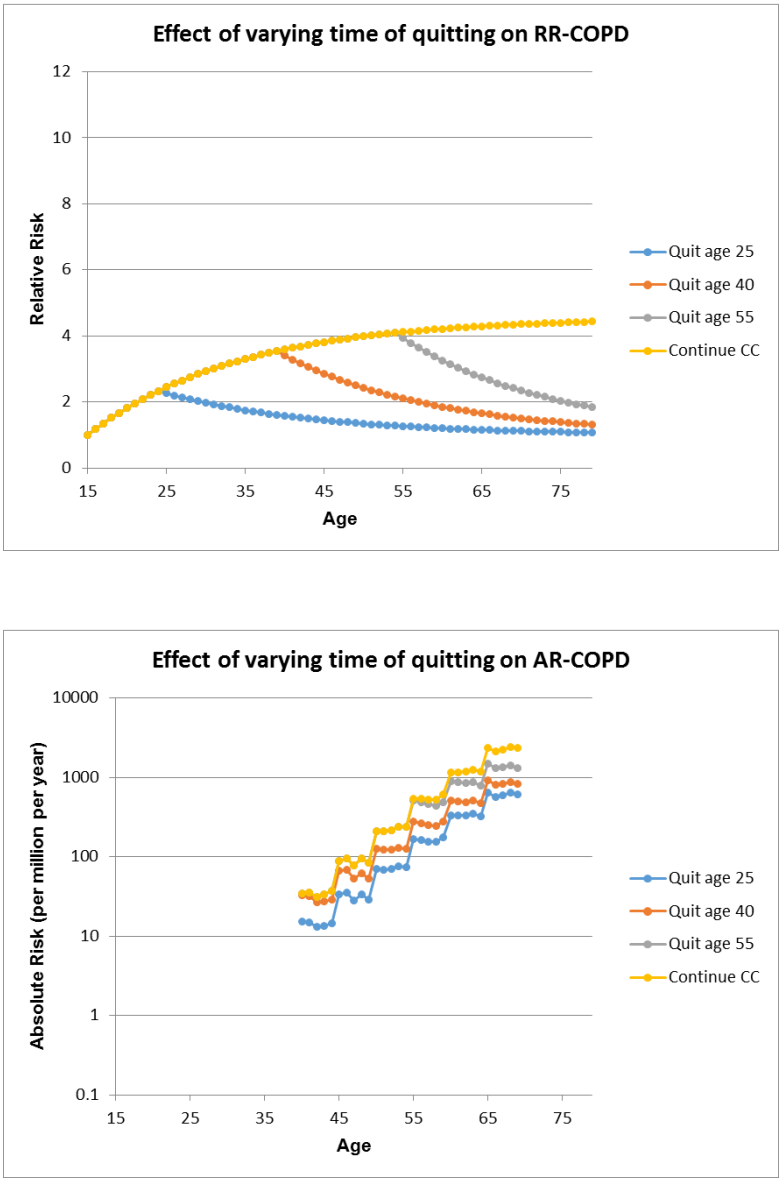


Figure 34 Effect of varying time of quitting CCs on on relative risk (top half) and absolute risk (bottom half) of COPD for an individual starting to smoke CCs at age 16. Ages of quitting are 25, 40, 55 or not at all.



ANNEX A Appendices for Simulation and Sensitivity Analyses

A1 Introduction

The SSA Report is mainly centred on 19 sets of analyses, the results of which are given in full in Appendices 1 to 19. Section A2 of this note describes the format of a typical output, while Section A3 explains the content of the different Appendices. Section A4 then explains Appendices 20 to 24. Appendices 20 and 22 are summary tables and Appendices 21 and 23 summary plots, all based on results extracted from Appendices 1 to 19. **Appendix 24** gives some extended results for the basic analysis.

Note that while the abbreviation TTP is used to describe the transition probabilities in this report, in the actual Appendices the alternative abbreviation STP is used.

A2 Format of a typical output

The reader is referred to APPENDIX_1_Basic_Analysis as a typical example of output.

A2.1 Headings for each page

Each page of output is headed by the time, date and page number on the top right, e.g. "13:48 Wednesday, March 30, 2016 15"

with the heading of the run, centred, given just below, as

"Results for PHIM for Run 2 (APPENDIX_1_Basic_Analysis. RTF)".

Here PHIM refers to the Population Health Impact Model. Each Appendix gives results for multiple runs. In the case of **Appendix 1** there are only two, males and females, but in other Appendices there may be more. For example, when testing the effect of varying the effective dose for MRTP only (F) in **Appendix 3**, there are 10 runs, as runs are carried out for five different values of F, each for males then females.

A2.2 Headings for each run

A2.2.1 Run and control file details

For each run the output first gives the System Date and Time, User, SAS Version and Project and Fixed Age at Starting Smoking (the assumed age in the absence of other information). It then presents the Control File Details. This consists of the values set for the 40 variable parameters. These parameters are described below:

1	Country, US, is the same for all analyses.
2	Sex is either male or female for alternate runs.
3-5	All the runs start at 1990, and follow up the subjects for 20 years in 12 month intervals.
6-7	Although the age range is 10-79, results of risk estimation are only presented for the age range 30-79.
8-13, 39-40	The value given for the effective doses (F and G), for the four TTP factors, and for the definitions of short-term use are always the same as for the basic analysis, except in Appendices 3-8, 17 and 18, where these parameters are varied, as described in section A2.3.
14,15	The number in the population to be simulated is always 10,000 and the number of simulations is always 1, except in **Appendix 2**, where it is 10.
16	The random number seed is always the same, 15975263, so that comparisons can be made between situations where the initial smoking distribution is the same.
17-21	The data sources for the population, current smoking prevalence, former smoking prevalence, quit-time distribution and mortality files are always the same, further details being given in the document "Notes on Data Files for PHIM project".

22, 23 The data sources for the relative risks (RRs) and half-lives (H), PNLEST, are always the basic ones described in "Notes on Data Files", except for **Appendices 9** and **10**, where the parameters are varied, as described in section A2.3. Where they do vary from the basic ones, the actual values used are shown on the output, as referred to in Sections A2.2.3 and A2.2.4.

24, 25 The TTP values used for the NULL and MRTP Scenario described as GUESSNULL1 and GUESSMRTP1 are the basic ones shown in Text-tables 1 and 2 of this Report. In Appendices 11-14 and 16-19 alternative values for the MRTP are used, as described in Section 4.4.2. The actual values of the TTPs used are in any case shown in each Appendix below the control file details, as described to in Section A2.2.2.

26-33, 35-38 The structure of the output required, which is the same for each of Appendices 1-19 is detailed.

34 This is the text which appears as part of the heading line.

A2.2.2 **TTP Values**

Following the control file details, the TTP values used in the run are given. These are given first for the NULL Scenario and then for the MRTP Scenario. Each Scenario starts by giving the Country and Sex and the name of the Assumption Set file. The TTP values are then shown by age (10-14, 15-29 ….. 75-79) and period of follow-up (1-3, 4+ months for NULL, 1-24, 24+ months for MRTP).

For the NULL Scenario there are three TTPs, with the column heading showing first the name (Initialisation – i.e. starting to smoke, Switch from current – i.e. quitting, and Re-initiation – i.e. quitters resuming smoking), then the smoking group switched from, then the smoking group switched to. Here there are only three smoking groups (Never, Current, Former). The TTPs are age-specific, but do not vary by time since MRTP introduction.

For the MRTP Scenario, the situation is more complex, as there are five smoking groups: Never smoker (Never), Current conventional cigarettes (CC) only (Curr CC), Current MRTP only (Curr Mrtp), Current dual use (Curr Dual) and Former smoker (Former). Again the second line of the column shows the group switched from, and the second the group switched to. The 15 TTPs, which are age-specific and do vary by time since MRTP introduction, are divided into five groups as described by the first line of heading:

Initialisation -	Never users becoming one of the three types of current tobacco user
Switch from current CC -	Current CC only smokers switching to one of the other two current tobacco use groups or quitting
Re-initialisation -	Former users becoming one of the three types of current user
Switch from current MRTP -	Current MRTP only users switching to one of the other two current tobacco use groups or quitting
Switch from current Dual -	Current dual users switching to one of the other two current tobacco use groups or quitting

A2.2.3 **Relative risk values**

These are only shown on the output if the basic values described in "Notes on Data Files" are not used. Here the country, sex and name of the assumption set are followed by, for each of the four causes of death, the RR values by age group (10-14, 15-19, …. 70-74, 75-79).

A2.2.4 **Half–life values**

These are only shown on the output if the basic values described in "Notes on Data Files" are not used. The layout of the results is the same as described for the RR values in the previous section.

A2.3 Results

The results for each run are divided into two sections, one from the P-Component which gives details of the smoking history, and the other from the E-Component which gives details of the attributable risks.

A2.3.1 Tobacco use prevalences

Results are shown firstly for the NULL Scenario, and then for the MRTP Scenario, each output being headed "Main Output for the Smoking History Summarized over Simulations", and giving details of country, sex, year of start of process and number of simulations at the start. Where there is more than one simulation, the output also includes standard errors of the various statistics shown.

The output for each Scenario is sorted by period of follow-up in five year intervals (1990:0, 1995:5, 2000:10, 2005:15 and 2010:20) and within each period gives the results by age (All ages, then ages 18-19, 20-24, 25-29, 30-34, …..70-74, 75-79). For each period (age combination, there is a line of results in the MRTP Scenario. The following results are given:

N	Number of subjects in the group.
%	Percentage of the total subjects in the group.
Ever quit (N)	The total number of current users who have ever quit.
Ever quit (%)	The percentage of all current users who have ever quit.
Mean years quit	The mean years quit for all former users.
Short term (n)	The number of short-term quitters, with short-term as given in the Control file details in years.

Short term (%)	The percentages of all former users who are short-term quitters.

A2.3.2 **Reductions in mortality**

This is separated into five blocks, in turn for the four diseases combined, lung cancer, IHD, stroke and COPD. The results are shown for the age groups combined (30-79), and with the exception of **Appendix 15**, are unadjusted for deaths in the MRTP Scenario. There is a set of results for each year from 1990 to 2009, and a summary result for years combined. As for the smoking history output, the output also includes standard errors of the various statistics shown where there is more than one simulation.

The results are as follows:

Number Deaths	Total number of deaths from the disease, for the given country, sex, year and age 30-79.
Null Attrib Deaths	The number of deaths attributed to smoking in the NULL Scenario.
MRTP Attrib Deaths	The number of deaths attributed to tobacco use in the MRTP Scenario
Drop Deaths	The reduction in deaths due to MRTP = Null Attrib Deaths – MRTP Attrib Deaths.
% Drop Deaths	The drop in deaths as a percentage of the total number of deaths.
% Drop Attrib Deaths	The drop in deaths as a percentage of the number of deaths attributed to smoking in the NULL Scenario.
Death Rates	The number of deaths per million population.
Null Attrib Rates	The number of attributable deaths in the NULL Scenario per million population.

MRTP Attrib Rates	The number of attributable deaths in the MRTP Scenario per million population.
Drop Rates	The reduction in death rates due to MRTP = Null Attrib Rates – MRTP Attrib Rates.

Note that % Drop Rates is not shown as it is equal to % Drop Deaths.

A3 Content of Appendices 1-19

A3.1 APPENDIX 1 - Basic analysis

This analysis is the basis for comparison for the simulation and sensitivity analyses. This consists of two runs, one for males and one for females. Each run involves the USA, a follow-up period of 20 years from 1990 in 12 month intervals, with smoking histories generated for subjects aged 10-79 years and risks estimated for the age range 30-79 years. The analyses use a standard set of population estimates (UN), mortality estimates (WHO), current and former smoking prevalence estimates (ISS), distribution of quit times (NHIS) and NULL Scenario TTPs which do not vary in any of the simulation and sensitivity analyses, described further in "Notes on data files for PHIM project". The fixed age of starting smoking is set at 16 years.

The sensitivity analyses involved variation in one (or more) parameters at a time, the meaning of the parameters, and the value assumed in the basic analysis becoming clear in the sections below which describe the sensitivity analysis.

A3.2 APPENDIX 2 - Ten simulations basic analysis

Whereas all other analyses presented in Appendices 1-17 are based on a single simulation of 10,000 individuals, the simulation analyses are conducted using 10 simulations, each of 10,000 individuals. The results presented are means over the 10 simulations, together with standard errors, giving information on the variability of the results.

A3.3 APPENDIX 3 - Varying F

F is the effective dose for current MRTP only users, expressed on a scale where 1 is equivalent to current CC smoking, and 0 is non-smoking (including quitters). The value of F used in the basic analysis is 0.2, and the 11 alternative values tested in the sensitivity analysis are 0, 0.05, 0.1, 0.15, 0.25, 0.3, 0.35, 0.4, 0.5, 0.6 and 0.7. In the first set of runs G was held at the basic analysis value of 0.6. In the second it was taken as (1+F)/2.

A3.4 APPENDIX 4 - Varying G

G is the effective dose for current dual users. The value of G used in the basic analysis is 0.6, the alternative values tested (12 runs) being 0.4, 0.8 1.0, 1.2, 1.5 and 2.0. Note that G = 0.6 corresponds to dual users using 50% CCs and 50% MRTPs, while G = 0.4 corresponds to dual users using 25% CCs and 75% MRTPs and G = 0.8 corresponds to dual users using 75% CCs and 25% MRTPs. Values of G greater than 1.0 allow for increased consumption. Thus G = 1.2 corresponds to a 20-a-day CC smoker becoming a dual user of 20 a day of each product.

A3.5 APPENDIX 5 - Varying TTP Factor 1 and TTP Factor 4

The TTP associated with the transition from MRTP use to CC smoking is multiplied by TTP Factor 1 if the individual has previously used CCs. The basic value of TTP Factor 1 is taken to be 2, with alternative values of 1, 1.5, 2.5 and 3 tested in the sensitivity analyses.

The TTP associated with the transition from MRTP use to CC smoking and that from MRTP use to dual use is multiplied by TTP Factor 4 if the individual has used MRTP continuously for more than a defined period. Note that if TTP Factor 4 is set to a value and MRTP has been used continuously for more than a defined period, TTP Factor 1 is not applied. The basic value of TTP Factor 4 is taken to be 0, with alternative values of 0.5, 1 and “ignore” tested in the sensitivity analyses (with the defined period taken as 2

years). The basic value of the defined period is taken to be 2 years, with alternative values of 1, 3 and 4 (with TTP Factor 4 taken as 0).

A3.6 APPENDIX 6 - Varying TTP Factor 2

The TTP associated with quitting is multiplied by TTP factor 2 if the individual has previously quit. This applies to both the NULL and the MRTP Scenario. As for TTP factor 1, the basic value is taken to be 2, with alternative values of 1, 1.5, 2.5 and 3 tested in the sensitivity analyses.

A3.7 APPENDIX 7 - Varying TTP Factor 3

The TTP associated with re-initiation is multiplied by TTP factor 3 if the individual is a short-term quitter. This applies to both the NULL and the MRTP Scenario. As for TTP factor 1, the basic value is taken to be 2, with alternative values of 1, 1.5, 2.5 and 3 tested in the sensitivity analyses.

A3.8 APPENDIX 8 - Varying short-term definition

TTP factor 3 requires the user to define short-term quitting. The basic value is taken as up to 2 years, with alternative values of up to 1 year and up to 3 years tested in the sensitivity analyses.

A3.9 APPENDIX 9 - Varying RR

The RR estimates used in the basic runs are from dataset PNLEST of the RR file, and were derived from meta-analyses. For the sensitivity analyses, one alternative dataset (PNLLOW) was created with each RR replaced by $1 + 0.8\ (RR-1) = 0.8\ RR + 0.2$, giving a 20% reduction in the excess RR. Another alternative (PNLHIGH) replaced each RR by $1 + 1.2\ (RR-1) = 1.2\ RR - 0.2$, giving a 20% increase in the excess RR. A third alternative (USSURG) used RR estimates for current smoking given in the 2014 US

Surgeon General's Report (US Surgeon General, 2014) as shown in Text-table 3 of this report.

A3.10 APPENDIX 10 - Varying H

The estimates of H used in the basic runs are from dataset PNLEST of the H file, and were derived from meta-analyses. For the sensitivity analyses, alternative datasets were created, with each H value replaced by either 0.8 H (dataset PNLLOW) or 1.2 H (dataset PNLHIGH).

A3.11 APPENDIX 11 - Varying starting and re-starting proportions

While the set of TTP values for the NULL Scenario remains unchanged throughout the sensitivity analyses, it is important to realize that the basic set of TTP values for the MRTP Scenario (shown in "Notes on Data Files") was constructed from that for the NULL Scenario.

In the sensitivity analyses investigating the effect of varying the relative frequency of initiation in the three current tobacco use groups, the rates P_{NM} and P_{ND} are either halved (Alternative 1) or multiplied by 1.5 (Alternative 2), while the rate P_{NC} is correspondingly altered so that the sum of the three MRTP rates $P_{NM,}$ P_{ND} and P_{NC} equals the NULL rate P_{NC}. Thus, for example, for age 20-24 in the first 24 months of follow-up, the MRTP rates for P_{NC}, P_{NM} and P_{ND}, instead of being 1520, 240 and 240 as in Text-table 2, become 1760, 120 and 120 in Alternative 1 and 1280, 360 and 360 in Alternative 2. Exceptionally, for age 30-34 for follow-up 25+ months, where multiplying P_{NM} and P_{ND} by 1.5 would make them both 300, and the total more than the rate of 500 for P_{NC} NULL, P_{NM} and P_{ND} is set to 250, and P_{NC} MRTP to 0.

In the sensitivity analyses investigating the effect of varying the relative frequency of re-initiation to the three current tobacco use groups, the MRTP rates P_{FM} and P_{FD} are either halved (Alternative 3) or multiplied by 1.5 (Alternative 4), while the MRTP rate P_{FC} is

altered so that the sum of the three MRTP rates will equal the NULL rate. Here there is no case where multiplying the two rates by 1.5 makes the other MRTP rate go negative.

A3.12 APPENDIX 12 - Varying starting and re-starting rates

While in **Appendix 11** the overall rates of initiation and re-initiation are kept constant, with only the relative frequency by type of product (CC only, MRTP only, dual use) varying, in **Appendix 12** the overall rates of initiation and re-initiation are varied. 14 alternatives are considered. In alternatives 1-3, initiation rates to MRTP and dual use only are multiplied by 1.5, 2 and 3, while in alternatives 4-8, all initiation rates are multiplied by 1.5, 2, 3, 4 and 8. In alternatives 9 and 10, re-initiation rates to MRTP and dual use only are multiplied by 1.5 and 2, while in alternatives 11-14, all re-initiation rates are multiplied by 1.5, 2, 5 and 10. Alternatives 7 and 8 (increasing initiation rates) and alternatives 13 and 14 (increasing re-initiation rates) relate to the zero benefit estimation.

A3.13 APPENDIX 13 - Varying quitting rates

In the basic analysis, the rates in the MRTP Scenario for quitting from each of the three current tobacco use groups are set equal to the quitting rate for the NULL Scenario. **Appendix 13** considers seven alternative situations. In alternatives 1 to 4, the quitting rate for CC only smokers is not changed, but the quitting rates of MRTP only users and dual users are each multiplied by the factors 0.5, 0.75, 1.5 or 2. In alternatives 5 to 7, the quitting rates for MRTP only users and dual users remain unchanged, but the quitting rate of CC only smokers is multiplied by the factors 0, 0.25 or 0.5, relating to zero benefit estimation.

A3.14 APPENDIX 14 - Varying switching between products

Of the 15 TTPs in the MRTP Scenario, six relate to switching between current tobacco use groups. 22 alternatives are investigated in the sensitivity analyses:

1-3 vary TTPs relating to switching to MRTPs (P_{CM} and P_{DM}),

4-6 vary TTPs relating to switching to dual use (P_{CD} and P_{MD}),

7-9 vary TTPs relating to switching to CCs (P_{MC} and P_{DC}),

10-12 vary TTPs relating to switching from CCs (P_{CM} and P_{CD}),

13-15 vary TTPs relating to switching from MRTPs (P_{MC} and P_{MD}), and

16-18 vary TTPs relating to switching from dual use (P_{DC} and P_{DM}).

In each case, the rates are multiplied by 0.5, 5 or 10. In alternatives 19-22, which relate to zero benefit estimation, the probabilities of switching to CC use are multiplied by 20, 50, 100 and 150.

A3.15 APPENDIX 15 - Adjusting for population size

Other sensitivity analyses make no adjustment for the fact that, because of the reduced mortality in the MRTP Scenario, the population at risk will increase relative to that in the NULL Scenario. **Appendix 15** repeats the basic analysis, but with adjustment made for the change in population size. This only affects the estimations of risk.

A3.16 APPENDIX 16 - Extreme situations

The basic and alternative analyses provide insight into the reduction in mortality resulting from MRTP introduction. To bring these results into context, it is useful to compare them with four extreme situations.

In the first extreme situation, all current smokers in the MRTP Scenario quit immediately and no further initiation or re-initiation of smoking occurs.

In the second extreme situation, CC smoking is totally replaced by MRTP use. Initiation rates in the MRTP Scenario for CC only and for dual use are added to those for MRTP only use, and then reset to zero. The same applies to the re-initiation rates. Thus, switching within current smokers is all to MRTP only.

In the third extreme situation, the whole population takes up MRTP only use at the start of the follow-up, with no further CC only smoking, dual use or quitting.

In the fourth extreme situation, current CC only smokers who would otherwise have switched to MRTP only or to dual use quit instead. Thus, the two TTPs for current CC only smokers switching are added to the quitting rate, and then reset to zero.

A3.17 **APPENDIX 17 - Varying parameter combinations – first analyses**

These analyses concern variation in four sets of parameters found, in preliminary runs, to have a major effect on the reduction in mortality associated with MRTP;

(v) the effective dose for MRTP only users (F),
(vi) the rate of switching to MRTP only (from CC only and from dual use),
(vii) the rate of switching to CC only (from MRTP only or dual use), and
(viii) the rate of quitting from MRTP only or dual use.

Note that variation in G, the effective dose for dual users, is considered indirectly by taking it as equal to (1 + F)/2 in all the alternatives considered, i.e. assuming, as in the basic analysis, that dual users used 50% CCs and 50% MRTPs, with no increase in overall cigarette consumption.

For each of the four sets of parameters, two alternatives were used, one producing larger and one smaller drops in mortality.

For variation in F, F = 0.1 and F = 0.5 are used to produce larger and smaller reductions in mortality.

For variation in the TTPs for switching to MRTP (from other current use), switching rates 10 times the basic rate are used to produce larger reductions in mortality, and switching rates half the basic rate are used to produce smaller reductions.

For variation in the TTPs for switching to CC only (from other current use), switching rates half the basic rate are used to produce larger reductions in mortality, and switching rates 10 times the basic rate are used to produce smaller reductions.

For variation in the TTPs for quitting from MRTP or dual use, doubling the basic quit rate is used to produce larger reductions in mortality, and halving the basic quit rate is used to produce smaller reductions.

The table below summarizes the 32 runs carried out; with runs 1 and 2 expected to produce the largest reductions in mortality and runs 31 and 32 the smallest. L indicates the parameter value used to produce larger reductions and S that value used to produce smaller reductions.

Runs	F	Switching to MRTP	Switching to CC only	Quitting from MRTP or dual use
1, 2	L	L	L	L
3, 4	L	L	L	S
5, 6	L	L	S	L
7, 8	L	L	S	S
9, 10	L	S	L	L
11, 12	L	S	L	S
13, 14	L	S	S	L
15, 16	L	S	S	S
17, 18	S	L	L	L
19, 20	S	L	L	S
21, 22	S	L	S	L
23, 24	S	L	S	S
25, 26	S	S	L	L
27, 28	S	S	L	S
29, 30	S	S	S	L
31, 32	S	S	S	S

A3.18 APPENDIX 18 – Varying parameter combinations – second analyses

These analyses are very similar to those described in section A3.17, except that the alternatives for each of the four parameters considered vary by fixed ratios (basic value/2, basic value x 2)..This allows more direct comparability between the effects of variation in the different parameters.

A3.19 APPENDIX 19 – Zero benefit estimation

Analyses already described give understanding of which parameter variations might eliminate the effect of MRTP introduction. These relate to:

Dual users increasing consumption	-	Appendix 4
Increasing initiation rates	-	Appendix 12
Increasing re-initiation rates	-	Appendix 12
Decreasing quit rates of CC only smokers	-	Appendix 13
Increasing switching rates to CC only smoking	-	Appendix 14

Based on these results, additional analyses were conducted to give insight into the joint effect of these parameters. Increasing initiation rates and increasing switching rates to CC only smoking were not studied as the effects were so small, but for the other parameters a sequence of five alternative values (V_1, V_2…V_5) was chosen which successively reduced the expected reduction in deaths associated with MRTP introduction. The first alternative set of analyses used all the V_1 values, the second all the V_2 values and so on. The values selected were as follows:

Effective dose for dual users, G	0.82, 1.04, 1.26. 1.48, 1.70
Re-initiation rates to CC only smoking	Basic rates x 1.1, 1.2, 1.3, 1.4, 1.5
Quit rate of CC only smokers	Basic rate x 0.964, 0.928, 0.892, 0.856, 0.820

A4 Appendices 20 to 24

A4.1 Reductions in mortality associated with MRTP Introduction

As the output described in sections A1 to A3 is extensive, **Appendix 20** gives some summary information from these analyses allowing ready comparison between the mortality results of the various analyses presented in Appendices 1 to 19.

The first page of output presents results for US males for 1995, giving for each of the simulation and sensitivity analyses presented in Appendices 1 to 10, a line of results consisting of the estimated percentage drop in deaths for the four diseases combined, and separately. The next four pages present the same output for 2000, 2005, 2009 and 1990 to 2009 combined. The next five pages then gives the corresponding results for the analyses presented in **Appendices 11** and **15**, while the next five give results for Appendices 16 to 19. This set of fifteen pages is then repeated for females. Then the whole set of 30 pages is repeated, but with the results presented being the percentage drop in attributable deaths rather than the percentage drop in deaths. Finally the whole set of 30 pages is repeated, but with the estimated percentage drop in deaths (or attributable

deaths) being replaced by the estimated drop in the number of deaths (equivalent to the drop in attributable deaths).

Appendix 21 is an Excel file, using **Appendix 20** as input data, which provides plots showing how the percentage reduction in deaths, and the percentage reduction in attributable deaths varies by level of each individual parameter studied in Appendices 1 to 14. There are separate sheets for males and females, and within each sheet the user can select the year (1990-2009 individually or combined) and disease (individually or combined). The user can also select the scale of the y-axis, which is kept constant in the plots for each sensitivity analysis to allow ready comparison across figures. Each plot shows two lines, one for the percentage reduction in deaths, and one for the percentage reduction in attributable deaths. On the left of the plot are two columns showing the data plotted. Hiding a column for a specific reduction will result in only the other reduction being shown on the figure.

A4.2 Summary tables for tobacco use prevalence

Corresponding to **Appendix 20** for mortality, **Appendix 22** gives some summary information allowing ready comparison between the tobacco use prevalence results of the various analyses presented in Appendices 1 to 19.

The first page of output presents results for US males aged 30-34 for 1995, giving for each of the simulation and sensitivity analyses presented in Appendices 1 to 10, a line of results consisting of the percentage prevalence of tobacco use, firstly for the three smoking groups in the NULL Scenario, and second for the five tobacco use groups in the MRTP Scenario. The next two pages present the same output for ages 50-54 and 70-74. The next three pages then give the corresponding results for the analyses presented in Appendices 11 to 15, while the next five give results for Appendices 16 to 19. This set of nine pages is then repeated for females. Further sets of 18 pages then give results for 2000, 2005 and 2010.

Appendix 23 is an Excel file, using **Appendix 22** as input data, which provides plots showing how the prevalence of tobacco use for the MRTP Scenario varies by level of each individual parameter studied in Appendices 1 to 14. There are separate sheets for males and females, and within each sheet the user can select the age group (30-34, 50-54, 70-74), and a year from 1990 to 2010. The user can also select the scale of the y-axis, which is kept constant in the plots for each sensitivity analysis to allow ready comparison across figures. Each plot shows five lines, one for each of the five MRTP use groups. On the left of the plot are five columns showing the data plotted. Hiding columns for specific smoking groups will lead to the prevalence not being shown in the figure.

A4.3 Extended output for the basic analysis

The output for the basic analysis shown in **Appendix 1** gives results for tobacco use prevalence by 5-year age for the years 1990, 1995, 2000, 2005 and 2010, and results for mortality for all ages combined for single years from 1990 to 2009, and for 1990-2009. In order to obtain some information on mortality effects by age, **Appendix 24** is an extended version showing mortality results by 5-year age group for 2009 and for 1990-2009.