7.4.2.: POPULATION MODEL

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LIST OF ABBREVIATIONS

Term or Abbreviation	Definition
Agent-Based Model	A class of computational models for simulating the actions and interactions of autonomous agents with a view to assessing their effects on the system as a whole.
ALCS	Altria Client Services LLC
Base Case	baseline population or status quo
CCI	ALCS Claims Comprehension and Intentions Study
CDC	Centers for Disease Control and Prevention
CI	confidence interval
Compartmental Model	A type of mathematical model used for describing the way resources are transmitted among the compartments of a system. Each compartment is assumed to be a homogeneous entity within which the entities being modeled are equivalent.
CS	current cigarette smokers
DU	dual user (current Cigarette Smoker and Current MRTP User)
EMR	excess mortality ratio
ERR	excess relative risk
FCS	former cigarette smoker
FDA	Food and Drug Administration
FDU	former dual user (both former cigarette smoker and former MST user)
FMRTP	former modified risk tobacco product user
FMST	former MST user
HR	hazard ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
KP	Kaiser-Permanente
LCL	lower confidence limit
MCMC	Markov Chain Monte Carlo
MCMCpack	A software package designed to allow users to perform Bayesian inference via Markov chain Monte Carlo used in R package. R is an extremely powerful language and environment for statistical computation and graphics.
MCMCpoisson	a function in MCMCpack
Metropolis-Hastings sampler	A Markov chain Monte Carlo method for obtaining a sequence of random samples from a probability distribution for which direct sampling is difficult.
Master Case	The most likely outcome if marketing of the MST with a label claim is authorized
Modified Case	A model scenario where at least one transition probability is changed from the Base Case scenario with the market authorization of the proposed claim
MR	mortality rate
MRTP	modified risk tobacco product
MRTPA	Modified Risk Tobacco Product Application
MST	moist smokeless tobacco
NHIS	National Health Interview Survey
NSDUH	National Survey on Drug Use and Health
NT	never-user of tobacco

pct	percentage
R Statistical programming	R is a language and environment for statistical computation and graphics.
RR	relative risk
ST	smokeless tobacco
SD	standard deviation
TUS-CPS	Tobacco Use Supplement to the Current Population Survey
UCL	upper confidence limit
U.S.	United States
YQSM	years since quitting smoking
YSM	years smoked

LIST OF DEFINITIONS

Term	Definition
Excess Relative Risk (ERR)	The differential amount of risk posed by one product relative to another product
$_nm_x$	Age-specific death rate calculated from the KP study data (i.e. Number of deaths due to all causes/ Pear-Years)
$_nq_x$	Mortality rate or probability of dying between age x and x+n estimated from the regression models using final data set which includes age, smoking status, years smoked, years since quit smoking, and $_nm_x$
nLx	Expected person-years lived between age x and x+n
Tx	Expected remaining person-years at age x
nSx	Survival probability is 1- $_nq_x$
Person-Years	As defined by KP study was obtained by adding the number of years a given person lived until aging out of the study or death

7.4.2. POPULATION MODEL

7.4.2.1. Population Model Development

7.4.2.1.1. Introduction

A Modified Risk Tobacco Product Application (MRTPA) must demonstrate that the modified risk tobacco product (MRTP) "will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products" [21 USC 387K (g) (1)]. In Section (VI) (B) (4) of its 2012 MRTPA Draft Guidance, the Food and Drug Administration (FDA) acknowledges "[t]he difficulties inherent in making premarket assessments of the effect that the introduction of a modified risk product would have on the population as a whole and the public health." The MRTPA draft guidance states that "[a]pplicants may opt to use currently available models in the scientific literature to forecast the harm to public health from tobacco use." The Institute of Medicine report "Scientific Standards for Studies on Modified Risk Tobacco Products" (2012) states that "[m]odeling analyses have multiple potential uses in the assessment of the societal effect of MRTPs, as required by the regulatory process." The authors of the Institute of Medicine report recommend that the FDA issue guidance on the development and use of simulation and modeling approaches to predict public health effects.

At a workshop organized by the FDA's Center for Tobacco Products, ("Modeling and Statistical Methods for the Regulatory Assessment of Tobacco Products: A Public Workshop (transcript)," 2013) members from the FDA, public health, and industry discussed the utility of population modeling in regulatory decisions within the context of the totality of the evidence. In a recent article titled "Population Health Standards for MRTPs," published in the proceedings of the 2016 Tobacco Science Research Conference (2016), C. Choiniere discussed three categories of studies (and combinations) that are commonly used by researchers to address the types of questions that may be asked about MRTPs: surveys, consumer perception studies, and computational modeling of population effects. In terms of computational modeling, Choiniere (2016) observes that models can provide an overall assessment of the potential effect that the introduction of an MRTP may have on overall tobacco-related morbidity and mortality. Mathematical models are becoming standard tools for use in tobacco research. Mathematical models have been applied to assess the effect of tobacco-control policy on public health outcomes, and SimSmoke, for example, has been used in several instances to simulate various scenarios for policy assessments (Levy & Friend, 2002). This model has been used recently for public policy assessments in Germany (Levy, Blackman, Currie, & Mons, 2013), the United Kingdom, and China (Levy, Rodriguez-Buno, Hu, & Moran, 2014), and for estimating the potential impact of tobacco control policies on adverse maternal and child health outcomes in the U.S. (Levy, Mohlman, & Zhang, 2015). Based on a request from the FDA, the Institute of Medicine convened a committee to conduct a study on the public health implications of raising the minimum age to purchase tobacco products, which also used mathematical modeling to quantify their predictions (Committee on

the Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products, 2015).

A recent review (Feirman et al., 2016) of mathematical modeling literature associated with tobacco products yielded 263 peer-reviewed articles. Eighteen different mathematical models were cited among these articles. Most of the model applications cited focused predominantly on evaluating the potential effect of tobacco policy changes on population health and not on evaluating the potential health impact of introducing a new MRTP into the market or allowing a label claim to be added on a product that already exists within the market.

In recent years, several mathematical models have assisted in predicting the potential public health impact of change in use of tobacco products with varying levels of inherent risk. Bachand et al. (2013) and (2017) used cohort-based compartmental models to assess the introduction of an MRTP on all-cause mortality. Vugrin et al. (2015) utilized a multistate, dynamic systems population modeling structure to assess the potential impact associated with use of a variety of tobacco products. Weitkunat et al. (2015) and Lee et al. (2017) used a Markov model combined with a negative exponential mortality model to estimate the effect of introducing a reduced risk MRTP on hypothetical European and U.S. population samples of 10,000 individuals, respectively. Hill et al. (2016) and (2017) used a system dynamics based compartmental stock and flow model to assess the potential health impact of launching a new MRTP into the marketplace and to reinforce their views that e-cigarette use is likely to benefit United Kingdom population health. Levy et al. (2016) applied a decision-theoretic model to estimate public health impact of introducing vaporized nicotine products such as e-cigarettes in the U.S. Cherng et al. (2016) applied agent-based model techniques to examine hypothetical scenarios of e-cigarette use by smoking status and the effect of e-cigarette availability on smoking initiation and smoking cessation. Poland et al. (2017) developed a statistical model to explore the effect on population mortality of an MRTP introduction resulting in reduced conventional cigarette smoking. A poster by Muhammad-Kah et al. (2016) discussed the development and validation of an agent-based model that can be used as a tool to assess the net benefit from introducing a MRTP within a hypothetical population.

ALCS has developed the model used in this MRTPA using similar principles as described in the literature, "to forecast the harm to public health from tobacco use." ALCS collaborated with Edward Boone, Ph.D., Associate Professor, Virginia Commonwealth University, in developing this model, which is described in Boone et al.(2016). Details of this model, henceforth referred to as the ALCS Cohort Model, are in Section 7.4.2.1.3, Section 7.4.2.1.4, and 7.4.2.1.5.

The ALCS Cohort Model utilizes best practices described by the Modeling Good Research Practices Taskforce, which was developed by The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) and the Society for Medical Decision Making to recommend best practices for developing mathematical models used in health care and public health decision-making. In 2012, ISPOR published a series of seven articles describing the expert opinions of the taskforce members: Caro et al., (2012), Roberts et al., (2012), Siebert et al., (2012), Karnon et al., (2012), Pitman et al., (2012), Briggs et al., (2012), and Eddy et al., (2012). These articles provide guidelines on designing the modeling approach; selecting the modeling technique; implementing and validating the model;

parameterizing the inputs and assessing uncertainty; and using the resulting tool to inform decision making. These guidelines represent individual opinions of the Task Force experts, rather than a consensus reached by the group as a whole. Differences, if any, are documented in the guidelines.

These guidelines also propose partitioning the model design process into two components: (1) conceptualization of the problem, which lays out the intended purpose(s) of the model; and (2) conceptualization of the mathematical model, which ties the attributes and characteristics of a particular model to the intended purpose of the model. The second step involves defining and developing the underlying mathematical construct based on the scope of the model, the populations of interest, the key model inputs, and outcome parameters of interest.

In terms of parameter estimation and uncertainty, the guidelines recommend reporting the following: data sources and quality; estimation processes used to obtain parameters for input into the model; and levels of uncertainty regarding inputs and their effect on the model through various forms of analyses.

The ISPOR-Society for Medical Decision Making guidelines also document best practices for model validation and transparency. Model validation encompasses various forms of validity (i.e., face validity, verification or internal validity, cross-validity, external validity, and predictive validity) and is ultimately used to demonstrate how well the model reproduces reality. Model transparency requires good documentation on all aspects of the model, including framework, assumptions, and limitations.

The ALCS Cohort Model was developed and validated in accordance with key elements found within the ISPOR-Society for Medical Decision Making published guidelines discussed above. In this section, we address inputs and assumptions used for modeling (Section 7.4.2.2) and modeling results (Section 7.4.2.3).

We also detail the ALCS Cohort Model's development as follows:

- Section 7.4.2.1.2 presents an overview of the conceptual framework of the proposed model.

- Section 7.4.2.1.3 explains the development of the data set used to create the mortality sub-models used within the ALCS Cohort Model.

- Section 7.4.2.1.4 details the development of the mortality models (including parameter estimates), how these mortality models can be extended using the concept of an excess relative risk (ERR), and gives numerical examples of how the method is employed.

- Section 7.4.2.1.5 explains the compartmental model and the Markov chain approach used to transition individuals through the 29 distinct states and provides numerical examples to improve understanding.

- Section 7.4.2.1.6 shows how the compartmental model and the mortality models can be combined to transition individuals through the various states of tobacco use and how the Bayesian approach is used to propagate uncertainty associated with the mortality models.

- Section 7.4.2.1.7 discusses model validation for the U.S. male and female populations.

- Section 7.4.2.1.8 discusses the model verification.

- Section 7.4.2.1.9 explores the sensitivity of the model to changes in parameters and provides an example of how the model can be used to create output maps.

- Section 7.4.2.1.10 discusses a multiple-cohort approach that can be employed to determine population estimates.

7.4.2.1.2. ALCS Cohort Model Conceptual Framework

This section describes ALCS's framework for developing a computational model to assess the overall difference in all-cause mortality of a hypothetical cohort population, between a Base Case scenario and a Modified Case scenario (Section 7.4.2.2.5 for a detailed description of the different scenarios). The Base Case scenario represents the status quo for a hypothetical population. Overall changes in all-cause mortality within a Modified Case scenario can occur as a result of changes in individual product risks and/or change in product use behaviors, emerging from regulatory actions such as FDA authorization of the proposed modified risk claim.

These two conceptual approaches for comparing the Base Case and Modified Case scenarios are illustrated in Figure 7.4.2-1 and Figure 7.4.2-2. The approach in Figure 7.4.2-1 assumes that cigarettes are the only tobacco product present in the Base Case scenario, while cigarettes and MST coexist in the Modified Case scenario. The latter framework would be most relevant for modeling the net benefit of authorization of the proposed claim for the candidate product.

In our framework depicted in Figure 7.4.2-2, our Base Case assumes cigarettes and Moist Smokeless Tobacco (MST) already coexist. In the Modified Case Scenarios, these products still coexist, but the proposed claim has been authorized. A Modified Case scenario is defined when at least one transition probability is changed from the Base Case scenario. Our Master Case scenario is defined as the final scenario involving authorization of the proposed claim and all the likely changes in use patterns occur simultaneously.

For population modeling analysis related to authorization of the proposed claim discussed in this MRTPA, we use the frameworks shown in Figure 7.4.2-1 and Figure 7.4.2-2, given that cigarettes and MST currently coexist in the U.S. market and the Master Case scenario, wherein potential changes in cigarette and MST use occur due to market authorization of the proposed claim.

Figure 7.4.2-1: **Modeling Effect of Introducing an MRTP into a Hypothetical Population**
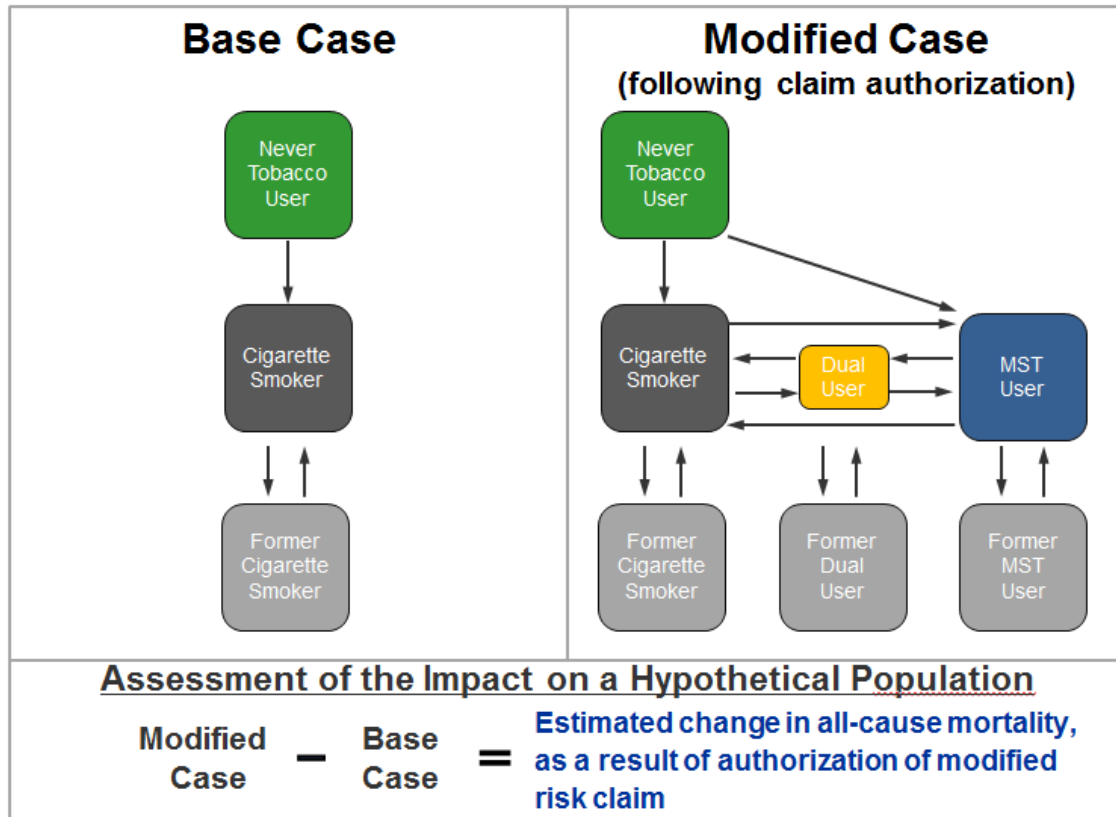
MST = Moist Smokeless Tobacco

Figure 7.4.2-2: **Modeling Effect of Adding an MRTP Claim to an Existing Product**
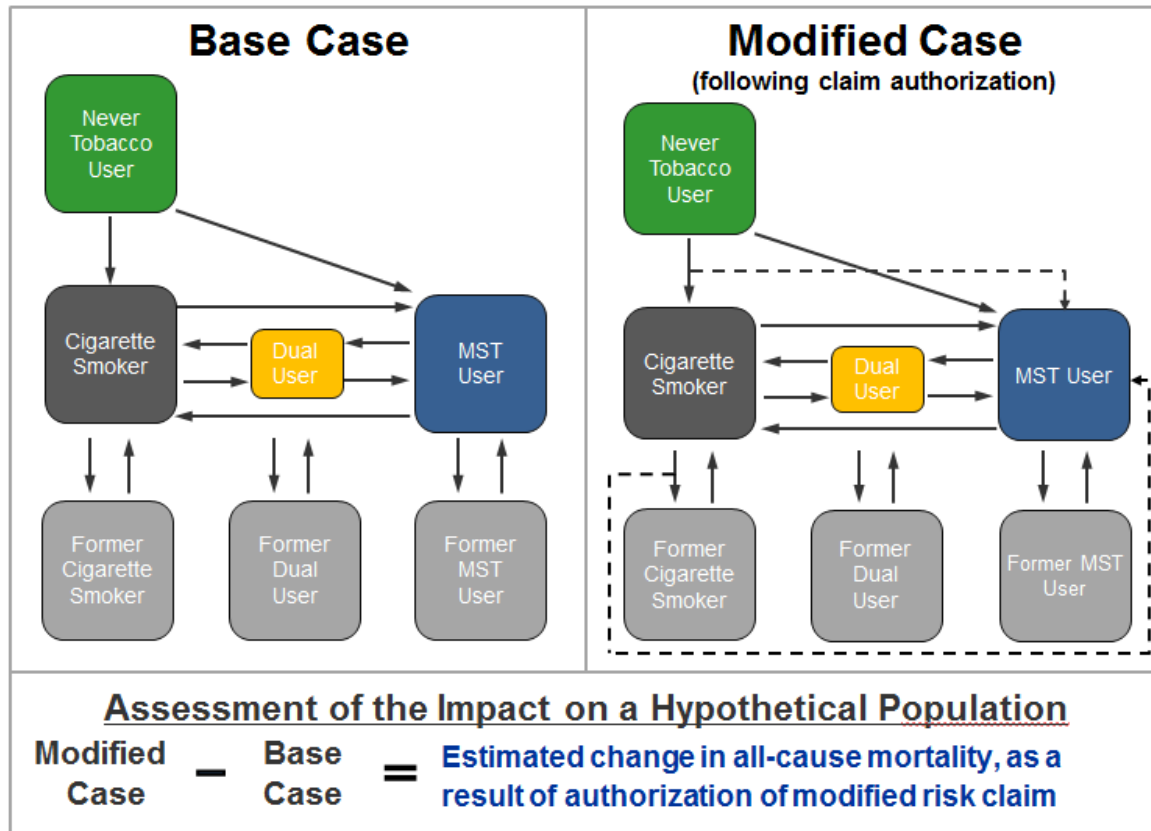
Note: The actual ALCS Cohort Model consists of 29 states and 30 transitions.
MST = Moist Smokeless Tobacco

In the ALCS Cohort Model, comparisons between the Base Case and Modified Case scenarios are achieved by following the survival of a hypothetical cohort population of 1,000,000 individuals in 5-year intervals, from the age of 13 years to the age of 73 years. A Markov compartmental model approach with 29 distinct states and 30 transition probabilities is used to account for the various states of transition within the model. Transition probabilities (i.e., demographic- and product-specific probabilities of moving between states) are used to propagate the cohort through the various states across time. The Markov model is coupled with mortality models developed using data from a Kaiser-Permanente (KP) study of smokers (Friedman, Tekawa, Sadler, & Sidney, 1997). Statistical models combined with ERRs are used to determine survival probabilities of the cohort at each time interval. This model structure is similar to one adopted by Bachand et al. (2013).

The model is implemented using a Bayesian framework with parameter estimates that use Markov Chain Monte Carlo (MCMC) techniques. The model accounts for uncertainties associated with mortality rates, as well as various other input parameters. The model serves as a tool for assessing "what if" scenarios and allows us to quantify changes that may occur

within a hypothetical population, between well-defined Base Case and Modified Case scenarios.

7.4.2.1.3. Data Set Utilized for Development of Mortality Models

The data set used to create the mortality models is based on a Kaiser Permanente (KP) Medical Care Program Cohort study. Friedman et al. (1997) provided a data set that addresses the relative mortality of current cigarette smokers, former cigarette smokers, and never user of tobacco at various ages. The KP Medical Care Program Cohort study obtained baseline information including age, sex, and smoking status history on more than 60,000 subjects, age 35 years and older and followed the cohort for mortality over a period of time. This is one of the few data sets available that contain information about how long a person has been a cigarette smoker, whether the person had quit smoking, and, if so, how long the person has been a former cigarette smoker. Appendix 7.4.2-1; Table 1 and Table 2 of show person years and number of deaths due to all causes for former and current cigarette smokers, respectively, by age group and sex (Friedman et al. (1997)). These data enable input values, including age-specific estimated mortality rates due to all causes by duration of cigarette smoking or duration of quitting cigarettes, to be calculated and used for the mortality models discussed in the next section. These mortality rates were calculated by dividing the number of deaths from all causes by person years reported in the KP study.

The data in Appendix 7.4.2-1; Table 1 and Table 2 have wide age intervals and, in selected cases, lack all the information needed in a concise format. For example, the information about smoking duration was not available in the former cigarette smoker data set. To address this, the data were divided into narrower intervals to better align with the age groups used in our modeling application.

To divide the data into narrower intervals, the age groups in Appendix 7.4.2-1; Table 1 and Table 2 were divided in half at the midpoint range and distributed evenly into two subintervals. This approach was deemed the most feasible because the varying and somewhat unconventional age intervals found in the source data (i.e., 35-49, 50-64, 65-74, and 75+ years), preclude the use of standard "age-splitting" methods such as the Karup-King Method (Judson & Popoff, 2004). For example, the "Never-Users of Tobacco" in the 35- to 49-year age group were divided into subintervals of 35 to 42 years and 43 to 49 years accordingly (as shown in Appendix 7.4.2-1; Table 3). The number of males in Appendix 7.4.2-1; Table 1 of under the "Person Years" category was 29,916, which was divided into 14,958 person years for each of the two groups as shown in Appendix 7.4.2-1; Table 3. Continuing with the example of subdividing the data in the initial age groups, the number of deaths due to all causes for "Never-Users of Tobacco" for age group 35-49 years was also divided into two subintervals, with 40 percent assigned to the younger subinterval and 60 percent assigned to the older subinterval. For example, the number of deaths due to all causes for males with the status of "Never-Users of Tobacco" in Appendix 7.4.2-1; Table 1 was 49, which was converted to 19.6 (40 percent) for the 35- to 42-year age subinterval and to 29.4 (60 percent) for the 43- to 49-year age subinterval in Appendix 7.4.2-1; Table 3. Modifications similar to those described for Appendix 7.4.2-1; Table 1 were made to expand the age groups shown in Appendix 7.4.2-1; Table 2. Results are shown in Appendix 7.4.2-1; Table 3. Notice that in Appendix 7.4.2-1; Table 3, several counts for "Person Years" and "Number of deaths (All

cause)" cells are missing. The lack of members in these cells is supported by knowledge of initiation patterns as described by Husten (2007) and Morbidity and Mortality Weekly Report (Centers for Disease Control and Prevention, 1991). Appendix 7.4.2-1; Table 4 shows the unadjusted mortality data set with all the data allocations.

The data displayed in Appendix 7.4.2-1; Table 1 and Table 2 were obtained from the KP Medical Care Program Cohort study (Friedman et al., 1997). As such, all the subjects in the data set had health insurance, the observation period was short, and the age-specific mortality rates are likely to be lower than the U.S. population. Therefore, we adjusted the KP mortality data as illustrated in Table 7.4.2-1 by using the concept of excess mortality ratio (EMR) (ratio of mortality rates in the U.S. population to the mortality rates reported in the KP data set). The 1991 U.S. mortality rates (1991) are averaged values that correspond to the KP age intervals. Notice that the U.S. mortality rates are provided in 5-year intervals; hence, the mortality rates for 35- to 39-year age group, the 40- to 44-year age group, and the 45- to 49-year age group were averaged to find a mortality rate that corresponds to the mortality rate for the KP age group of 35 to 49 years. This procedure was similarly applied to calculate average U.S. mortality rates for all the age groups. We divided the U.S. mortality averages by the corresponding KP mortality rates to obtain an EMR for the age groups. For example, to obtain the EMR for the 50- to 64-year age group, the U.S. mortality average of 1,263 is divided by the KP mortality rate of 612.9, resulting in an EMR of 2.0607. This signifies that a person in the 50- to 64-year age group in the general U.S. population is more likely to die than a person included in the KP study.

Table 7.4.2-1: Age-Specific Male MRs and Ratios (per 100,000) for the U.S. and Kaiser-Permanente Medical Care Program Cohort Study (Friedman et al., 1997)

Kaiser-Permanente		U.S. MRs 1991			Adjusted Mortality Ratio	
Age (y)	MR	Age (y)	MR	Average	Age (y)	EMR
35 to 49	375.7	35 to 39	280.5	374.6	35 to 49	0.9971
		40 to 44	345.8			
		45 to 49	497.5			
50 to 64	612.9	50 to 54	736.7	1,263	50 to 64	2.0607
		55 to 59	1,189.9			
		60 to 64	1,862.4			
65 to 74	1,639.8	65 to 69	2,814.1	3,523.65	65 to 74	2.1488
		70 to 74	4,233.2			
75 and older	4,915.9	75 to 79	6,376.6	6376.6	75 and older	1.2971

EMR = excess mortality ratio; MR = mortality rate; U.S. = United States.

These EMR values are then multiplied by the corresponding age groups in the unadjusted data in Appendix 7.4.2-1; Table 4 to obtain the adjusted data in Appendix 7.4.2-1; Table 5. To illustrate the calculation, consider the mortality for a 39-year-old male with zero "Years

Smoked." In Appendix 7.4.2-1; Table 4, the "Number of deaths due to all causes" value is 19.6, which was multiplied by the EMR of 0.9971 (Table 7.4.2-1) to obtain the number of deaths due to all causes of 19.54, as shown in Appendix 7.4.2-1; Table 5.

Appendix 7.4.2-1; Table 6 and Table 7, reflect the final data set used to estimate the parameters in the mortality models, which includes age, smoking status, years smoked, years since quit smoking, person-years, number of deaths due to all causes, and calculated mortality rate (i.e., number of deaths/person-years) ($_nm_x$). The ultimate goal through the use of this final data set is to estimate mortality rate ($_nq_x$) using the mortality models described below.

7.4.2.1.4. Development of Mortality Models

This section details the development of the mortality models (including parameter estimates), describes how these mortality models can be extended using the concept of an ERR, and gives numerical examples of how the method is employed.

To model mortality associated across age, we used a Poisson response regression model. We estimated the parameters in the model using a Bayesian approach via the Markov Chain Monte Carlo (MCMC) procedure from the MCMCpack package in the R statistical programming environment. The goal of a Bayesian analysis was to determine the posterior distribution for the parameters. For notation, let $p(\beta)$ be the prior distribution for the parameter β, and let $L(D|\beta)$ be the likelihood of data D, given the parameter β. To obtain the posterior distribution $p(\beta|D)$, we used Bayes theorem given by:

$$p(\beta|D) = \frac{p(\beta)L(D|\beta)}{\int p(\beta)L(D|\beta)d\beta}$$

Often, the posterior distribution is not analytically tractable; hence, the posterior distribution must be explored using computer sampling. By taking a large number of samples from the posterior distribution, one can use sample quantities to make inferences. The MCMCpack in R utilizes the Metropolis-Hastings Algorithm to obtain samples from the posterior distribution. Additional information on Bayesian analysis can be obtained in the following references: Gelman et al. (2013), Albert (2009), Robert and Casella (2009), and Lee (2012).

The goal for the mortality model was to relate the mortality rate to the following predictors: age (*AGE*), years smoked (*YSM*), and years since quitting smoking (*YQSM*). Second order term (*AGE^2*) and interaction terms (*AGE*YSM* and *AGE*YQSM*) were also included in the models which improved their overall fit. Models were created for Never-Users of Tobacco (NT), Current Cigarette Smokers (CS), and Former Cigarette Smokers (FCS). Since the mortality rates (MR_i) correspond to each 100,000 people, they can be modeled using a Poisson regression, where the mean λ (i.e., mean mortality rate) is modeled as a function of the covariates and the Poisson distribution is used to construct the likelihood. The parameters β_j in the Poisson regression relate the covariates to the natural logarithm of the mean λ. To adequately address the issue of model parameter uncertainty, a Bayesian analysis was used, which required that prior probability distributions for the regression parameters β_j be specified. For this modeling, we have specified the prior probability distributions for each β_j to be a normal distribution with a mean of zero and a standard deviation of 100. This reflects that, *a priori*, we have very little information about the values of the regression parameters β_j.

Three distinct sub-models are fit to their corresponding data sets:

1. For NT, the following model is used:

$$MR_i \sim Poisson(\lambda_i)$$
$$\ln(\lambda_i) = \beta_0 + \beta_1 AGE_i + \beta_2 AGE_i^2$$
$$\beta_j \sim N(0,100)$$

where i represents members in the never-user of tobacco group.

2. For the CS, the following model is used:

$$MR_i \sim Poisson(\lambda_i)$$
$$\ln(\lambda_i) = \beta_0 + \beta_1 AGE_i + \beta_2 AGE_i^2 + \beta_3 YSM_i + \beta_4 YSM_i \times AGE_i$$
$$\beta_j \sim N(0,100)$$

where i represents members in the current cigarette smokers group.

3. For the FCS, the following model is used:

$$MR_i \sim Poisson(\lambda_i)$$
$$\ln(\lambda_i) = \beta_0 + \beta_1 AGE_i + \beta_2 AGE_i^2 + \beta_3 YSM_i + \beta_4 YQSM_i + \beta_5 YSM_i \times AGE_i + \beta_6 YSQM_i \times AGE_i$$
$$\beta_j \sim N(0,100)$$

where i represents members in the former cigarette smokers group.

Separate models were fit for males and females using the adjusted mortality data set in Appendix 7.4.2-1; Table 6 and Table 7. For more on survival models, see Kalbflesch and Prentice (2002) and Lawless (2002).

The MCMCpoisson function in MCMCpack utilizes a Metropolis-Hastings sampler to draw samples from the posterior distributions of the parameters. For each model, 10,000 samples were drawn from the posterior distributions after a 2,000-sample burn-in at the beginning of the run. As is a well-accepted practice in MCMC analysis, the burn-in samples were discarded, and all inferences about the mortality models were made using the 10,000 samples or functions of those samples. Basic diagnostics such as trace plots and the potential reduction factors were examined to ensure the quality of the resulting samples. For more on MCMCpack, see Martin et al. (2011).

Table 7.4.2-2 summarizes the posterior distributions of the mortality model parameters for females. Based on the data in Appendix 7.4.2-1; Table 6, the mean, standard deviation, and quantiles (2.5%, 50%, and 97.5%) are provided. The 2.5% and 97.5% quantile intervals form a 95% credible interval for the parameter of interest. For example, consider the coefficient for *YSM* in the "Current Cigarette Smoker" model with 2.5% and 97.5% quantiles of 0.02355 and 0.02737, respectively. The intervals (0.02355, 0.02737) form a 95% posterior credible interval for the parameter. For this model, posterior credible intervals that do not contain a zero value are considered statistically significant. The quantiles set off in bold in Table 7.4.2-2 correspond to posterior credible intervals that do not contain zero and, hence, are deemed statistically significant.

Table 7.4.2-2: Female Posterior Distribution Summaries for Mortality Model Parameters

Model	Variable	Mean	SD	Quantiles		
				2.50%	50%	97.50%
Never-User of Tobacco	Intercept	2.47231	0.05400	**2.36520**	**2.47328**	**2.57726**
	AGE	0.18659	0.00165	**0.18339**	**0.18655**	**0.18985**
	AGE2	-0.00074	0.00001	**-0.00076**	**-0.00074**	**-0.00072**
Current Cigarette Smoker	Intercept	-2.05000	0.03429	**-2.11500**	**-2.05100**	**-1.98248**
	AGE	0.34570	0.00107	**0.34360**	**0.34580**	**0.34782**
	AGE2	-0.00217	0.00001	**-0.00219**	**-0.00217**	**-0.00215**
	YSM	0.02550	0.00099	**0.02355**	**0.02551**	**0.02737**
	YSM × AGE	0.00009	0.00002	**0.00006**	**0.00009**	**0.00013**
Former Cigarette Smoker	Intercept	4.12500	0.02908	**4.06800**	**4.12400**	**4.18500**
	AGE	0.09682	0.00112	**0.09460**	**0.09684**	**0.09901**
	AGE2	0.00002	0.00001	**0.00000**	**0.00002**	**0.00004**
	YSM	0.12900	0.00067	**0.12770**	**0.12900**	**0.13030**
	YQSM	0.00372	0.00080	**0.00216**	**0.00376**	**0.00527**
	YSM × AGE	-0.00138	0.00001	**-0.00140**	**-0.00138**	**-0.00136**
	YQSM × AGE	0.00005	0.00001	**0.00003**	**0.00005**	**0.00007**

Source: Appendix 7.4.2-1; Table 6
Note: Posterior credible intervals are based on the 2.50% and 97.50% quantiles. Quantiles in bold do not contain zero and could be considered statistically significant. Results are based on 10,000 posterior samples.
AGE2 = AGE*AGE; *YQSM* = years since quitting smoking; *YSM* = years smoked.

Table 7.4.2-3 provides the posterior distribution summaries for the male mortality model parameters based on the data in Appendix 7.4.2-1; Table 7. Note that all the parameters in both the female and male mortality models are considered statistically significant, since none of the posterior credible intervals contained a zero value.

Table 7.4.2-3: Male Posterior Distribution Summaries for Mortality Model Parameters

Model	Variable	Mean	SD	Quantiles		
				2.50%	50%	97.50%
Never-User of Tobacco	Intercept	2.86656	0.04031	**2.78760**	**2.86748**	**2.94392**
	AGE	0.19256	0.00123	**0.19019**	**0.19253**	**0.19497**

				Quantiles		
	AGE2	-0.00078	0.00001	**-0.00080**	**-0.00078**	**-0.00076**
Current Cigarette Smoker	Intercept	0.08566	0.02355	**0.04088**	**0.08582**	**0.13290**
	AGE	0.22454	0.00073	**0.22305**	**0.22459**	**0.22591**
	AGE2	-0.00031	0.00001	**-0.00032**	**-0.00031**	**-0.00030**
	YSM	0.19373	0.00072	**0.19229**	**0.19373**	**0.19515**
	YSM × AGE	-0.00320	0.00001	**-0.00323**	**-0.00320**	**-0.00318**
Former Cigarette Smoker	Intercept	3.85700	0.02134	**3.81500**	**3.85700**	**3.90100**
	AGE	0.13960	0.00083	**0.13800**	**0.13960**	**0.14120**
	AGE2	-0.00040	0.00001	**-0.00042**	**-0.00040**	**-0.00039**
	YSM	0.10460	0.00049	**0.10370**	**0.10460**	**0.10550**
	YQSM	0.00308	0.00058	**0.00196**	**0.00310**	**0.00419**
	YSM × AGE	-0.00105	0.00001	**-0.00106**	**-0.00105**	**-0.00103**
	YQSM × AGE	0.00006	0.00001	**0.00004**	**0.00006**	**0.00007**

Source: Appendix 7.4.2-1; Table 7
Note: Posterior credible intervals are based on the 2.50% and 97.50% quantiles. Quantiles in bold do not contain zero and could be considered statistically significant. Results are based on 10,000 posterior samples.
AGE2 = AGE*AGE; *YQSM* = years since quitting smoking; *YSM* = years smoked.

To estimate mortality related parameters from the authorization of the proposed claim, the model includes the following use states: NT; CS; FCS; Current MST Users (MST); Former MST Users (FMST); Dual Users (DU) (i.e., both current cigarette and MST users); and Former Dual Users (FDU). We employ the concept of ERR to adjust the risk associated with smoking and to approximate the risks associated with both use of MST and dual use (Section 7.4.2.2.1). In the following scenarios, we assign the mortality risk of dual use to be the same as the mortality risk of exclusive cigarette use based on published literature (Accortt, Waterbor, Beall, & Howard, 2002; Frost-Pineda, Appleton, Fisher, Fox, & Gaworski, 2010). Levy et al. (2004) provides more information on relative risks.

Below is an illustration of how survival probabilities are calculated using the estimated survival models combined with ERRs. For example, if we consider a 46-year-old male smoker who has smoked for 26 years, using the median value of the model parameters in Table 7.4.2-3 as point estimates, the risk of mortality can be estimated by:

$$
\begin{aligned}
\ln(\lambda_{CS}) &= 0.08566 + 0.22454 AGE - 0.00031 AGE^2 + 0.19373 YSM - 0.00320 AGE \times YSM \\
&= 0.08582 + 0.22459(46) - 0.00031(46)^2 + 0.19373(26) - 0.00320(46 \times 26) \\
&= 10.97078
\end{aligned}
$$

The inverse logarithm is calculated as

$$\lambda_{CS} = e^{10.97078} = 58149.9$$

and adjusted for mortality table and estimation adjustments, to obtain a risk of mortality ($_nq_x$)

$$r_{CS}(46) = 0.00581499$$

We can then convert this into a survival probability by the following calculation:

$$S_{CS}(46) = 1 - 0.00581499 = 0.99418.$$

To find the mortality risk of a current MST user after authorization of the proposed claim, we first must find the mortality of a Never-User of Tobacco at the same age. Using the median parameter values for Never-Users of Tobacco in Table 1-3, we find:

$$\ln(\lambda_{NT}) = 2.86656 + 0.19256 AGE - 0.00078 AGE^2$$
$$= 2.86748 + 0.19253(46) - 0.00078(46)^2$$
$$= 10.07338.$$

The inverse logarithm is calculated as:

$$\lambda_{NT} = e^{10.07338} = 23703.5475$$

and adjusted for mortality table and estimation adjustments to arrive at:

$$r_{NT}(46) = 0.00237035$$

From the quantities found above for $r_{NT}(46)$ and $r_{CS}(46)$, and supposing that a hypothetical ERR value for MRTP use is $ERR_{MRTP} = 0.11$, we can combine these values to find the mortality risk ($_nq_x$)by:

$$r_{MRTP}(46) = ERR_{MRTP} \times [r_{cs}(46) - r_{NT}(46)] + r_{NT}(46)$$
$$= 0.11 \times [0.00581499 - 0.00237035] + 0.00237035$$
$$= 0.00274926$$

This results in the survival probability for a 46-year-old male who has used MRTP for 26 years as:

$$S_{MRTP}(46) = 1 - 0.00274926 = 0.99725.$$

This is a survival probability for a single year (i.e. at age 46).

To find the survival probability from age a_1 to age a_2 denoted by $S(a_1, a_2)$, we can take the product of the survival probabilities across those years as follows:

Equation A

$$S(a_1, a_2) = \prod_{Age=a_1}^{a_2} [1 - r(Age)].$$

We can extend our example for this 46-year-old never-tobacco user. Suppose that we want to determine this user's five-year survival probability using the technique described above.

We first obtain the risk of mortality (nqx) for each year between ages 46 and 50 as listed below. (For simplicity, we have limited the values to 5 decimal points):

$$r_{NT}(46) = 0.00237$$
$$r_{NT}(47) = 0.00267$$
$$r_{NT}(48) = 0.00301$$
$$r_{NT}(49) = 0.00338$$
$$r_{NT}(50) = 0.00379$$

Using

Equation A and the values above, we can calculate the 5-year survival probability as:

$$S_{NT}(a_1, a_2) = \prod_{Age=a_1}^{a_2} [1 - r_{NT}(Age)]$$

$$= \prod_{Age=46}^{50} [1 - r_{NT}(Age)]$$

$$= [1 - r_{NT}(46)] \times [1 - r_{NT}(47)] \times [1 - r_{NT}(48)] \times [1 - r_{NT}(49)] \times [1 - r_{NT}(50)]$$

$$= [1 - 0.00309] \times [1 - 0.00332] \times [1 - 0.00357] \times [1 - 0.00384] \times [1 - 0.00413]$$

$$= 0.99691 \times 0.99668 \times 0.99643 \times 0.99586 \times 0.99587$$

$$= 0.98215$$

Figure 7.4.2-3 shows examples of survival curves for NT, CS, FCS, MRTP and FMRTP. This example was solved employing a hypothetical $ERR_{MRTP} = 0.11$ and a hypothetical $ERR_{FMRTP} = 0.11$. Notice that the probability of survival is lowest for CS at the higher ages followed by FCS. The probabilities of survival for NT, MRTP, and FMRTP are very similar, which can be explained by the low value of the two ERRs (i.e., 0.11) used in this example.

Relative risk ratios result in an estimate of how many more times one activity is risky over another activity and can be useful measures. In the example above, the relative risk of mortality due to smoking for a 46-year-old male who has smoked 26 years to the risk of a Never-User of Tobacco is:

$$RR_{CS}(age) = \frac{r_{CS}(46)}{r_{NT}(46)} = \frac{0.00275}{0.00237} = 1.15985.$$

This can be interpreted to mean that a 46-year-old male who has smoked for 26 years has a 1.16 times greater risk of mortality by age 47 years than a 46-year-old male Never-User of Tobacco.

Figure 7.4.2-3:   **Example Survival Curves**
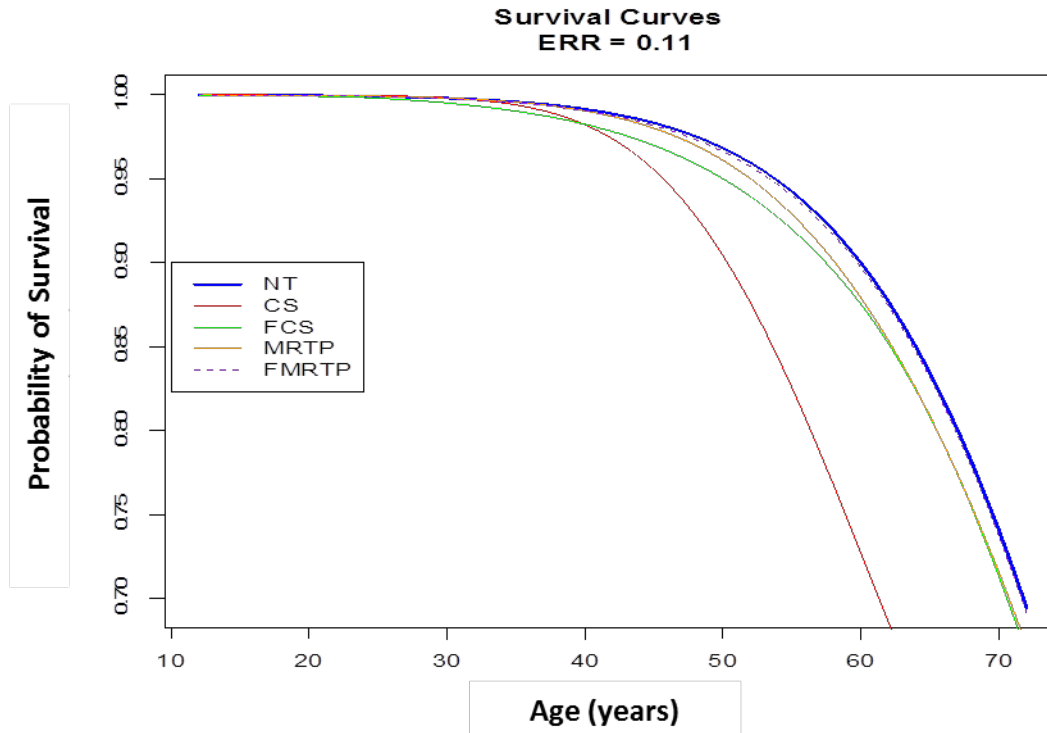
Note: Hypothetical values of $ERR_{MRTP} = 0.11$ and $ERR_{FMRTP} = 0.11$ were used for this example.
CS = current cigarette smoker; ERR = excess relative risk; FCS = former cigarette smoker; FMRTP = Former MRTP
User; MRTP = Current MRTP User; NT = never-user of tobacco.
MRTP intended to reflect transitions to MST at category level.

7.4.2.1.5.   Compartmental Model Overview

This section explains the compartmental model and the Markov chain approach used to transition individuals through the 29 distinct transition states. Numerical examples are provided to help improve understanding of how individuals transition between states.

Compartmental models allow us to develop modeling processes involving defined states. Each state is a category where an individual may reside. At any time, an individual may reside in only one state. A compartmental model attempts to model how individuals transition between states through time. While there are many different types of compartmental models, one common type is the Markov chain (Ross, 2009; Siebert et al., 2012) that uses probabilities to transition individuals from one state to the next. Typically, the probability of transitioning from one compartment or state to another is organized in a transition matrix format, which allows easier calculations since standard matrix operations can be applied.

For example, consider a simple Markov chain consisting of three states: Never-User of Tobacco (NT), Current Cigarette Smoker (CS), and Former Cigarette Smoker (FCS). This is representative of the Base Case illustrated in Figure 7.4.2-1. Consider the following transition matrix for our example:

$$
\begin{array}{c c c c}
 & \text{NT} & \text{CS} & \text{FCS} \\
\text{NT} & 0.9 & 0.1 & 0 \\
\text{CS} & 0 & 0.8 & 0.2 \\
\text{FCS} & 0 & 0.05 & 0.95
\end{array}
$$

Here, the rows correspond to the states from which an individual can transition, and the columns correspond to the states into which an individual can transition. For example, row NT and column NT correspond to the probability of staying in the NT state, which in this example is 0.9. The value at the intersection of the NT row and CS column indicates that the probability of transitioning from NT to CS is 0.1. Similarly, the NT row and FCS column have the probability of 0, which states that an individual cannot transition from NT to FCS. The remainder of the matrix can be interpreted in a similar manner.

To use the Markov matrix to transition the individuals to a new state, we need to define the population and matrices. Let $\mathbf{M}$ be the Markov chain transition matrix and $\mathbf{x}_t$ be the row vector containing the number of individuals in each state at time t. To determine the number of individuals in each state at time $t+1$, we use matrix multiplication:

$$\mathbf{x}_{t+1} = \mathbf{x}_t \mathbf{M}$$

To continue with our example, at time t, suppose that we have a population of 100 NT, 40 CS, and 40 FCS. The matrices would be:

$$\mathbf{x}_t = (100 \quad 40 \quad 40) \text{ and } \mathbf{M} = \begin{pmatrix} 0.9 & 0.1 & 0 \\ 0 & 0.8 & 0.2 \\ 0 & 0.05 & 0.95 \end{pmatrix}.$$

Hence, we can calculate $\mathbf{x}_{t+1}$ as:

$$
\begin{aligned}
\mathbf{x}_{t+1} &= \mathbf{x}_t \mathbf{M} \\
&= (100 \quad 40 \quad 40) \begin{pmatrix} 0.9 & 0.1 & 0 \\ 0 & 0.8 & 0.2 \\ 0 & 0.05 & 0.95 \end{pmatrix} \\
&= (90 \quad 44 \quad 46)
\end{aligned}
$$

This shows that at time $t+1$ there are 90 NT, 44 CS, and 46 FCS. This simple example helps to illustrate what we will do next in a much more complicated setting in the ALCS Cohort Model.

The Markov chains approach we implemented starts with a hypothetical cohort of 1,000,000 subjects of the same sex (male or female), and survival is calculated in 5-year intervals from age 13 years to age 73 years. The membership of each compartment or state was determined. The following states were considered:

- Never-User of Tobacco (NT)

- Current Cigarette Smoker (CS)

- Former Cigarette Smoker (FCS)

- Current MST User (MST)

- Former MST User (FMST)

- Dual User (DU) (Current Cigarette Smoker and Current MST user)

- Former Dual User (FDU) (Both former Cigarette Smoker and former MST User, but currently uses neither product)

To assess these states, we had to consider the paths that a participant (cohort member) could progress along between these states. Figure 7.4.2-4 shows the states, transitions, and transition probabilities for the compartmental model used. Notice that, the pathways that an individual could progress through result in 29 states and 30 transition probabilities. Actually, in the manner the model was employed, there were 30 transition probabilities specified for each age group. This results in a vector of 29 states and a 29×29 transition matrix, which is too large to be displayed here. Instead, we will use Figure 7.4.2-4 to visually depict the matrix and its probabilities. For a detailed explanation, see Figure 7.4.2-4 for probabilities associated with initiating MRTP from smoking and Table 7.4.2-5 for probabilities associated with initiating MRTP directly from Never-Tobacco Use. The ALCS Cohort Model uses 30 transition probabilities, which we believe represent the most plausible pathways given that these transitions occur every 5 years. We describe the general framework that can be applied to a potential MRTP; however, for the purposes of this application we refer to transitions related to MST, at the category level, that were derived from the CCI Study to represent a future state where the proposed modified risk claim is authorized by FDA..

Figure 7.4.2-4: **Compartmental Model with States, Transitions, and Transition Probabilities**
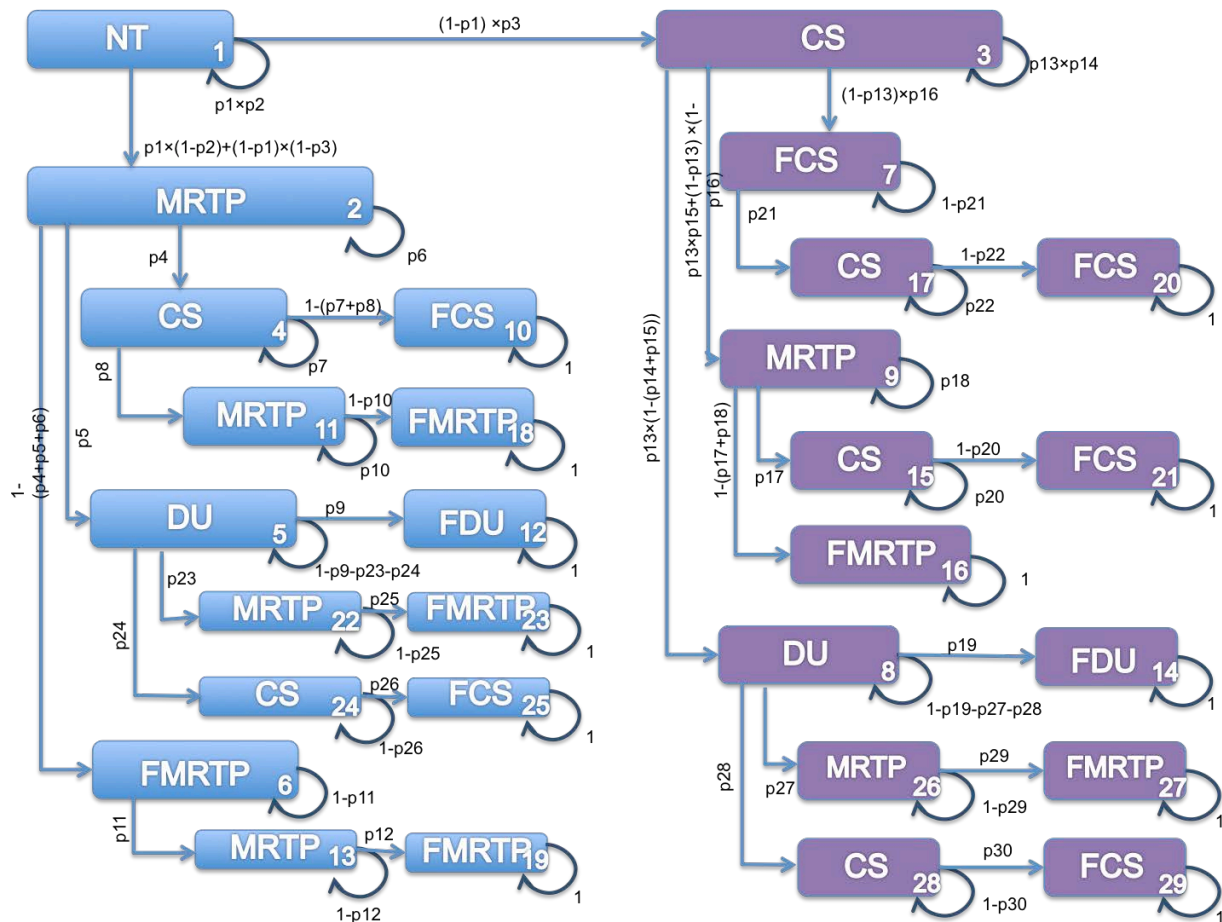
Note: The numbers in the right bottom of each box represents the corresponding State number (e.g., State 1 is an NT state, while State 17 is a CS state).
CS = current cigarette smoker; DU = dual user; FCS = former cigarette smoker; FDU = former dual user; FMRTP = former modified risk tobacco product user; MRTP = current modified risk tobacco product user; NT = never-user of tobacco.
The figure reflects a general framework for a MRTP that is applied to MST at the category level.

Table 7.4.2-4: Explanation of Model Transition Probabilities Associated with Initiating MRTP from Smoking

Population Transitions		Related to
P1	NT	The probability of cigarette initiation defined as (1-P1)
P13	NT→Smoking	The probability of cigarette cessation defined as (1-P13).
P14	NT→Smoking	The probability of switching to dual use among people who initiate smoking from never-tobacco use.
P15	NT→Smoking	The probability of switching to MRTP among people who initiate

	Population Transitions	Related to
		smoking from never-tobacco use.
P16	NT→Smoking	The probability of switching to MRTP instead of quitting smoking.
P17	NT→Smoking→MRTP	The probability of switching to smoking among people who initiate smoking from never-tobacco use and then switch from smoking to MRTP.
P18	NT→Smoking→MRTP	The probability of quitting MRTP among people who initiate smoking from never-tobacco use and then switch from smoking to MRTP.
P19	NT→Smoking→Dual Use	The probability of quitting dual use among people who initiate smoking from never-tobacco use and then switch from smoking to dual use.
P20	NT→Smoking→MRTP→Smoking	The probability of quitting smoking among people who initiate smoking from never-tobacco use and then switch from smoking to MRTP and then back to smoking.
P21	NT→Smoking→Quit	The probability of reinitiating smoking among people who initiate smoking from never-tobacco use and then quit.
P22	NT→Smoking→Quit→ Smoking	The probability of quitting smoking among people who initiate smoking from never-tobacco use, then quit, and then resume smoking.
P27	NT→Smoking→Dual Use	The probability of switching to MRTP among people who initiate smoking from never-tobacco use and then switch from smoking to dual use.
P28	NT→Smoking→Dual Use	The probability of switching to smoking among people who initiate smoking from never-tobacco use and then switch from smoking to dual use.
P29	NT→Smoking→Dual Use →MRTP	The probability of quitting MRTP among people who initiate smoking from never-tobacco use, then switch from smoking to dual use, and then to MRTP.
P30	NT→Smoking→ Dual Use→Smoking	The probability of quitting smoking among people who initiate smoking from never-tobacco use, then switch from smoking to dual use, and then to smoking.

MRTP = modified risk tobacco product; NT = never-user of tobacco.
This table includes a general framework for a MRTP that is applied to MST at the category level.

Table 7.4.2-5: Explanation of Model Transition Probabilities Associated with Initiating MRTP from Never-Tobacco Users

	Population Transitions	Related to
P2	NT	The probability of initiating MRTP defined as (1-P2).
P3	NT	The probability of initiating MRTP instead of initiating smoking defined as (1-P3).

	Population Transitions	Related to
P4	NT→MRTP	The probability of switching to smoking among people who initiate MRTP from never-tobacco use.
P5	NT→MRTP	The probability of switching to dual use among people who initiate MRTP from never-tobacco use (Gateway Effect).
P6	NT→MRTP	The probability of quitting MRTP among people who initiate MRTP from never-tobacco use.
P7	NT→MRTP→Smoking	The probability of quitting smoking among people who initiate MRTP from never-tobacco use and then switch from MRTP to smoking.
P8	NT→MRTP→Smoking	The probability of switching to MRTP among people who initiate MRTP from never-tobacco use and then switch from MRTP to smoking (Gateway Effect).
P9	NT→MRTP→Dual Use	The probability of quitting dual use among people who initiate MRTP from never-tobacco use and then switch from MRTP to dual use.
P10	NT→MRTP→Smoking→MRTP	The probability of quitting MRTP among people who initiate MRTP from never-tobacco use and then switch from MRTP to smoking and then to MRTP again.
P11	NT→MRTP→Quit	The probability of re-initiating MRTP among people who initiate MRTP from never-tobacco use and quit.
P12	NT→MRTP→Quit→ MRTP	The probability of quitting MRTP among people who initiate MRTP from never-tobacco use and then quit and then start MRTP again.
P23	NT→MRTP→Dual Use	The probability of switching to MRTP among people who initiate MRTP from never-tobacco use and then switch from MRTP to dual use.
P24	NT→MRTP→Dual Use	The probability of switching to smoking among people who initiate MRTP from never-tobacco use and then switch from MRTP to dual use.
P25	NT→MRTP→Dual Use→MRTP	The probability of quitting MRTP among people who initiate MRTP from never-tobacco use and then switch from MRTP to dual use and then to MRTP again.
P26	NT→MRTP→Dual Use →Smoking	The probability of quitting smoking among people who initiate MRTP from never-tobacco use and then switch from MRTP to dual use and then to smoking.

MRTP = modified risk tobacco product; NT = never-user of tobacco.
This table includes a general framework for a MRTP that is applied to MST at the category level.

Note that in Table 7.4.2-5, there are no specific probabilities for each of the pathways. For example, the transitions associated with NT are:

- NT to NT has probability $p1 \times p2$.
- NT to CS has probability $(1 - p1) \times p3$.
- NT to MRTP has probability $p1 \times (1 - p2) + (1 - p2) \times (1 - p3)$.

Here $p1$, $p2$, and $p3$ are not specified, since the Markov transition matrix may use different transition probabilities at each time point (the sum of these three transition probabilities above

is equal to one at each time point). The other transition probabilities can be listed in a similar manner. Hence, we will have a transition matrix for each age interval. For notation, we will refer to $\mathbf{M}_t$ as the transition matrix for transitioning from age a_t to age a_{t+5}.

When performing the risk analysis, if the Base Case involves only cigarettes (shown in Figure 7.4.2-1), an individual in the NT state can only transition out of this state to the CS state. Furthermore, there can be no transitions to any MRTP states or DU states. Table 7.4.2-6 and Table 7.4.2-9 provide the probabilities used to create the transition probabilities for the male and female Base Cases, respectively. Note that many of the transition probabilities are zero, reflecting the fact that an MRTP does not exist in this type of a Base Case.

Also, notice in Table 7.4.2-6 and Table 7.4.2-9 that p1 and p13 change as the age groups progress. These values impact initiation and cessation rates, which change as the cohort ages. In this model, $(1 - p1)$ and $(1 - p13)$ represent the age-specific cigarette initiation and cessation rates, respectively. Since this Base Case validation scenario represents a single-product environment (i.e., cigarettes are the only tobacco product on the market), transition probabilities p2 and p3 are both set to a value of one, reflecting that there can be no transitions to the MRTP states, since no MRTP exists.

To introduce uncertainty in transition probabilities associated with initiation rates, p1 is drawn from a truncated normal distribution, with the mean parameter being the value of point value of p_1 from Table 7.4.2-6 and Table 7.4.2-9 and a standard deviation of 0.02. The distribution is truncated at a value of one, to ensure that $p1 < 1$. Uncertainty for the p13 parameter is also introduced in a similar manner.

Table 7.4.2-6: Transition Probabilities for Male Base Case with One Product Only

Age (y)	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
13-17	0.77	1	1	0	0	0	0	0	0	0	0	0	0.975	1	0
18-22	0.88	1	1	0	0	0	0	0	0	0	0	0	0.955	1	0
23-27	0.92	1	1	0	0	0	0	0	0	0	0	0	0.955	1	0
28-32	1	1	1	0	0	0	0	0	0	0	0	0	0.95	1	0
33-37	1	1	1	0	0	0	0	0	0	0	0	0	0.945	1	0
38-42	1	1	1	0	0	0	0	0	0	0	0	0	0.945	1	0
43-47	1	1	1	0	0	0	0	0	0	0	0	0	0.945	1	0
48-52	1	1	1	0	0	0	0	0	0	0	0	0	0.925	1	0
53-57	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
58-62	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
63-67	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
68-72	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
Age (y)	**p16**	**p17**	**p18**	**p19**	**p20**	**p21**	**p22**	**p23**	**p24**	**p25**	**p26**	**p27**	**p28**	**p29**	**p30**
13-17	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Age (y)	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
18-22	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23-27	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28-32	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
33-37	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38-42	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43-47	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48-52	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53-57	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58-62	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63-67	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68-72	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

7.4.2.1.6. Construction of a Life Table by Combining the Models

This section discusses how the compartmental model and the mortality models can be combined to transition individuals through the states and how the Bayesian approach is used to propagate uncertainty associated with the mortality models.

By combining the data set, the mortality models, and the compartmental model, we construct a life table. Connecting the data set and the mortality model has already been discussed in Section 7.4.2.1.3 and Section 7.4.2.1.4. Incorporating the mortality models with the compartmental model is discussed in this section.

At each time step, we use both the mortality and compartmental models. The mortality model determines how many members of the cohort have survived at each time step. Once that has been determined, the cohort must be assigned to its next state by passing it through the compartmental model.

For simplicity, consider the model that does not incorporate parameter uncertainty associated with the mortality parameters β_k or ERRs (i.e., all the aforementioned parameters will be held constant). For notation, let $\mathbf{M}_t$ be the transition matrix for transitioning from age a_t to age a_{t+1} and $\mathbf{S}_t$ be the diagonal survival matrix of the probability of surviving from age a_t to age a_{t+1}. Note that $\mathbf{S}_t$ incorporates the states that an individual can be in and any ERRs needed to calculate the individual's survival probabilities. Both $\mathbf{M}_t$ and $\mathbf{S}_t$ can be combined to calculate the life table, which is the number of survivors in each state, $\mathbf{x}_t$, at time t using:

$$\mathbf{x}_{t+1} = \mathbf{x}_t \mathbf{S}_t \mathbf{M}_t.$$

This is calculated across each age group to form a life table for each state. To create the life table LT_t for the cohort, one simply sums $\mathbf{x}_t$ at each time by:

$$LT_t = \mathbf{x}_t \mathbf{1},$$

where $\mathbf{1}$ is a 29×1 vector of ones.

To incorporate parameter uncertainty, we use the m samples from the posterior distribution to create m samples from the posterior predictive distribution:

$$p(\mathbf{S}_t|D) = \int L(\mathbf{S}_t|\beta, D)p(\beta|D)d\beta.$$

The mth sample of $\mathbf{S}_t$, denoted $\mathbf{S}_t^{(m)}$, forms a distribution of the survival probabilities, and these can then be used to create m samples of $\mathbf{x}_t$, denoted $\mathbf{x}_t^{(m)}$ by:

$$\mathbf{x}_{t+1}^{(m)} = \mathbf{x}_t^{(m)}\mathbf{S}_t^{(m)}\mathbf{M}_t.$$

This can then be used to create m samples of LT_t, denoted $LT_t^{(m)}$. These m samples of $LT_t^{(m)}$ form a posterior predictive distribution for the life table and incorporate the parameter uncertainties in the model. Furthermore, inferences such as posterior intervals on the life table can also be created.

To calculate $\mathbf{S}_t^{(m)}$, we must first select the state and age group that we are interested in estimating. Using the state AGE, YSM, and $YQSM$ as necessary, we can calculate for the mth sample from the posterior distribution of β_j, denoted by $\beta_j^{(m)}$, and the corresponding $\lambda_{new}^{(m)}$ is calculated using the appropriate model and coefficient. The mth sample of the risk $r_{new}^{(m)} \sim Poisson\left(e^{\lambda_{new}^{(m)}}\right)$ is drawn and adjusted to reflect the correct training population. Then, the corresponding state $ERR^{(m)}$ is drawn from the appropriate distribution and applied to the risks. The risks are calculated on a 1-year time scale in contrast to the age groups that are calculated on a 5-year time scale. To convert to a 5-year time scale,

Equation **A** is used to compute $S_t^{(m)}$ for each state. These survival probabilities are then combined into a diagonal matrix to form $\mathbf{S}_t^{(m)}$. This is done for all 10,000 posterior samples of β_j, resulting in 10,000 survival probability matrices for each age group.

Note that the compartmental model does not record the age at which an individual who is in a former smoking category actually stopped smoking. The mortality model requires *YQSM* as an input for all individuals who are former cigarette smokers, which cannot be obtained from the compartmental model. We assign the value zero for *YQSM* for individuals whose ages are less than 28 years. For individuals aged 28 years and older, *YQSM* is assigned the difference between the individual's current age and 28 years. This value was chosen using a least squares algorithm to minimize the squared error loss in the predictions from the model to the male U.S. life table from National Vital Statistics Report, Arias (2010). The benchmark of 28 years used in the surrogate value of *YQSM* was chosen by varying the value to find the value that resulted in the best fit to the U.S. male life table.

The use of ERRs and calculated relative risk can be very useful for accurately determining the mortality rates for states that have a complex pathway to their end-of-study state. For example, a participant who initiates cigarette smoking between the ages of 18 and 22 years and remains a smoker for his or her entire life has a simple pathway, namely from State 1 (NT) to State 3 (CS) (Figure 7.4.2-4). In this simple pathway, there is an explicit model to estimate the participant's risk (r), namely $r_{CS}(AGE)$. In contrast, a participant whose end-of-study state is State 27 has a complex pathway, namely State 1 (NT) to State 3 (CS) to State 8 (DU) to State 26 (MRTP) to State 27 (FMRTP). Using ERRs, one can attempt to accumulate the risks associated with spending time in each state. Table 7.4.2-7 lists the formulae used to define the risk for each state. In the absence of availability of perfect information on mortality rates under each of these use scenarios, this approach attempts to assign a representative approximation to the accumulated risk involved.

Table 7.4.2-7: States with Associated Risk Formulae

State (s)	Risk Formula
1	$r_{NT}(age)$
2, 11, 13	$r_{MRTP}(age) = r_{NT}(age) \times [ERR_{MRTP} \times RR_{CS}(age) + (1 - ERR_{MRTP})]$
3, 15, 17, 24, 28	$r_{CS}(age)$
4, 22	$r_{MRTP,CS}(age) = r_{NT}(age) \times RR_{CS}(age) \times RR_{MRTP}(age)$
5, 8	$r_{DU}(age) = r_{CS}(age) \times [ERR_{DU} \times r_{NT}(age) + (1 - ERR_{DU})]$
6, 18	$r_{FMRTP}(age) = r_{NT}(age) \times [ERR_{FMRTP} \times RR_{CSFS}(age) + (1 - ERR_{FMRTP})]$
7, 20, 21, 23, 29	$r_{FS}(age)$
9, 26	$r_{CS.MRTP}(age) = r_{NT}(age) \times RR_{cs}(age) \times \left(ERR_{MRTP} \times RR_{CS}(age) + (1 - ERR_{MRTP})\right)$ $\times \left(((1 - ERR_{MRTP}) * RR_{FS}(age)) + ERR_{MRTP}\right)$
10, 25	$r_{CS,MRTP,FMRTP}(age) = r_{NT}(age) \times RR_{FS}(age) \times RR_{mrtp}(age) \times (((1 - ERR_{MRTP}) \times$

State (s)	Risk Formula
	$\left(RR_{FS}(age) \right) + ERR_{MRTP} \big)$
12, 14	$r_{FDU}(age) = ERR_{FDU} \times r_{CS}(age) \times RR_{FS}(age) + (1 - ERR_{FDU}) \times r_{FS}(age)$
16, 19, 27	$r_{CS,MRTP,FMRTP}(age) = r_{NT}(age) \times RR_{CS}(age) \times RR_{FRMRTP}(age) \times \big((1 - ERR_{MRTP}) \times RR_{FS}(age) + ERR_{MRTP} \big)$

Note: $RR_{CS}(age) = \frac{r_{CS}(age)}{r_{NS}(age)}$, $RR_{FMRTP}(age) = ERR_{FMRTP} \times RR_{FS}(age) + (1 - ERR_{FMRTP})$, and $RR_{FS}(age) = \frac{r_{FS}(age)}{r_{CS}(age)}$.

CS = current cigarette smoker; FCS = former cigarette smoker; DU = dual user; ERR excess relative risk; FDU = former dual user; FMRTP = Former Modified Tobacco Product User; FS = former cigarette smoker (risk only); MRTP = Current Modified Risk Tobacco Product User; NT = never-user of tobacco; RR = relative risk. MRTP references intended to reflect MST at the category level.

7.4.2.1.6.1. Demographic Variables

In this section, we present a summary of the demographic variables and measurements used to assess the differences between the Base Case and the Modified Case. The two output variables we present are from demographic life tables:

- l_x: notation for the number of males who survive to age x.
  - BCl_x: The number of "Base Case" males who survive to age x from the original cohort of 1,000,000.
  - MCl_x: The number of "Modified Case" males who survive to age x from the original cohort of 1,000,000.
- T_x: notation for the total number of expected years remaining by males who survive to age x.
  - BCT_x: The total number of "Base Case" expected years of life remaining by males who survive to age x from the original cohort of 1,000,000.
  - MCT_x: The total number of "Modified Case" expected years of life remaining by males who survive to age x from the original cohort of 1,000,000.

The key measures taken from the preceding variables are the differences between:

- the number of Base Case survivors (BCl_x) and the number of Modified Case survivors (MCl_x); and
- the Base Case cumulative number of expected years remaining (BCT_x) and the Modified Case cumulative number of expected years remaining (MCT_x).

7.4.2.1.6.2. Demographic Model

In the demographic model, we apply the functions of a life table, specifically an abridged life table (this is a life table with age groups, rather than single years of age) (Kinter, 2004; Yusuf, Martins, & Swanson, 2014). The major function in any life table is $_nq_x$, which is defined as the

probability of dying between age x and $x + n$. Given a set of $_nq_x$ values and starting with 1,000,000 males followed from age 13 years in our hypothetical population, both the number of deaths ($_nd_x$) between age x and $x + n$ and the number of survivors (l_x) at each age group are estimated, where the age groups are 13-17, 18-22,…, 68-72 years. For this purpose, the following equations are used:

Equation B

$$_nd_x = {}_nq_x \cdot l_x$$

Equation C

$$l_{x+n} = l_x - d_x$$

Note that the terminal cohort age is 73 years in our ALCS Cohort Model. This is not like most abridged population life tables, which have open (e.g., 73+ years), rather than closed, terminal age groups.

With $_nq_x,$ $_nd_x$, and l_x estimated for the Base Case and the Modified Case, we can calculate the remainder of the life table to estimate the total expected years remaining (T_x) by the male cohort from the radix (1,000,000) through any age group to the model terminal age of 73 years.

T_x is estimated in two steps. We first estimate the number of person–years lived in each age group (also known as an age interval). Next, we sum these numbers, starting with the oldest age group and working backward through the successively younger age groups.

There are two parts to the first step. In the first part, we estimate the number of person–years lived within a given age interval from x to $x + n$, $_nL_x$, by using the number of survivors at age x, l_x, and the number of survivors to age $x + n$,l_{x+n}, as follows. Let l_x be the number of survivors reaching age x. Of these, $_nd_x$ will die before reaching age x + n, as determined by $_nq_x$. If a single person survives over the period from age x to age $x + n$, then he or she has lived n years (the width of a given age group). This implies that we can multiply l_{x+n} (the number of survivors from age x to age $x + n$) by the width of the age interval (n) to obtain the number of person years these "survivors" lived in the interval.

In the second part of Step 1, we deal with those who did not survive from age x to age x + n. If we assume that the deaths that occur within the interval are uniformly distributed, it is the same as assuming each decedent lived $n/2$ years. Thus, by dividing the total number of deaths in the interval by two ($_nd_x/2$) and multiplying this product by the width of the age interval (n), we have an estimate of the years lived in the interval by the decedents.

Putting these two parts together, we can obtain the total years lived in an interval both by those who survive to the next interval and those who do not:

Equation D

$$_nL_x = n\left(l_{x+n} + {}_nd_x/2\right)$$

As a heuristic device, Equation D is useful, but it usually does not lead to realistic estimates of $_nL_x$ for most populations. There are other, more complex, methods that can be used to estimate life table functions that lead to more realistic estimates of $_nL_x$, in that they better approximate mortality by age (Kinter, 2004; Yusuf et al., 2014). In the case of the MRTP, we used one of these methods, namely one introduced by Ferangy (1971) to generate $_nL_x$.

As with all methods used in life table construction, the key component of the Ferangy method is how it calculates q_x, which is $q_x = 1 - e^{(-n^* {_n}m_x)}$, where n is the width of the age interval and $_nm_x$ is the death rate for the population aged x to $x + n$ (Yusuf et al., 2014). The other key component of the Ferangy method relevant here is calculating $_nL_x$, where $_nd_x = l_x *{_n}q_x$ and $_nm_x$ is the corresponding age-specific death rate found in the population from which the life table was constructed.

Because the input data we have includes l_x for the Base Case and the Modified Case, we calculate q_x directly from l_x values: $_nq_x = (l_x - l_{x+n})/l_x$, which is equivalent to $_nq_x = {_n}d_x/l_x$. What we needed is to implement the Ferangy method for estimating $_nL_x$ was $_nm_x$, which we calculated from $_nq_x$ by solving Ferangy's equation ($_nq_x = 1 - e^{(-n^* {_n}m_x)}$) for $_nm_x$. This reduces to $_nm_x = (\ln(1 - {_n}q_x))/-n$. As an example, let $_5q_5 = 0.00055$, which in solving for $_nm_x$ reduces to $_nm_x = 0.00011 = (\ln(1 - 0.00055))/-5$.

Once we have $_nL_x$ values estimated, we can proceed with the second step needed to estimate T_x, which is to sum the values of $_nL_x$, starting with the oldest age group and working backward through the successively younger age groups. Recall that our oldest age group starts at age 73 years. For this group, the total expected years lived (T_{73}) and the number of years lived in the interval ($_5L_{73}$) are one and the same. To obtain total expected years lived for those in the preceding age group of 68-72 years, we sum T_{73} and $_5L_{68}$. In general, $T_x = {_n}L_x + T_{x+n}$.

7.4.2.1.7. Model Validation: Comparison of Base Case Model Outputs to Values Estimated from U.S. Life Tables

This section discusses validation of the ALCS Cohort Model. The goal of the validation process is to compare outcomes from the model with the number of survivors estimated using mortality data reported in U.S. Life Tables by the Centers for Disease Control and Prevention (CDC) (Arias, 2010). We performed model validations for both the male and female cohorts. In addition, as discussed in Section 7.4.2.1.2, depending on the use case, the ALCS Cohort Model can employ two different Base Cases, as shown in Figure 7.4.2-1 and Figure 7.4.2-2. For validation purposes, we present below results from both Base Cases:

1. *One-product Base Case environment*: This Base Case is illustrated in Figure 7.4.2-1 and assumes that cigarettes are the only tobacco product present in the Base Case scenario.

2. *Two-product Base Case environment*: This Base Case is illustrated in Figure 7.4.2-2 and assumes that both cigarettes and MST already coexist in the Base Case. In this framework, these two products also coexist in the Modified Case scenario, but reflect MST upon authorization of the proposed claim.

7.4.2.1.7.1. One-Product Base Case Environment

The one-product Base Case model is validated for both the U.S. male and female populations. In a one-product environment (Figure 7.4.2-1), we assume the Base Case scenario is a world of never-tobacco users, current cigarette smokers, and former smokers.

To validate the model, we compared the model predictions against the number of survivors estimated using mortality data reported in the 2006 U.S. life table by CDC in the National Vital Statistics Reports (Arias, 2010; Pierce, 1989). Initiation and cessation rates in Table 7.4.2-6 reflect those in 1980 (Messer et al., 2007; Pierce, 1989). To validate the performance of the model for the U.S. male population, we used a hypothetical cohort population of 1,000,000 males and transitioned them through various states starting at age 13 years, using the method detailed in previous sections. For this male, one-product Base Case scenario, we employed the transition probabilities listed in Table 7.4.2-6 and mortality data for the male population in Appendix 7.4.2-1; Table 7. We obtained 10,000 samples from the posterior predictive distribution of LT_t and, using these samples, calculated the mean and standard deviations and the percent difference between the predicted mean and the reported mean for each age group. Table 7.4.2-8 shows the results of this validation. Notice that when the outcomes of the model are compared with the number of survivors estimated using mortality data reported in the 2006 U.S. life table by CDC, the percent difference between the predicted mean and the reported mean is quite low for all age groups, with the largest percent difference of 3.29 percent, at the 48- to 53-year age group. As the cohort progresses through time, the initial percent differences are small. They gradually increase, peaking at age 48 to 53 years, and then start to decline.

To assess the performance of the model for the U.S. female population, a similar analysis was conducted. For this analysis, we used mortality data for the female population in Appendix 7.4.2-1; Table 6 in conjunction with the transition probabilities found in Table 7.4.2-9. The results from the model are presented in Table 7.4.2-10, which gives the mean and difference between the predicted mean and the reported mean for each age group. From these results, we can see that the model performs well, with the highest percent difference of 2.26 percent at age group 53 to 58 years. On average, the overall model trends in the percent differences are similar for the male and female cohorts.

Table 7.4.2-8: Model Validation Results for Males Based on the 2006 U.S. Life Table Report in a One-Product Base Case Scenario Using Transition Probabilities

Age	Estimation from U.S. Life Table 2006[1]	Model Results	%Difference[2]
18	997,059	999,885	0.28%
23	990,519	999,660	0.92%
28	983,192	999,112	1.62%
33	976,111	997,675	2.21%
38	967,974	994,105	2.70%

Age	Estimation from U.S. Life Table 2006[1]	Model Results	%Difference[2]
43	956,428	986,038	3.10%
48	938,961	969,854	3.29%
53	912,829	941,402	3.13%
58	876,559	897,892	2.43%
63	826,599	838,342	1.42%
68	757,310	761,661	0.57%
73	663,656	666,471	0.42%

Source: Appendix 7.4.2-1; Table 8

[1] The method used for estimating the number of survivors from the 2006 U.S. Life Table data (Arias E. United States Life Tables, 2006. National Vital Statistics Reports; Vol.58 No. 21. Hyattsville, MD: National Center for Health Statistics. 2010).

[2] % Difference is calculated as $100 \times [$(predicted mean - reported mean) / reported mean].

Note: In the model, survival of an initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.

Table 7.4.2-9: Transition Probabilities for Female Base Case with One Product Only

Age (y)	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
13-17	0.78	1	1	0	0	0	0	0	0	0	0	0	0.975	1	0
18-22	0.9	1	1	0	0	0	0	0	0	0	0	0	0.955	1	0
23-27	0.95	1	1	0	0	0	0	0	0	0	0	0	0.955	1	0
28-32	0.99	1	1	0	0	0	0	0	0	0	0	0	0.955	1	0
33-37	1	1	1	0	0	0	0	0	0	0	0	0	0.95	1	0
38-42	1	1	1	0	0	0	0	0	0	0	0	0	0.945	1	0
43-47	1	1	1	0	0	0	0	0	0	0	0	0	0.945	1	0
48-52	1	1	1	0	0	0	0	0	0	0	0	0	0.925	1	0
53-57	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
58-62	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
63-67	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
68-72	1	1	1	0	0	0	0	0	0	0	0	0	0.915	1	0
Age (y)	p16	p17	p18	p19	p20	p21	p22	p23	p24	p25	p26	p27	p28	p29	p30
13-17	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18-22	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23-27	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
28-32	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Age (y)	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
33-37	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
38-42	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
43-47	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
48-52	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
53-57	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
58-62	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
63-67	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
68-72	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Table 7.4.2-10:   Model Validation Results for Females Based on the 2006 U.S. Life Table Report in a One-Product Base Case Scenario Using Transition Probabilities

Age	Estimation from U.S. Life Table 2006[1]	Model Results	% DifferenceTable[2]
18	998,645	999,928	0.13%
23	996,380	999,796	0.34%
28	993,726	999,508	0.58%
33	990,544	998,849	0.84%
38	986,081	997,369	1.14%
43	979,041	994,133	1.54%
48	968,118	987,357	1.99%
53	952,393	973,951	2.26%
58	930,051	949,437	2.08%
63	896,727	908,534	1.32%
68	847,924	847,261	-0.08%
73	777,779	765,493	-1.58%

Source: Appendix 7.4.2-1; Table 8

[1] The method used for estimating the number of survivors from the 2006 U.S. Life Table data (Arias E. United States Life Tables, 2006. National Vital Statistics Reports; Vol.58 No. 21. Hyattsville, MD: National Center for Health Statistics. 2010).

[2] % Difference is calculated as $100 \times$ [(predicted mean - reported mean) / reported mean].

Note: In the model, survival of an initial cohort of 1,000,000 females is followed in 5-year intervals, starting from age 13 years.

7.4.2.1.7.2. Two-Product Base Case Validation

To validate the two-product Base Case model illustrated in Figure 7.4.2-2, we compared the results of the model against the number of survivors estimated using mortality data reported in the 2006 U.S. life table from the National Vital Statistics Report (Arias, 2010). Initiation and cessation rates for the two products (i.e., cigarettes and ST) in Table 7.4.2-11 reflect those in 1980 Messer et al. (2007), Pierce (1989), and Tam et al. (2015). Using the same methods as the ones employed in the one-product environment validation, the mean, standard deviations, and the percent difference between the predicted mean and the reported mean were calculated. Table 7.4.2-12 shows the validation results, which yielded a low percent difference for all age groups. The largest difference (3.24 percent) occurred in the 48- to 53-year age group.

Table 7.4.2-11: Base Case Transition Probabilities for a Two-Product Environment for United States Males

Age (y)	p1	p2	p3	p4	p5	p6	p7	p8	p9	p10	p11	p12	p13	p14	p15
13-17	0.77	0.97	1	0.255	0.143	0.448	0.787	0.008	0.141	0.448	0.05	0.152	0.975	0.956	0.008
18-22	0.88	0.97	1	0.255	0.143	0.448	0.787	0.008	0.141	0.448	0.05	0.152	0.955	0.956	0.008
23-27	0.92	0.9825	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.955	0.954	0.014
28-32	0.99	0.9825	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.95	0.954	0.014
33-37	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.945	0.954	0.014
38-42	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.945	0.954	0.014
43-47	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.945	0.954	0.014
48-52	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.925	0.954	0.014
53-57	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.915	0.954	0.014
58-62	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.915	0.954	0.014
63-67	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.915	0.954	0.014
68-72	1	1	1	0.009	0.025	0.766	0.797	0.014	0.113	0.766	0.05	0.201	0.915	0.954	0.014
Age (y)	p16	p17	p18	p19	p20	p21	p22	p23	p24	p25	p26	p27	p28	p29	p30
13-17	0.787	0.255	0.448	0.141	0.787	0.045	0.787	0.342	0.312	0.152	0.169	0.342	0.312	0.152	0.169
18-22	0.787	0.255	0.448	0.141	0.787	0.045	0.787	0.342	0.312	0.152	0.169	0.342	0.312	0.152	0.169
23-27	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
28-32	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
33-37	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
38-42	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
43-47	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
48-52	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
53-57	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
58-62	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
63-67	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157
68-72	0.797	0.009	0.766	0.113	0.797	0.045	0.797	0.174	0.27	0.201	0.157	0.174	0.27	0.201	0.157

Table 7.4.2-12: Model Validation Results for Males Based on the 2006 U.S. Life Table Report in a Two-Product Base Case Scenario Using Transition Probabilities

Age (y)	Estimation from U.S. Life Table 2006[1]	Model	%Difference[2]
18	997,059	999,885	0.28%
23	990,519	999,659	0.92%
28	983,192	999,112	1.62%
33	976,111	997,654	2.21%
38	967,974	993,989	2.69%
43	956,428	985,739	3.06%
48	938,961	969,342	3.24%
53	912,829	940,850	3.07%
58	876,559	897,629	2.40%
63	826,599	838,642	1.46%
68	757,310	762,409	0.67%
73	663,656	667,201	0.53%

Source: Appendix 7.4.2-1; Table 8

[1] The method used for estimating the number of survivors from the 2006 U.S. Life Table data (Arias E. United States Life Tables, 2006 National Vital Statistics Reports; Vol.58 No.21. Hyattsville, MD: National Center for Health Statistics. 2010). Note: In the model, survival of an initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.

[2] % Difference is calculated as $100 \times$ [(predicted mean - reported mean) / reported mean].

7.4.2.1.8. Model Verification

We verified the model using the following procedures:

- The code was independently checked by three individuals with considerable experience in both statistical methodology and computer programming. The model programmer was not part of this process.

- A flow diagram was created that included logical possible actions in the model when an event occurs, and the model logic was followed for each action by the modeling team.

- At each stage of code development, values generated by the computer code for selected cases were checked against hand calculations performed by the programmer and one qualified individual. Any discrepancies found during this process were resolved.

- Output from the completed model under typical and extreme scenarios was checked against hand calculations, where all stochastic components were held constant at their median value. This process showed that the model was correctly coded.

- Two individuals other than the model developer verified all data sets and transition probabilities for accuracy. All input values were derived from and supported by quantities found in relevant peer-reviewed literature.

- The model output was closely examined for reasonableness under a variety of scenarios constructed by varying input parameters.

- Comments were incorporated to make the computer code as self-documenting as possible, using a precise definition of every variable and documenting a general description of the purpose of each major section of code. The code, with the self-documentation is found in Appendix 7.4.2-2.

7.4.2.1.9. Sensitivity Analysis

This section explores the sensitivity of the model to changes in parameters and illustrates how an output map can be created by simultaneously varying more than one input within the model.

7.4.2.1.9.1. Varying Key Input Parameters

Understanding how multiple input values influence the result is important for understanding the sensitivity of the ALCS Cohort Model. Section 7.4.2.2.7 discusses results from the sensitivity analysis. In this section, we present examples of model sensitivity to various input parameters.

Sensitivity Analysis Example 1: Varying Mortality Adjustment Ratios – Section 7.4.2.1.3 describes the development of the mortality data sets and the need to adjust the mortality data found in Friedman et al. (1997), which were taken from the KP Medical Care Program Cohort study, to be more representative of mortality for the U.S. population. A sensitivity study was conducted applying the same method to derive the mortality ratios using annual reports from the "Vital Statistics of the United States, Volume II, Mortality" for 1989, 1991, 1995, 1996, and 1998. The mortality models were fit to each of the adjusted data sets, and the Base Case transition probabilities for males (Table 7.4.2-6) were used to obtain the model output for each age group. The model outputs were compared against the number of survivors estimated using mortality data reported in the National Vital Statistics Report (Arias, 2010). Table 7.4.2-13 shows the results of this analysis.

From Table 7.4.2-13, the number of survivors at age 73 years ranges from 662,077 for the 1989 adjustment ratios to 698,342 for the 1998 adjustment ratios. All the values in this age group are within 5 percent of the value of 663,656, estimated using CDC data. This analysis indicates that the adjusted values produced acceptable results and that the adjustment ratios across the 1989-1998 time frame remained fairly consistent and do not affect the inferences made from the model.

Table 7.4.2-13: Sensitivity of Model Outputs for Males Using Adjustment Ratios Derived from Various U.S. Life Table Reports (1989, 1991, 1995, 1996, and 1998) Using Transition Probabilities

Census Report Year		1989	1991	1995	1996	1998
Age (y)		Ratio				
35 to 49		0.989	0.997	1.036	0.950	0.860
50 to 64		2.119	2.061	1.959	1.920	1.800
65 to 74		2.163	2.149	2.037	2.010	1.944
75+		1.340	1.297	1.229	1.210	1.164
Age	Estimation from U.S. Life Table 2006[1]	Model Results				
18	997,059	999,876.9	999,885.1	999,849.6	999,886.6	999,915.4
23	990,519	999,639.4	999,659.6	999,569.9	999,666.1	999,743.7
28	983,192	999,069	999,111.6	998,925	999,134.8	999,313.6
33	976,111	997,583.4	997,675.4	997,314.2	997,754.5	998,157.7
38	967,974	993,901.7	994,105.1	993,476.4	994,348.8	995,223.7
43	956,428	985,603.3	986,038.2	985,118.3	986,703.4	988,469.3
48	938,961	969,000.7	969,853.8	968,844.8	971,430	974,667.4
53	912,829	939,934.5	941,402.2	940,893.5	944,640.7	949,945.5
58	876,559	895,713.7	897,892	898,821.8	903,648.2	911,387.4
63	826,599	835,482.4	838,342	841,729	847,394.3	857,586.2
68	757,310	758,142.3	761,661.3	768,458.8	774,682.9	787,128.4
73	663,656	662,077.6	666,471.3	677,398.7	683,949.9	698,342.9

Source: Source: Appendix 7.4.2-1; Table 8

[1] The method used for estimating the number of survivors from the 2006 U.S. Life Table data (Arias E. United States Life Tables, 2006. National Vital Statistics Reports; Vol.58 No. 21. Hyattsville, MD: National Center for Health Statistics. 2010).

Note: In the model, survival of an initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.

Sensitivity analysis example 2: Varying ERRs - Another input parameter that may strongly influence the results is the ERR of the modified risk product (ERR_{MRTP}). In this second example, the sensitivity analysis is used to show how much lower the risk must be to correspond to a positive outcome under the specific modeled scenarios. For this sensitivity analysis, we use the transition probabilities in Table 7.4.2-13 with $ERR_{FMRTP} = 0.04$, $ERR_{DU} = 1$, and $ERR_{FDU} = 1$. The value of ERR_{MRTP} was varied from 0 to 1 in increments of 0.1, and the difference in survival to age 73 years in the Base Case is provided. Figure 7.4.2-5 shows the results of this analysis with the 95 percent credible intervals.

The difference in survival shifts from positive to negative outcome when the $ERR_{MRTP} \approx$ 0.4. These outcomes only applies to this hypothetical scenario with the specified transition probabilities and ERRs, which was created for demonstration purposes only.

Figure 7.4.2-5: **Sensitivity of the Change in Number of Survivors to Age 73 Years to Changes in ERR$_{MRTP}$ with 95% Credible Intervals**
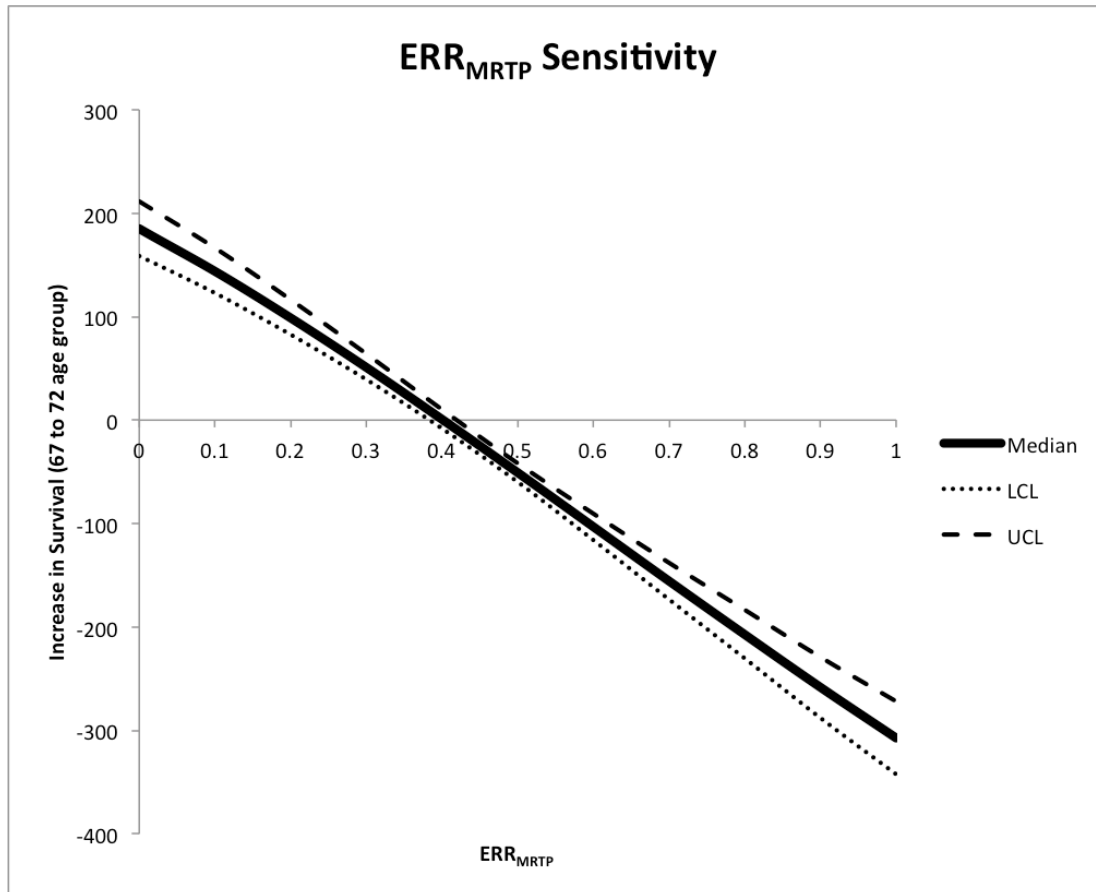
LCL = lower confidence limit; UCL = upper confidence limit; ERR=Excess Relative Risk; MRTP = Current Modified Risk Tobacco Product user.

Similarly, one can study the sensitivity to the specification of ERR_{FMRTP} on the change in the number of survivors to age 73 years. Using the transition probabilities in Table 7.4.2-13 and the Base Case with $ERR_{MRTP} = 0.09$, $ERR_{DU} = 1$, and $ERR_{FDU} = 1$ on a cohort of 1,000,000 males and varying ERR_{FMRTP} from 0 to 1, results in a decrease in survival at age 73 years (Figure 7.4.2-6). From these results, we observe that the rate of change across the values of ERR_{FMRTP} is slow and that this modeling paradigm is not very sensitive to the value of ERR_{FMRTP}.

Figure 7.4.2-6:   Sensitivity of the Change in Number of Survivors to Age 73 Years to Changes in ERR$_{FMRTP}$ with 95% Credible Intervals
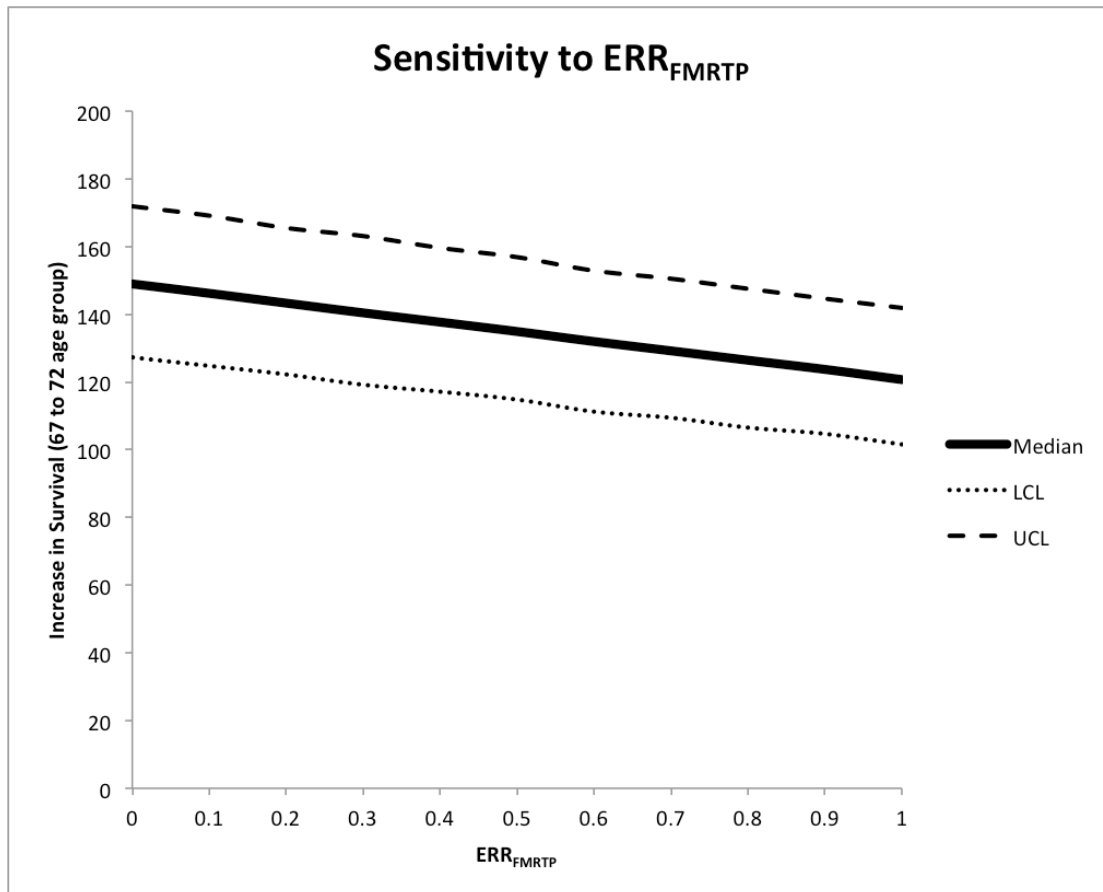
ERR_{FMRTP} = excess relative risk of former modified risk tobacco product user; LCL = lower confidence limit; UCL = upper confidence limit.

The sensitivity of the model to the ERR of dual use of both products, ERR_{DU}, is also of interest. The current specification of $ERR_{DU} = 1$ implies that dual use has the same risk as cigarette smoking. We performed a sensitivity analysis on the specification of ERR_{DU} and the change in number of survivors to age 73 years. Using the transition probabilities in Table 7.4.2-13 and the similar Base Case with $ERR_{MRTP} = 0.09$, $ERR_{FMRTP} = 0.04$, and $ERR_{FDU} = 1$ on a cohort of 1,000,000 males and varying ERR_{DU} from 1 to 10.0, resulted in very little change in the total survival across the values of ERR_{DU}, as shown in Figure 7.4.2-7. The lack of major changes may be due to the fact that not many participants transition into the DU category under the modeled scenario. Hence, in this scenario, the modeling paradigm is not very sensitive to the value of ERR_{DU}. Note that this result does not represent a claim that the value of ERR_{DU} has no effect on the overall survival in general.

Figure 7.4.2-7:   **Sensitivity of the Change in Number of Survivors to Age 73 Years to Changes in ERR$_{DU}$ with 95% Credible Intervals**
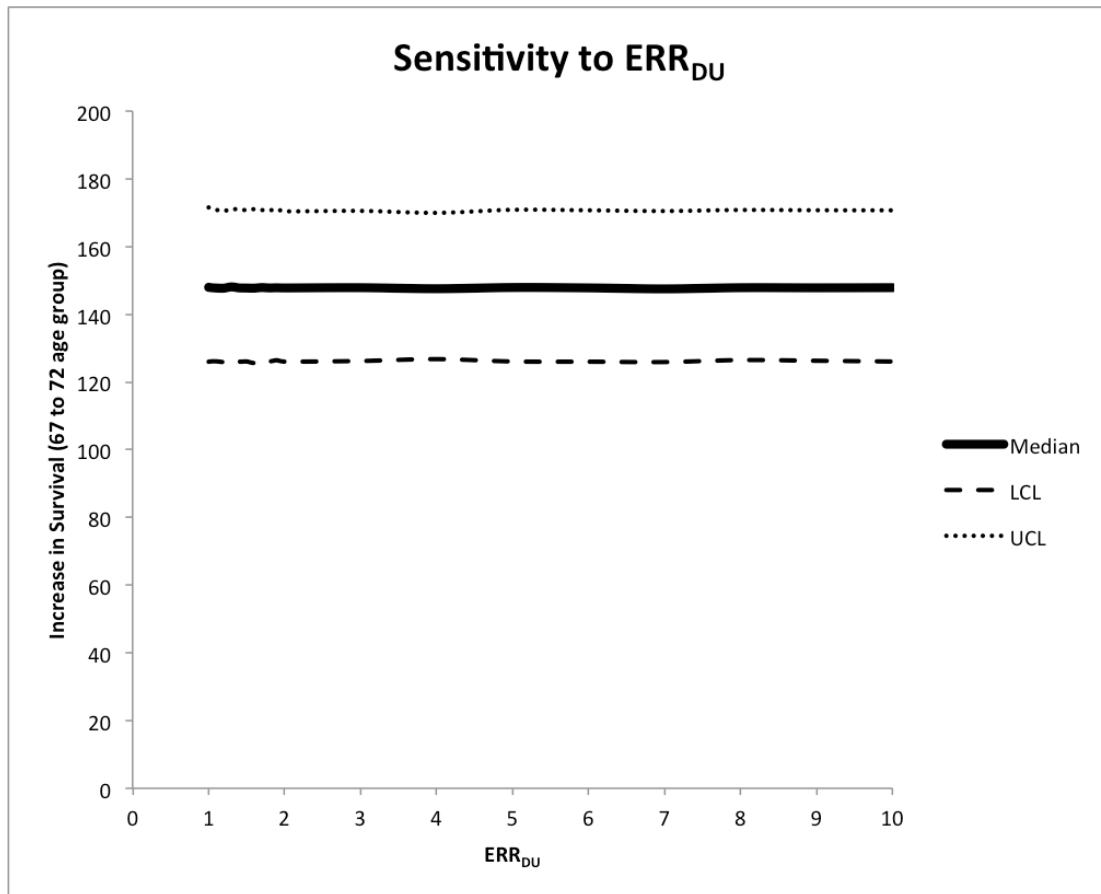
ERR_{DU} = excess relative risk of dual user; LCL = lower confidence limit; UCL = upper confidence limit.

7.4.2.1.9.2. Output Maps

Authorization of the proposed claim may potentially have both positive and negative implications on public health. For example, with the authorization of the proposed claim, a subset of current smokers could stop smoking and switch to the lower risk candidate product. This single change alone should induce a positive benefit to overall public health. However, there may also be some never-tobacco users who adopt the candidate product. This single change alone would induce a negative effect and increase overall risks to public health. In such cases, output maps can provide quantitative insights into how combinations of key input parameters impact cohort longevity, under defined scenarios.

To demonstrate the concept of an output map, let us vary two input parameters simultaneously in the Modified Case scenarios. As shown in Figure 7.4.2-8, we can vary "the proportion of potential smokers, initiating tobacco use with the candidate product, instead of initiating tobacco use through smoking" by 1%, 3%, 5%, 7%, and 10%, and we can vary the ERR of the candidate product using values of 0.02, 0.11, 0.3, 0.5, 0.7, and 0.9.

Figure 7.4.2-8: **Parameters Varied for Generating Example of an Output Map**
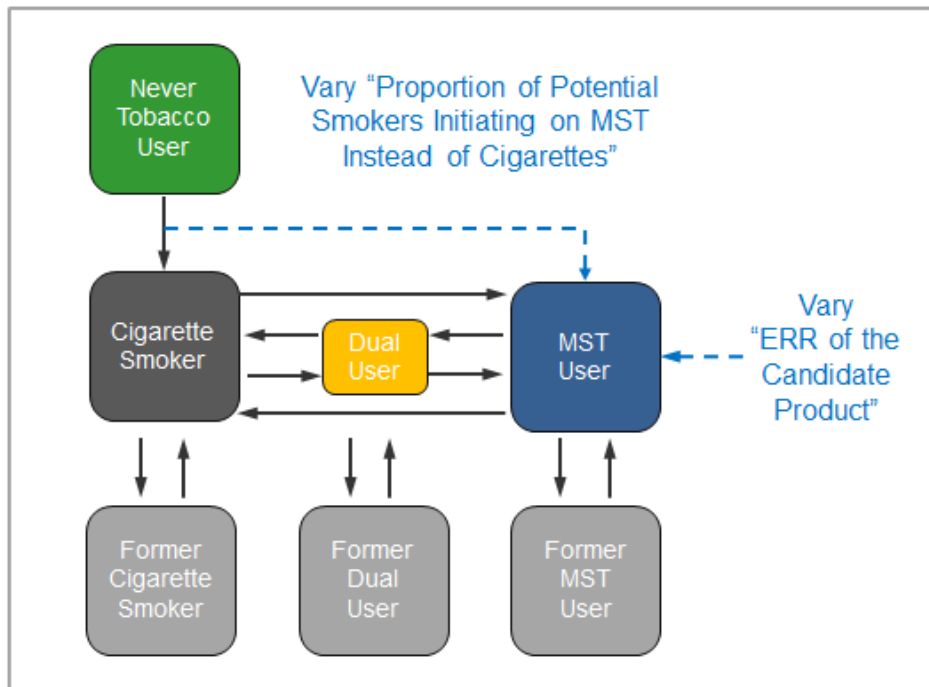
ERR=Excess Relative Risk; MST = Moist Smokeless Tobacco

The resulting output map is shown in Figure 7.4.2-9. The values on the y-axis indicate mean difference in the number of survivors at age 73 years between the Base Case and the different Modified Cases, which were run using the aforementioned values. Such maps are valuable in understanding and demonstrating that a particular benefit state can be attained in multiple different ways. For example, if a candidate product had a ERR of 0.58, we would require 10 percent of potential smokers to initiate tobacco use with the candidate product, instead of initiating tobacco use through smoking, to realize a mean difference of 1,000 survivors. On the other hand, under these defined conditions if the candidate product had a significantly lower ERR of 0.16, we would require only 5 percent of potential smokers to initiate tobacco use with the candidate product, instead of through smoking, to realize a mean difference of 1,000 survivors.

Other such output maps can be created to understand the influence of simultaneously varying multiple key inputs. Note that the output map below is provided as an example and reflects outputs for this example scenario only.

Figure 7.4.2-9:   **Example of Output Map: Change in Survival with Variation of ERR and Tobacco Product Initiation**
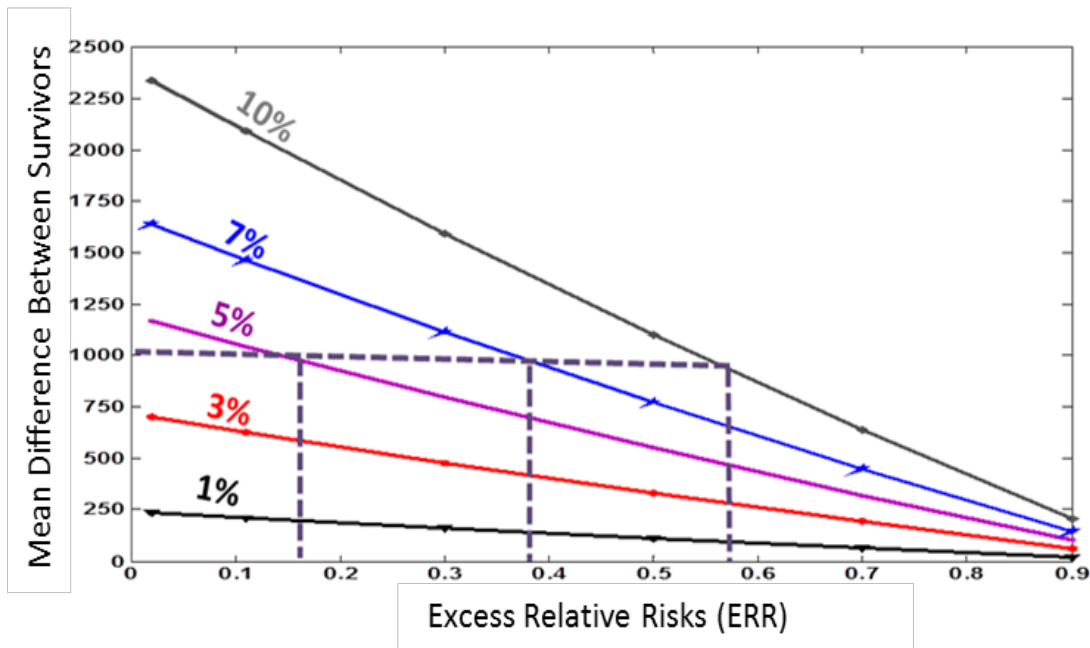
Mean difference between survivors is calculated using the difference in survivors at age 73 years, between the Base Case and Modified Case scenarios. 1%, 3%, 5%, 7%, and 10%: the proportion of potential smokers, initiating tobacco use with the candidate product, instead of initiating tobacco use through smoking.

7.4.2.1.10. Multiple-Cohort–Modeling Approach: Determining Population Estimates

Single-cohort models are designed to follow the survival of a specific homogeneous group over time, using defined transition probabilities and mortality rates. As demonstrated in the examples presented in previous sections, single-cohort models can be useful for understanding the impact of an intervention on a specific health outcome, such as all-cause mortality and for inferring causation. In the case of this MRTPA, the intervention would be authorization of the proposed claim. If the intervention is successful, then the group that received the intervention (Modified Case) will have an improved state (i.e., reduced all-cause mortality) compared with the group that did not receive the intervention (Base Case).

One limitation of the single-cohort approach is that the inferences are tied to the homogeneous cohort group and cannot be directly extended to the general population, which is inherently heterogeneous in nature. For example, if a single-cohort model based on 1,000,000 males is used, one could not simply multiply the result by a factor to scale up the number of participants to the population of interest to make valid inferences about the population. To do so would incorrectly assume that the entire population is homogeneous to that of the 1,000,000 males who were followed since age 13 years and all started as Never-Users of Tobacco, which would not accurately reflect the wide variety of ages and health histories in the population.

One way to extend inferences from a single-cohort approach to a more heterogeneous population is to use a multiple-cohort approach built from a series of individual cohorts that are internally homogeneous but different from each other. This allows for a heterogeneous population to be constructed from numerous homogenous subpopulations. The underlying principle is that a multiple-cohort approach will allow for stronger inferences and provide the ability to extend inferences to the populations of interest. A simple example is considering sex effects. One can construct an individual cohort for each sex, which will allow for the removal of any specific effects due to sex. Age, too, may cause an effect; therefore, cohorts for each age group may be constructed to remove any effects that age may have on the resulting inferences.

When modeling using a multiple-cohort approach, a *time-synced* approach or a *time-staggered* approach may be employed. In the *time-synced* approach, all participants are presented with the intervention at an equivalent time in the study. For example, in a study where a baseline measurement must be established, each participant may be given the intervention at a specific time after joining the study. This ensures the intervention data are synced to a specific time in the study, where the participants are the most homogeneous at their individual intervention times. In the *time-staggered* approach, the intervention is given at the same time to the entire population of interest, regardless of when a participant joined the study – for example, market introduction of the proposed claim. In this case, all cohorts of interest are exposed to the candidate product with the claim at the same point in time, regardless of their homogeneity. The grouping of such multiple cohorts allows for population level inferences for the population of interest.

In this MRTPA, we implement the multiple-cohort approach in the *time-staggered* manner, since marketing of the candidate product with a modified risk claim will occur simultaneously for everyone in the population of interest. Regardless of the homogeneity in age or sex, this is a clear example of a *time-staggered,* multiple-cohort scenario.

Dynamic population models incorporate births, mortality, and net immigration (immigration and emigration), which in a simple difference equation can be written as:

$$N_{t+1} = N_t + \beta_t - M_t + I_t - E_t,$$

where N_t is the total number in the population at a point in time t; β_t is the number of births at that point in time t; M_t is the mortality at that point in time t; I_t is the number of immigrants at that point in time t; and E_t is the number of emigrants at that point in time t.

If an intervention influences everybody in the population, it is important to incorporate all the parameters listed in the equation above for both sexes, to quantitate the overall impact at a population level. Since the individual cohorts are homogenous and are followed for survival, the inability to capture the influence of immigration is a limitation of the multiple-cohort approach. Nevertheless, we neglect the impact of immigration in this instance, because the intervention of interest -- marketing of the candidate product with a modified risk claim -- predominantly affects a select population group: U.S.-born males. This supports our decision to extend the single cohort to this particular population of interest using the multiple-cohort approach.

The justification for our select population group, U.S.-born males, is based on historical data that shows that the candidate product and similar products in this category have very low prevalence among females in the U.S. According to the 2015 National Health Interview Survey (NHIS), females were 3.0% and 7.0% of the everyday and someday smokeless tobacco user population, respectively. The National Survey on Drug Use and Health (NSDUH) 2014 report (Substance Abuse and Mental Health Services Administration, 2014) estimated the trends in smokeless tobacco use from 2002 to 2012. The past-month smokeless tobacco use among persons aged 12 or older ranges from 6.4% for male (0.4% for female) in 2002 to 6.7% for male (0.4% for female) in 2012 with little fluctuation. The overall past month smokeless tobacco use rates were 3.3% in 2002 and 3.5% in 2012. For all categories of comparison, the prevalence of smokeless tobacco use was substantially higher among men. Also according to the Morbidity and Mortality Weekly Report (1993), the Centers for Disease Control and Prevention's (CDC's) 1991 National Health Interview Survey-Health Promotion and Disease Prevention supplement (NHIS-HPDP), an estimated 5.3 million (2.9 percent) U.S. adults were current users of smokeless tobacco, including 4.8 million (5.6 percent) men and 533,000 (0.6 percent) females. These nationally representative sources confirm a trend over time: there is a low prevalence of female smokeless tobacco use when compared to males.

To employ a multiple-cohort modeling approach in the context of this MRTPA, it is imperative that the combination of the single cohorts resembles the population of interest. To achieve this, each age-group cohort must be created at birth and be moved forward through time using the single-cohort model. Once enough single-cohort groups are developed, the combination of these single-cohort groups should resemble the population of interest, provided that mortality and birth rates are adequately specified. Each age group needs specific tobacco initiation and cessation rates and other transition probabilities through time in order to account for variation in these rates at different ages. In addition, a robust mortality model needs to be employed so that each cohort's estimated mortality rates adequately reflect the true mortality rates.

For validating the feasibility of employing this approach, we used the multiple-cohort approach to build a population of U.S.-born males in the year 2015, with ages ranging from 0 to 104 years. We validated our projection method by comparing the total population generated by the multiple-cohort approach to that reported by the U.S. Census. Since our single-cohort model operates in 5-year intervals, we initiated the first cohort of age 0 to 4 in the years of 1910-1914 and modeled the survival of that cohort over a period of 104 years up to the year 2015. Survivors from this single cohort represent males who are 100 to 104 years of age in the 2010-2014 time period. Similarly, we initiated a second cohort of age 0 to 4 years for the time period 1915-1919 and modeled its survival over a period of 99 years. Survivors from this single cohort represent males who are 95-99 years of age in the 2010-2014 time period. Similarly, each age cohort has its corresponding birth period. We followed this approach multiple times to populate the number of survivors in all age categories for the period 2010-2014 (Table 7.4.2-14).

For each cohort, we incorporated initiation and cessation rates for the single-cohort model from Anderson et al. into the transition rates (Anderson, Burns, Dodd, & Feuer, 2012); the

same mortality model is employed across all age group cohorts. The supplemental data by Anderson et al. reported initiation and cessation rates by age for 5-year birth cohorts of males born between 1910 and 1980 on a yearly basis. Given that our age groups are in 5-year intervals, we calculated initiation and cessation rates to reflect this same time frame by averaging the yearly values across 5 years. For initiation and cessation rates of males born after 1980, we used data from Tam et al. For simplicity, we employed the same mortality model across all single cohorts. Also, for transition probabilities involving MST and DU, we used rates reported in Tam et al. (2015) and kept them constant over the entire period.

To build the multiple-cohort model, each age group cohort must begin at its corresponding birth time interval, which requires that the cohort size correspond with the number of native-born U.S. males ages 0 to 4 years, as reported by the U.S. Census Bureau since 1900 (U.S. Census Bureau, 2016).

Figure 7.4.2-10 shows a plot of the 0- to 4-year-old population sizes from 1900 to 2010 based on U.S. Census data. Notice that the plot shows the "baby boom" in the 0- to 4-year-old population from 1940 to 1965, before declining afterwards. This multiple-cohort model allows the "baby boom" artifact to be reflected in the resulting inferences.

As mentioned above, we applied the single-cohort model to each age group cohort beginning with their corresponding birth year starting with that year's corresponding population size of U.S. native-born males. Table 7.4.2-14 shows the development of the age group cohorts from 1910 to 2014. For visual aid of tracking a specific cohort through time, a color-coding scheme of the cohorts is employed. Each age group cohort has its own corresponding color. Consider the 0- to 4-year age group in 1910-1914 (colored yellow). The initial cohort size of 5,745,000 was found using the U.S. Census data (Figure 7.4.2-10). In the 1915-1919 time period, the age of this cohort is no longer between 0 and 4 years, but 5 to 9 years with a cohort size of 5,735,141. Similarly, in the 1920-1924 time period, this cohort is now aged 10 to 14 years, and in the 1925-1929 time period they are aged 15 to 19 years, and so on until 2010-2014, where this cohort is now aged 100 to 104 years. In order to build a full representative combination of cohorts, we repeated this process for cohorts beginning every five years from 1915 to 2015. In each age category, we applied both the corresponding transition rates and the mortality models using a single-cohort model, which always produces a reduction in the cohort size as the cohort moves through time. This example illustrates the concept of a time-staggered, multiple-cohort study as each cohort begins at a different time in order to reflect the heterogeneity of the age groups.

Figure 7.4.2-10:   U.S. Male Population Aged Between 0 and 4 Years from 1910 to 2010 (U.S. Census Bureau)
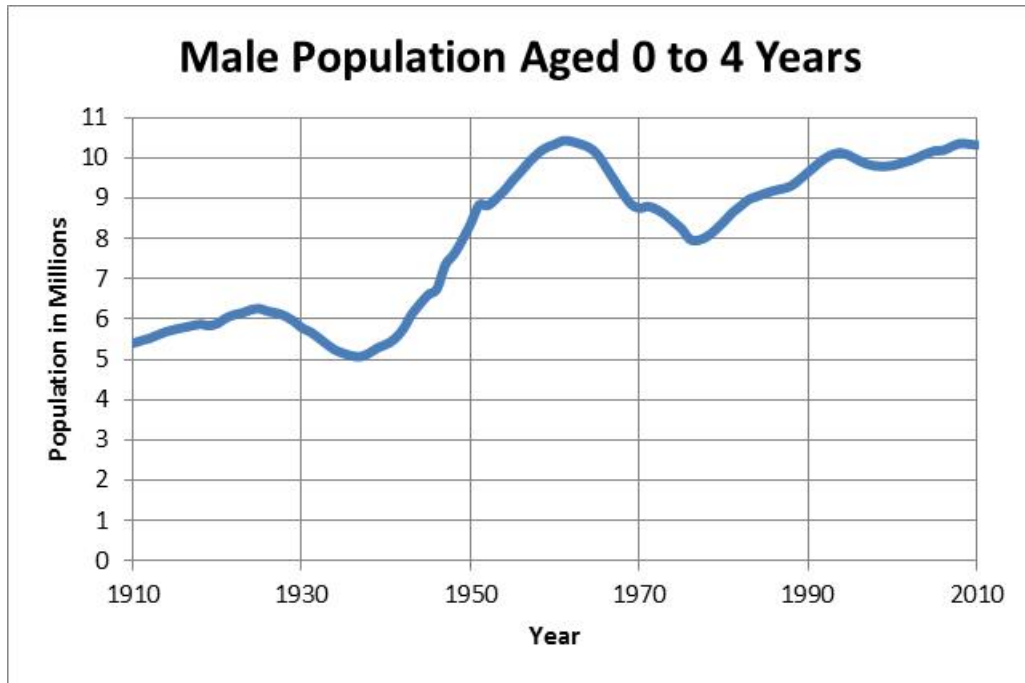
Table 7.4.2-14: Cohort Population Sizes by Age Group from 1915 to 2015

AGE GROUPS	1915 / 1910-1914	1920 / 1915-1919	1925 / 1920-1924	1930 / 1925-1929	1935 / 1930-1934	1940 / 1935-1939	1945 / 1940-1944	1950 / 1945-1949	1955 / 1950-1954	1960 / 1955-1959	1965 / 1960-1964	1970 / 1965-1969	1975 / 1970-1974	1980 / 1975-1979	1985 / 1980-1984	1990 / 1985-1989	1995 / 1990-1994	2000 / 1995-1999	2005 / 2000-2004	2010 / 2005-2009	2015 / 2010-2014
0-4	5,745,000	5,889,000	6,260,000	5,787,000	5,147,600	5,372,700	6,608,900	8,362,000	9,449,100	10,338,800	10,089,800	8,751,100	8,240,000	8,414,200	9,126,900	9,649,600	10,044,500	9,810,600	10,175,600	10,317,900	10,065,000
5-9		5,735,141	5,878,895	6,249,257	5,777,069	5,138,766	5,363,480	6,597,558	8,347,648	9,432,887	10,321,057	10,072,487	8,736,083	8,225,861	8,399,762	9,111,239	9,633,042	10,027,264	9,793,766	10,158,139	10,300,195
10-14			5,723,460	5,866,921	6,236,528	5,765,300	5,128,298	5,352,556	6,584,120	8,330,645	9,413,673	10,300,033	10,051,966	8,718,287	8,209,108	8,382,655	9,092,680	9,613,420	10,006,839	9,773,816	10,137,448
15-19				5,709,327	5,852,433	6,221,128	5,751,063	5,115,636	5,339,338	6,567,863	8,310,071	9,390,427	10,274,598	10,027,145	8,696,756	8,188,834	8,361,954	9,070,226	9,589,680	9,982,128	9,749,680
20-24					5,691,869	5,834,537	6,202,105	5,733,478	5,099,993	5,323,011	6,547,779	8,284,661	9,361,712	10,243,180	9,996,487	8,670,162	8,163,795	8,336,385	9,042,491	9,560,357	9,951,605
25-29						5,664,203	5,805,811	6,172,304	5,705,317	5,075,067	5,297,066	6,516,594	8,246,130	9,318,914	10,197,883	9,952,938	8,632,351	8,127,625	8,300,333	8,994,419	9,509,532
30-34							5,617,985	5,757,784	6,123,859	5,660,020	5,035,426	5,256,438	6,468,727	8,188,029	9,255,875	10,131,849	9,889,870	8,577,449	8,075,488	8,250,766	8,910,368
35-39								5,549,486	5,687,742	6,053,947	5,594,890	4,978,522	5,198,368	6,400,661	8,105,495	9,166,562	10,038,557	9,800,916	8,500,282	8,004,376	8,183,908
40-44									5,453,510	5,589,869	5,956,259	5,503,997	4,899,156	5,117,297	6,305,690	7,990,109	9,041,597	9,907,792	9,676,582	8,395,340	7,907,831
45-49										5,323,523	5,457,490	5,823,544	5,380,626	4,791,242	5,007,003	6,176,060	7,831,874	8,869,569	9,726,992	9,508,959	8,253,932
50-54											5,152,903	5,283,934	5,648,177	5,217,786	4,648,526	4,860,903	6,003,034	7,619,372	8,637,308	9,486,952	9,285,499
55-59												4,940,905	5,068,209	5,428,329	5,013,999	4,469,635	4,677,119	5,783,733	7,348,137	8,336,955	9,173,452
60-64													4,680,653	4,802,969	5,154,974	4,760,999	4,246,739	4,447,008	5,506,304	7,000,690	7,949,850
65-69														4,359,189	4,474,561	4,812,127	4,443,880	3,966,114	4,155,736	5,150,042	6,552,272
70-74															3,954,929	4,060,613	4,374,347	4,039,083	3,606,279	3,779,274	4,686,909
75-79																3,437,255	3,529,573	3,806,388	3,514,026	3,137,564	3,288,464
80-84																	2,776,359	2,850,893	3,074,701	2,838,648	2,534,707
85-89																		1,974,578	2,027,920	2,184,653	2,018,930
90-94																			1,126,028	1,158,578	1,243,008
95-99																				448,060	463,860
100-104																					130,863

	2015
Total Model Population	140,297,313
*Projected Native male Population (US Census)	137,187,000
Percent Difference	2.27%

Note: cells with the same color correspond to the same cohort.
*Projected Native Male population for 2010-2060 is from Table 4 of http://www.census.gov/population/projections/data/national/2014/summarytables.html

To validate our multiple-cohort approach, the summation of the cohorts across age groups for the 2010-2014 population in Table 7.4.2-14 is compared with the estimate of the 2015 U.S. native-born male population reported by the U.S. Census Bureau. The value of 140,297,313 males projected by the model compares well with the 2015 U.S. Census estimate of 137,187,000 native-born males. The comparison shows that the percent difference between the population generated using our multiple cohort approach and the estimate reported in the U.S. Census data is only 2.27 percent, indicating the appropriateness of using the multiple-cohort approach for such analysis.

To further assess and validate our multiple-cohort approach, the cohorts were advanced in time in 5-year increments to 2060. Information on the 0- to 4-year population needed to initiate future cohorts was obtained from the U.S. Census Bureau (2014), (Table 4), which reported projected native-born population by sex and selected age groups, including native-born males under 5 years (i.e., 0-4 years) from 2015 to 2060. The multiple-cohort model was validated by predicting the U.S. native-born male population and comparing against U.S. Census Bureau predictions (U.S. Census Bureau, 2014), (Table 4).

Table 7.4.2-15 shows the multiple-cohort model future predictions and the comparison with the U.S. native-born male population estimates from the U.S. Census and the percent difference between the two. The percent differences are only shown from 2015 to 2060, as the most recent U.S. Census Bureau predictions (U.S. Census Bureau, 2014), (Table 4) do not report population predictions after 2060. The comparison of the model results to future projection in Table 7.4.2-15 shows that the percent difference of the model is less than 6 percent for any considered 5-year span. One explanation for the increasing discrepancy between the U.S. Census-based values and outputs of the multiple-cohort model is that the U.S. Census predictions employ models that take into account improvements in health care as well as other improvements in standard of living, whereas the mortality models we used held those variables constant over time. We believe that the mortality model assumption is reasonable, given that future projections were still within 10 percent of census projections, as well as the fact that the mortality models would equally influence both the Base Case and the Modified Case, and our approach of determining net benefit is based on the difference between the number of survivors in the Modified Case and Base Case outputs. This approach shows that using the single-cohort model in a multiple-cohort setting with a time-staggered structure is capable of modeling the U.S. native-born male population. Furthermore, because the multiple-cohort approach is simply an extension of the single-cohort approach, we believe validation of the multiple-cohort approach further supports the use of the ALCS Cohort Model to test interventions on public health outcomes.

Table 7.4.2-15: **Multiple Cohort Model Forecasts for 2020 to 2060 with Predicted Total Native-Born Male Population from Multiple Multiple-Cohort Models and the Corresponding U.S. Census Projections and Percent Model Difference**

	2020	2025	2030	2035	2040	2045	2050	2055	2060
AGE GROUPS	**2015-2019**	**2020-2024**	**2025-2029**	**2030-2034**	**2035-2039**	**2040-2044**	**2045-2049**	**2050-2054**	**2055-2059**
0-4	10,362,000	10,581,000	10,660,000	10,701,000	10,799,000	10,951,000	11,137,000	11,315,000	11,456,000
5-9	10,047,729	10,344,219	10,562,844	10,641,708	10,682,638	10,780,469	10,932,209	11,117,890	11,295,584
10-14	10,279,214	10,027,263	10,323,149	10,541,328	10,620,032	10,660,878	10,758,511	10,909,941	11,095,243
15-19	10,112,414	10,253,830	10,002,501	10,297,656	10,515,296	10,593,806	10,634,551	10,731,943	10,882,999
20-24	9,719,868	10,081,492	10,222,476	9,971,915	10,266,168	10,483,143	10,561,412	10,602,033	10,699,127
25-29	9,898,700	9,668,195	10,027,897	10,168,131	9,918,902	10,211,591	10,427,412	10,505,266	10,545,670
30-34	9,420,667	9,806,198	9,577,847	9,934,188	10,073,112	9,826,212	10,116,166	10,329,970	10,407,096
35-39	8,787,478	9,290,739	9,670,953	9,445,752	9,797,178	9,345,186	9,690,691	9,976,646	10,187,501
40-44	8,093,399	8,613,804	9,107,119	9,479,819	9,259,068	9,603,549	9,737,849	9,499,166	9,779,470
45-49	7,777,731	7,970,967	8,376,512	8,856,237	9,218,669	9,004,000	9,338,990	9,469,591	9,237,484
50-54	8,065,045	7,603,608	7,805,474	8,063,895	8,525,717	8,874,623	8,667,965	8,990,454	9,116,180
55-59	8,991,184	7,815,057	7,372,172	7,582,312	7,704,867	8,146,127	8,479,499	8,282,042	8,590,173
60-64	8,764,170	8,602,802	7,483,161	7,063,360	7,279,275	7,289,383	7,706,847	8,022,242	7,835,433
65-69	7,447,042	8,225,049	8,085,184	7,038,058	6,647,052	6,863,397	6,790,278	7,179,159	7,472,958
70-74	5,966,572	6,786,333	7,507,044	7,388,320	6,435,373	6,080,797	6,288,773	6,165,469	6,518,567
75-79	4,080,235	5,196,348	5,913,171	6,547,753	6,449,154	5,619,561	5,311,565	5,498,751	5,358,157
80-84	2,656,799	3,296,844	4,199,044	4,778,629	5,291,770	5,212,193	4,541,809	4,292,960	4,444,280
85-89	1,803,055	1,889,909	2,343,766	2,983,677	3,393,124	3,751,007	3,689,488	3,212,762	3,035,145
90-94	1,152,531	1,029,688	1,079,089	1,335,049	1,696,270	1,924,017	2,113,923	2,069,108	1,797,406
95-99	490,536	459,962	411,350	430,666	528,232	666,371	748,729	804,556	773,486
100-104	138,287	139,030	135,472	121,480	126,660	150,590	184,958	200,436	196,751
Total Model Population	144,054,656	147,682,337	150,866,225	153,370,933	155,227,557	156,037,900	157,858,625	159,175,385	160,724,710
*Projected Native male Population (US Census)	141,607,000	145,858,000	149,752,000	153,201,000	156,320,000	159,327,000	162,456,000	165,863,000	169,562,000
Percent Difference	1.73%	1.25%	0.74%	0.11%	-0.70%	-2.06%	-2.83%	-4.03%	-5.21%

*Projected native-born male population for 2010-2060 is from Table 4 of http://www.census.gov/population/projections/data/national/2014/summarytables.htm

7.4.2.2.   Input Parameters for the ALCS Cohort Model

As discussed in Section 7.4.2.1, the outcomes of the ALCS Cohort Model depend on estimation of ERRs; transition probabilities between never-user of tobacco, cigarette, and MST use states; and the impact on those transition probabilities upon authorization of the proposed modified risk claim. Details on the input parameters calculations are located in the following sections:

- Section 7.4.2.2.1 describes the calculation of ERRs on the basis of the ALCS 2015 Linked Mortality Analysis.

- Section 7.4.2.2.2 describes the sources used to estimate transition probabilities between tobacco use and never-user of tobacco states derived from the published scientific literature for the Base Case scenario in the ALCS Cohort Model.

- Section 7.4.2.2.3 reviews the populations of interest based on FDA's Draft MRTPA Guidance.

- Section 7.4.2.2.4 describes the percent changes in transition probabilities resulting from single exposure to the proposed modified risk claims. The percent changes for a majority of the transitions are derived from the ALCS Claim Comprehension and Intention Study, and, in select cases we estimated the transition probabilities when such values could not be derived. We discuss the assumptions for such cases, and conduct sensitivity analyses for the estimated values.

- Section 7.4.2.2.5 discusses the architecture of the model in terms of plausible scenarios. It is important to note that throughout each one of these sections, assumptions are made to identify the most likely modified outcome, the Master Case.

- Section 7.4.2.2.6 describes the sources (published scientific literature and publicly available databases) used to estimate baseline transition probabilities and the starting cohort populations for the multiple-cohort analysis.

- Section 7.4.2.2.7 discusses the assumptions and limitations of the ALCS Cohort Model.

The ALCS cohort-modeling approach uses reasonable assumptions supported largely by uncertainty analyses, sensitivity analyses, and other statistical testing.

7.4.2.2.1.   Excess Relative Risk

ERR is the differential amount of risk posed by one tobacco product (e.g., ST) relative to another tobacco product (e.g., cigarettes) measured in terms of mortality rates. As described in detail in Section 7.4.2.1, the mortality models employed in these analyses estimated the mortality rate of current MST users by adjusting the mortality rate of current cigarette smokers using the ERR of current ST users relative to current cigarette smokers.

The ALCS 2015 Linked Mortality Analysis assessed the relationship between mortality and tobacco use in the form of smokeless tobacco use or cigarette use by using nationally

representative, cross-sectional public health surveys linked to prospective mortality follow-up data.

Cox proportional hazards models were used to fit the data and inferences were made on the basis of model-adjusted hazard ratios (HRs) (Appendix 7.4.1-3). The following covariates were included: age, race, sex, body mass index, education, family income, self-assessed health status, tobacco use, and cigarettes per day. Smokeless tobacco use was defined as snuff use, chewing tobacco use, or both. Pooling snuff and chewing tobacco use is reasonable because the all-cause mortality risks associated with snuff and chewing tobacco use are not different (Henley, Thun, Connell, & Calle, 2005).[1], We assume the all-cause mortality risk of MST to be equal to the mortality risks of ST obtained from the ALCS 2015 Linked Mortality Analysis. HRs derived from the ALCS 2015 Linked Mortality Analysis[2] and calculated ERRs are shown in Table 7.4.2-16.

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[1]Comparison of health effects associated with MST and chewing tobacco use is discussed in Section 6.1.
[2] HRs used to derive ERRs are based on analysis of the National Health Interview Survey public use files (survey years: 1987, 1991, 1992, 1998, 2000, 2005) linked to the 2011 National Death Index update.

Table 7.4.2-16: **All-Cause Mortality Hazard Ratios for Male Survey Respondents: Users of Various Tobacco Products versus Never-Users of Tobacco Products; Mortality Follow-up through December 31, 2011***

Tobacco User	Definition	Notation	Hazard Ratio[1] (95%CI)
Never User of Tobacco	Respondents who have never used any tobacco products	HR_{NT}	Reference
Inputs for the calculation of the ERR of current MST users compared with <u>current</u> cigarette smokers			
Current ST and Never-Smoker	Respondents who are using ST and have never used cigarettes	HR_{MST}	1.110 (0.959, 1.285)
Current Smokers and Never-ST	Respondents who are currently smoking and have never used STs	HR_{CS}	2.130 (2.048, 2.215)
Inputs for the calculation of the ERR of former MST users compared with <u>former</u> cigarette smokers			
Former ST and Never-Smoker	Respondents who have quit ST and have never used cigarettes	HR_{FMST}	1.010 (0.906, 1.126)
Former Smoker and Never-ST	Respondents who have quit smoking and have never used STs	HR_{FCS}	1.280 (1.202, 1.362)

CI = confidence interval; CS = current smoker; ERR = excess relative risk; FCS = former cigarette smoker; FMST = former moist smokeless tobacco user; HR = hazard ratio; MST = moist smokeless tobacco; NHIS = National Health Interview Survey; ST = smokeless tobacco.

*Cox proportional hazards models are limited to respondents who are never-users of tobacco, or respondents who are never-users of pipe tobacco or cigars and who are current or former ST users, current or former smokers. All Cox proportional hazards models control for tobacco use, age, race/ethnicity, body mass index, educational attainment, family income, and self-assessed health status at the time the survey was administered.

Results are based on data from NHIS 1987, 1991, 1992, 1998, 2000, and 2005 and reflect only male respondents:
- counts of total records = 58,615 with 10,287 deaths;
- never-users of tobacco = 27,531 with 3,162 deaths;
- current smokers = 15,815 with 3,239 deaths;
- former smokers = 13,091 with 3,669 deaths;
- current ST users = 2,575 with 400 deaths; and
- former ST users = 3, 463 with 555 deaths.

[1] We used the HR estimates from the publicly available NHIS dataset because we wanted others in public health to be able to replicate our analysis. The publicly available HR estimates were different from the restricted dataset; however, we believe that this will not impact the model outcome significantly, since we conducted a sensitivity analysis using a wider range of ERR values.

The ERR for a product is derived from relative risk, where:

$$ERR_{Product} = \frac{RR_{Product} - 1}{RR_{CS} - 1} \qquad \text{(Bachand \& Sulsky, 2013)}$$

The baseline ERR for never-tobacco users is 0, while the baseline ERR for current cigarette smokers is 1. In this context, we can calculate the ERRs of current MST users compared with current cigarette smokers and former MST users compared with former cigarette smokers.

The ERR of current MST users compared with current cigarette smokers is calculated as 0.09:

$$ERR_{MSTCS} = \frac{HR_{MST}-1}{HR_{CS}-1} = \frac{1.101-1}{2.120-1} = 0.097,$$
where the HR values 1.101 and 2.120 are taken from Table 7.4.2-16

The ERR of former MST users compared with former cigarette smokers is 0.04:

$$ERR_{FMSTFCS} = \frac{HR_{FMST}-1}{HR_{FCS}-1} = \frac{1.010-1}{1.280-1} = 0.04,$$
where the HR values 1.101 and 1.280 are taken from Table 7.4.2-16

Our use of HRs to derive ERRs is reasonable because the HR is generally equivalent to the relative risk.[3]

We assigned the mortality risk of dual cigarette and ST use to be the same as the mortality risk of exclusive cigarette use, based on findings from published literature (Accortt et al., 2002; Frost-Pineda et al., 2010) and from our ALCS 2015 Linked Mortality Analysis.

We did not use the all-cause mortality HR for white, male, current ST users from the National Longitudinal Mortality Study mortality linkage[4], which has a point estimate that is less than 1.0 (HR: 0.872, 95% CI: 0.592-1.285). This would imply that the risk of MST is lower than that of no tobacco usage, which is counterintuitive and would unreasonably benefit the outcomes of the model.

We also found that the all-cause mortality HR for current cigarette smokers that we derived from the National Health Interview Survey mortality linkage is consistent with other publicly available estimates. The all-cause mortality hazard for males derived from the American Cancer Society's Cancer Prevention Study II cohort was 2.80 (95% CI: 2.72-2.88) (Surgeon General Report & U.S. Department of Health and Human Services, 2014). Based on 13 published studies, Shavelle et al. (2008) derived pooled all-cause mortality risks for light, medium, and heavy cigarette smokers. The pooled all-cause mortality relative risk estimates among males were 1.47 for light smokers, 2.02 for medium smokers, and 2.38 for heavy smokers. The consistency of our estimate of the all-cause mortality risk associated with cigarette smoking with published values further supports the validity of our ERR input data. Furthermore, we conducted a sensitivity analysis using a wide range of ERR values (Figure 7.4.2-7).

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[3] https://www.nps.org.au/australian-prescriber/articles/interpreting-risks-and-ratios-in-therapy-trials
[4] The 2015 ALCS Linked Mortality Analysis, includes two independent data sets; one based on the National Health Interview Survey and the other based on the TUS-CPS. The TUS-CPS is referred to as the National Longitudinal Mortality Study.

7.4.2.2.2. Transition Probabilities Base Case from Published Scientific Literature

As discussed in Section 7.4.2.1.2, the conceptual framework of the ALCS Cohort Model is to assess the overall difference in all-cause mortality of a hypothetical cohort population, between a Base Case scenario and a Modified Case scenario. The Base Case scenario represents the status quo for a hypothetical population. For population modeling analyses related to this MRTPA, we employ the framework described in Figure 7.4.2-2. Both cigarettes and MST currently coexist in the Base Case and favorable consideration of this MRTPA would result in a Modified Case scenario, wherein cigarettes and MST would still coexist, but the candidate product would be marketed with a modified risk claim on it.

The ALCS cohort model requires estimation of 30 transition probabilities that allow for moving the population between 29 current and former MST use states, cigarette smoking use states, and never-tobacco use states as seen in Figure 7.4.2-4.

In this section, we discuss the underlying sources used to estimate the transition probabilities for the Base Case scenario. Tam et al. (2015) conducted a systematic review of published literature on transitions between ST and cigarette use in the United States. All published articles from January 2000 to March 2014 that presented relevant estimates of transitions in U.S. youth and adult study populations over time were included. The reviewers discussed six studies of U.S. populations (Haddock et al., 2001; O'Hegarty, Pederson, Asman, Malarcher, & Mirza, 2012; Severson, Forrester, & Biglan, 2007; Tomar, 2003; Wetter et al., 2002; Zhu et al., 2009), wherein longitudinal data were presented on some or all of the transitions that users can undergo between never-tobacco use, ST use, cigarette use, and dual use states.

We used transition rates from three of these studies (Tomar, 2003; Wetter et al., 2002; Zhu et al., 2009) because the underlying populations assessed in these studies were the most generalizable to U.S. population and the transition periods were most similar to those used in our modeling analyses.

- Male adolescent transitions
  - Tomar (2003) reported transition probabilities from the Teenage Attitudes and Practices Survey-I and Teenage Attitudes and Practices Survey-II (TAPS-I and II), which were nationally representative cohort studies conducted in 1988/1989 and 1993 and included 3,996 males with ages ranging from 11 to 19 years. This study had a 4-year follow-up between 1989 and 1993.

- Adult male transitions
  - Wetter et al. (2002) studied secondary trial data from the Working Well Trial on cancer prevention, which included 1,224 adult male tobacco users residing in the southeastern United States, with baseline in 1990 and follow-up 4 years later. The average age of the participants in this study was 37.5 years.
  - Zhu et al. (2009) reported the results from the 2002 Tobacco Use Supplement to the Current Population Survey, a nationally representative cross-sectional survey including both males and females over the age of 18 years. Follow-up interviews for 15,056 households were conducted in 2003.

Based on our analysis of the information presented within Tam et al. (2015) and the associated references, we summarize in Table 7.4.2-17 the male adolescent Base Case transition probabilities based on the 4-year follow up TAPS-I and II study by Tomar et al. (2003). We make the assumption that the 4 year follow up data in Table 7.4.2-17 can be used as model inputs for 5-year estimates.

Table 7.4.2-17: **Percentage of Male Adolescents Transitioning between Tobacco Product Use Categories: 4-Year Follow-up (Tomar, 2003)**

Baseline Status	Follow-up Status			
	Neither	**Exclusive Smokeless Tobacco User**	**Exclusive Smoker**	**Dual User**
Neither	82.2%	3.1%	13.5%	1.1%
Exclusive smokeless tobacco user	15.2%	44.8%	25.5%	14.3%
Exclusive smoker	16.9%	0.8%	78.7%	3.6%
Dual user	14.1%	34.2%	31.2%	20.4%

Note: Due to the effect of rounding, not all percentages sum exactly to 100.

We further summarized the male adult Base Case transition probabilities in Table 7.4.2-18 based on the 1-year follow-up study by Zhu et al. (2009) and the 4-year follow-up study by Wetter et al. (2002). For 1 year follow-up data, we adjusted the yearly rates to obtain rates in appropriate for our 5 year increments. This adjustment involves multiplying the transition probability by 2.5, the average person-time at risk of smoking initiation in each 5 year age category. For example, in the 13-17 years of age category with 5-year follow up, a person aged 15 years is only at the risk of smoking initiation at ages 16 and 17 years (i.e., he has 2 years of risk of smoking initiation). For the 4 year follow-up study data, we made the same assumption as we have for adolescents that the 4-year follow up transitions can be used as model inputs for 5-year transition estimates.

Table 7.4.2-18: **Percentage of Male Adults Transitioning Between Tobacco Product Use Categories (1-Year Follow-Up from Zhu Et Al. (2009) and 4-Year Follow-Up from Wetter Et Al. (2002))**

Baseline Status	Follow-up Status			
	Neither	**Exclusive Smokeless Tobacco User**	**Exclusive Smoker**	**Dual User**
Neither	96.7% 1-year follow-up	0.7% 1-year follow-up	2.5% 1-year follow-up	0.1% 1 year follow-up
Exclusive smokeless tobacco user	20.1%	76.6%	0.9%	2.5%

Baseline Status	Follow-up Status			
	Neither	**Exclusive Smokeless Tobacco User**	**Exclusive Smoker**	**Dual User**
	4-year follow-up	4-year follow-up	4-year follow-up	4-year follow-up
Exclusive smoker	15.7% 4-year follow-up	1.4% 4-year follow-up	79.7% 4-year follow-up	3.2% 4-year follow-up
Dual user	11.3% 4-year follow-up	17.4% 4-year follow-up	27.0% 4-year follow-up	44.3% 4-year follow-up

Note: Due to the effect of rounding, not all percentages sum exactly to 100.

Appendix 7.4.2-1; Table 9 provides the complete set of Base Case transitions probabilities by five year age intervals. Appendix 7.4.2-1; Table 10 (i.e., Estimated Mortality rates for Males for the year 2000) are used for analysis presented in Section 7.4.2.3.

7.4.2.2.3. FDA Guidance: Populations of Interest

In its 2012 MRTPA Draft Guidance, the FDA recommends that applicants address the net benefit to the population by providing quantitative estimates of the likely effect of authorization of the proposed claim, on the health of the population as a whole. The FDA further recommends that the applicants estimate the attributable risk of all of the various health, tobacco use behavioral effects, and tobacco use initiation for various types of individuals within the population. These populations include, but are not limited to, those discussed below.

Among current tobacco users, FDA requests "scientific studies submitted by the applicant should inform the FDA's evaluation of the tobacco product's impact on tobacco use behavior, including:

- The likelihood that current tobacco product users will start using the [candidate] product;

- The likelihood that tobacco users who adopt the [candidate] product will switch to or switch back to other tobacco products that present higher levels of individual health risk;

- The likelihood that consumers will use the [candidate] product in conjunction with other tobacco products;

- The likelihood that users who may have otherwise quit using tobacco products will instead use the [candidate] product; and

- The likelihood that consumers will use the [candidate] product as intended or designed."

Among **nonusers of tobacco**: the FDA requests "[t]o address the effect of the MRTP on tobacco use initiation, FDA recommends that applicants provide evidence regarding the likelihood of population benefit or harm from the proposed product, including:

- "The likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product;

- The likelihood that nonusers who adopt the tobacco product will switch to other tobacco products that present higher levels of individual health risk; and

- The likelihood that former users of tobacco products will re-initiate use with the tobacco product."

Several of these transitions and their impact on population as a whole will be discussed in detail in Section 7.4.2.3 (Population Model Outcomes).

7.4.2.2.4. Modified Cases Transitions Estimated from ALCS Claim Comprehension & Intentions Study

As previously discussed, a key outcome of the model is to estimate differences in all-cause mortality between the Base Case and Modified Case scenarios, which are interpreted to represent positive and negative health effects of authorization of the proposed claim for the candidate product on the population of interest (see details in Section 7.4.2.1). This requires us to estimate the change in transition probabilities that would occur in the Modified Case, compared with the Base Case. Where possible, we estimate relative percent change in transition rates by evaluating the percent difference between the relevant responses of the test condition (exposed to advertisement with the proposed modified risk claim) and control condition (exposed to advertisement without the proposed claim) from pre to post-ad exposure from the ALCS Claim Comprehension & Intentions (CCI) Study (Appendix 7.3.2-1) and then to apply the relative percent change factor to the transition rates used in the Base Case, which are obtained from nationally representative studies reported in Tam et al. (Table 7.4.2-2 and Table 7.4.2-3). The methodology applied to estimate these percent differences for all the relevant transitions is discussed in this section.

The CCI Study is a cross-sectional, self-administered, computerized survey study. Details of this study are provided in Appendix 7.3.2-1. The study population was composed of a non-probability sample of qualified adult (legal age to purchase tobacco products or older), self-reported tobacco product users and non-users. The study assesses intentions to try, use, dual use, and switch to the test product among adult self-reported tobacco product users and non-users. The outcomes showed in Table 7.4.2-20 are extracted for modeling purposes and are not expected to be comparable to the Base Case transition probabilities presented in Section 7.4.2.2.2.

As a hypothetical example, consider the transition rate for current exclusive smokers transitioning to current exclusive MST use, which is 1.4 percent for the male adult group (Table 7.4.2-18). In order to estimate the percent by which this Base Case transition rates would be changed to calculate the estimated transition rates for the Modified Case, we analyzed the percent difference between the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without the modified risk claim)

in the ALCS CCI (Appendix 7.3.2-1). To illustrate, consider a hypothetical example where at pre-test within the control condition 2.0% of current exclusive smokers intend to switch to the test product, 2.5% intend to switch post-test, 3.0% of exclusive smokers in the test condition at pre-test intend to switch to the test product and 4.0% intend to switch at post-test. The relative percentage change calculation would compute 6.7% probability of switching to the test product. That is, the ratio of test condition respondents (post-test vs pre-test) minus the ratio of control condition respondents (post-test vs pre-test) divided by the ratio of control condition respondents will generate the relative percentage change. Applying this change of 6.7 percent to the Base Case value of 1.4 percent would make the probability of this transition 1.49 percent.

In the CCI Study, ALCS created different user groups as listed in Table 7.4.2-19 and examined their possible behaviors. These groups align with the user groups recommended in the FDA guidance. The behaviors observed were divided into three groups, and an analysis was conducted as discussed below to generate the values presented in Table 7.4.2-20. The behaviors are based on survey respondents having a "positive affect" (Section 7.3.2):

- *Initiation* is defined as a composite score of 3.5 or higher on intention to use and positive purchase intent. Intention to use is measured with four items, each asked before and after viewing the promotional material(s) for Copenhagen® Snuff. Each item is measured on a 6-point scale, ranging from "*Strongly Agree to Strongly Disagree*",

  – "I would consider using Copenhagen® Snuff more than once."

  – "I expect to use Copenhagen® Snuff."

  – "It is likely that I will regularly use Copenhagen® Snuff in the next 6 months."

  – "Copenhagen® Snuff will be my regular brand of snuff/dip/smokeless tobacco in the next 30 days."

- *Switching* is defined as a composite score of 3.5 or higher on intention to switch and positive purchase intent. Intention to switch is measured with three items, each asked before and after viewing the promotional material(s) for Copenhagen® Snuff. Each item is measured on a 6-point scale, ranging from "*Strongly Agree to Strongly Disagree*". These questions are asked only of current cigarette users.

  – "I plan to gradually switch from regular cigarettes to a Copenhagen® Snuff." [5]

  – "I plan on Copenhagen® Snuff as a complete replacement for regular cigarettes."

  – "I intend on switching from cigarettes to Copenhagen® Snuff in the next 6 months."

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[5] Berg et al. (2014)

- *Switching to dual use* is defined as a score of 4 or higher on intention to dual use and positive purchase intent. Intention to dual use is measured by one item.

  – "I plan to use Copenhagen® Snuff in addition to regular cigarettes."

Population of Nonusers of tobacco are defined below:

- A *Nonuser Never-Trier of Tobacco* is defined a respondent who has never tried tobacco products in his or her lifetime. A *Nonuser Ever-Trier of Tobacco* is a respondent who has tried tobacco but has smoked less than 100 times and/or dipped less than 20 times in his/her lifetime. They have not smoked and/or dipped in the past 30 days and do not currently use tobacco.

- A *Former Tobacco User* is defined a respondent who has smoked 100+ times and/or dipped 20+ times in his or her lifetime, but he or she currently has quit tobacco completely for at least 6 months.

- We combine the two study groups, Nonuser Never-Trier of Tobacco and Nonuser Ever-Trier of Tobacco to obtain the total rate of never-users of tobacco initiating candidate product use after authorization of the proposed claim. While the MRTP initiation behaviors of never-triers and past-user triers can be different, the CCI Study has a representative sample of each group, and each is represented proportionately from the Population Assessment of Tobacco and Health Survey (2013-2014).

Among the populations of interest described by FDA in the 2012 draft guidance, "[t]he likelihood that consumers who have never used tobacco products, particularly youth and young adults, will initiate use of the tobacco product" is not available, as ALCS does not conduct any research among youth. The percentage changes in adults that were observed in the CCI Study were applied to all relevant age groups. It is important to note that the Base Case values for these transitions were obtained from nationally representative studies, Tam et al. (2015).

- *Would-be smokers* are defined as adult never-tobacco users who would otherwise initiate cigarette smoking but initiate use of MST after authorization of the proposed claim instead of initiating smoking. A direct measurement of the change in this value is not possible in our study as this would require respondents to speculate if they think they would ever become smokers.

Population of Current MST users are described below:

- *Current MST User, Non-smoker* is defined as a user who has dipped 20+ times in his or her lifetime and has dipped in the past 30 days. They currently use dip/snuff every day, some days or rarely. They have not smoked in the past 30 days and do not currently smoke cigarettes every day, some days, or rarely.

- A *MST user switching to an exclusive cigarette user* is defined as one reducing all current consumption of MST and replacing it with cigarette consumption after exposure to the proposed claim.

Population of current cigarette smokers is discussed below:

- *Current Exclusive Smoker* is defined as a user who has smoked 100+ cigarettes in his or her lifetime and has smoked in the past 30 days. They currently smoke every day, some days, or rarely. They have not dipped in the past 30 days and currently do not dip every day, some days, or rarely. Current exclusive smokers planning to quit are those who plan to quit cigarettes in the next 30 days. Current exclusive smoker not planning to quit are those who do not plan to quit cigarettes in the next 30 days.

  The CCI Study includes approximately an equal proportion of adult smokers planning to quit and adult smokers not planning to quit. We combine these two groups at a ratio of 13 percent to 87 percent based on 2013-2014 Population Assessment of Tobacco and Health (United States Department of Health and Human Services et al., 2017).

- An *exclusive cigarette smoker switching to MST use* is defined as one having non-zero usage for stated cigarette use and likelihood to use MST in post-test. An *exclusive cigarette smoker switching to dual use* is defined as one having an intention to dual use composite score of 4.0 or higher and intend to purchase the candidate product.

- *Would-be Smoking quitters* are defined as adult cigarette smokers who would otherwise quit cigarette smoking but, in the Modified Case, initiate use of MST after authorization of the proposed claim instead of quitting cigarette smoking. A direct measurement of the change in this value is not possible in our study as this theoretical state would require respondents to speculate whether they would quit smoking or not.

Population of dual users switching to exclusive use as discussed below:

- *Current Dual (MST + Cigarette) User* is defined as a user who has smoked 100+ cigarettes and dipped 20+ times in his or her lifetime. He or she has smoked and dipped in the past 30 days and currently smokes and dips every day, some days, or rarely.

- *A dual user switching to exclusive use* is defined as a user having an intention to switch composite score of 3.5 or higher and intends to purchase the product.

- Population of tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication and nonusers who experience health risks from the product cannot be addressed with our model and these populations are discussed further in Appendix 7.5.6-1 and Appendix 7.5.6-2 (literature summary sections have FDA-approved tobacco cessation medication, if any) and Section 8.1 (postmarket surveillance).

A summary of the FDA requirements and the corresponding 2017 CCI Study is found in Table 7.4.2-19.

As previously discussed, a key outcome of the model is to estimate differences in all-cause mortality between the Base Case and Modified Case scenarios. The net benefit of authorization of the proposed claim is estimated by the all-cause mortality estimate as

translated to lives saved and years of lives saved (Section 7.4.2.2.3). This requires us to estimate the change in transition probabilities that would occur in the Modified Case, compared with the Base Case. Where possible, the approach we have adopted is to estimate percent change in transition rates by evaluating the percent difference between the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without modified risk claim) from the ALCS Claim Comprehension and Intentions Study and then to apply the percent change factor to the transition rates used in the Base Case, which are obtained from nationally representative studies reported in Tam et al. (2015).

Table 7.4.2-19: **User Group Definitions from the FDA Draft Guidance and the ALCS Claim Comprehension & Intentions Study**

FDA Recommended Population	2017 ALCS Claim Comprehension & Intentions Study
Nonusers who initiate tobacco use with the proposed product, such as youth, never-users, former users	*"MRTP Initiation"* Group • Nonusers never tried any tobacco products • Nonusers ever tried cigarette or MST but have not reached numerical thresholds • Former MST users and nonsmokers, would-be smokers • Does not include youth Behavior • Initiate MRTP
Tobacco users and nonusers who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk	*"MRTP to Smoking"* • Not Applicable
Tobacco users who switch from other commercially marketed tobacco products to the proposed product	*"Smoking to MRTP"* Group • Exclusive cigarette smokers not planning to quit • Exclusive cigarette smokers planning to quit • Smoking quitters Behavior • Switch to MRTP
Tobacco users who opt to use the proposed product rather than cease tobacco use altogether	*"Smoking to Dual"* Group • Exclusive cigarette smokers not planning to quit • Exclusive cigarette smokers planning to quit Behavior • Switch to Dual (MRTP and cigarettes)

FDA Recommended Population	2017 ALCS Claim Comprehension & Intentions Study
Tobacco users who use the product in conjunction with other tobacco products	*"Dual to Exclusive"* Group • Cigarette and MST/MRTP dual users Behavior • Switch to MRTP
Tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication	• Not Applicable
Nonusers who experience health risks from the product	• Not Applicable

ALCS = Altria Client Services, LLC; FDA = Food and Drug Administration; MRTP = modified risk tobacco product; MST = moist smokeless tobacco. MRTP in this table is intended to represent MST use at the category level after authorization of the proposed claim.

The likelihood of use by tobacco user group and intended behavior is illustrated in Table 7.4.2-20.

Table 7.4.2-20:   Likelihood of Use With and Without Claim from ALCS Claim Comprehension & Intentions Study

Section	User and Non-user Groups	Intended Behavior	Column A Control Group without Ad Exposure	Column B Control Group with Ad Exposure	Column C Test Group without Claim Exposure	Column D Test Group with Claim Exposure	Column E[1] Relative Percentage Change
**Nonusers Who Initiate Tobacco Use with the Proposed Product, Never-Users, and Former Users** *"MRTP Initiation"*						
7.4.2.2.4.1	Never-user of tobacco (ever-past trier/never-trier)	Initiate Candidate Product	0.031	0.024	0.048	0.036	-4.8%[2]
	Former MST user		0.031	0.000	0.073	0.035	0.0%
	Would-be smoker		NA				+1.0%
	Tobacco Users and Nonusers Who, after Adopting the Proposed Product, Switch … *"MRTP to Smoking"*						

Section	User and Non-user Groups	Intended Behavior	Column A Control Group without Ad Exposure	Column B Control Group with Ad Exposure	Column C Test Group without Claim Exposure	Column D Test Group with Claim Exposure	Column E[1] Relative Percentage Change
7.4.2.2.4.2	Current exclusive MST user	Switch to Cigarette	Not measured in the study				
Tobacco Users Who Switch from Other Commercially Marketed Tobacco Products to the Proposed Product *"Smoking to MRTP"*							
7.4.2.2.4.3	Current cigarette smokers (planning to quit/not planning to quit)	Switch To Candidate Product	0.177	0.159	0.140	0.151	20.8%
	Would-be Smoker quitters		NA				+5.0%
Tobacco Users Who Opt to Use the Proposed Product Rather than Cease Tobacco Use Altogether *"Smoking to Dual Use"*							
7.4.2.2.4.4	Current cigarette smokers (planning to quit/not planning to quit)	Switch to Dual (Candidate Product & cigarettes)	0.240	0.199	0.179	0.183	24.0%
Tobacco Users Who Use the Product in Conjunction with Other Tobacco Products *"Dual to Exclusive"*							
7.4.2.2.4.5	Dual users (MST and cigarette)	Switch to Candidate Product	0.341	0.324	0.355	0.356	5.7%
	Dual users (MST and cigarette)	Switch to Cigarette	Not measured in the study				

ALCS = Altria Client Services, LLC; MRTP = Modified Risk Tobacco Product; MST = Moist Smokeless Tobacco
NA = Not Available

[1] Recreating Column E from the values in the table above may not equate to the probabilities reported due to rounding. The transition probabilities in Column E are computed with the following formula:

$$\frac{\dfrac{Column_D}{Column_C} - \dfrac{Column_B}{Column_A}}{\dfrac{Column_B}{Column_A}}$$

[2] The relative percentage change was estimated as a negative value suggesting that exposure to proposed claim actually reduces their likelihood of initiating with the candidate product, compared to the control.

Note: (1) These values are rounded. (2) Would-be smoker initiating candidate product and would-be smoking quitter switching to candidate product are absolute percentage increases, not percentage changes. (3) Details of how the ALCS CCI study data was analyzed to obtain input data used in our modified case scenarios can be found in Appendix 7.4.2-4.

A detailed description of the 2017 ALCS Claims Comprehension and Intentions Study (CCI) results follows (Section 7.4.2.2.4.1).

7.4.2.2.4.1. Nonusers Who Initiate Tobacco Use with MST: Never-Users and Former Users

In the CCI Study, respondents within two categories of never tobacco users assessed their likelihood of initiating use of the proposed product: never users of tobacco and former MST users. For each category, the proportion of respondents who expressed the intention to start using (transition to) the MRTP was calculated.

The relative percentage change (-4.8%) was computed as described in Table 7.4.2-20.

Among former MST users, there was no change in initiating the candidate product with the addition of the proposed modified risk claim percentage. In the control condition at pre-test, 1 of 31 respondents stated they would initiate Copenhagen Snuff, while post ad, in the post test condition (without the proposed modified risk claim) 0 of 31 respondents stated they would initiate the Copenhagen Snuff (Appendix 7.4.2-3; Table 1). In the test condition at pre-test, 2 of 28 respondents stated they would initiate Copenhagen Snuff, while in the post-test group, only 1 of 28 stated they would initiate the candidate product (with the proposed modified risk claim language). Aside from the obvious impracticality of division by zero, the characterization of this finding as "no percentage change" is statistically defensible from two perspectives. First, the characterization of this finding as "no percentage change" is justified because the event of interest (initiating) is extremely rare and subject to the false positive paradox. Second, this one respondent can be classified as a rare event based on a statistical sampling test showing that, if this research were repeated, it is likely that we would never have identified this respondent. We provide a detailed explanation of these two arguments in Appendix 7.4.2-3.

7.4.2.2.4.2. Nonusers, Tobacco Users, and Nonusers Who, after Adopting the Proposed Product, Switch to or Switch Back to Other Tobacco Products That May Present Higher Levels of Individual Health Risk

We do not assess intentions to switch to cigarette in the CCI Study. The study was designed to assess changes in behavior intentions for the candidate product. For analysis and modeling purposes, we assume there is no change in switching rates to cigarettes with a market authorization of the candidate product with a modified risk claim on it. We assume that the Base Case transition rates (i.e. exclusive MST use to Cigarette use) established in the literature (Tomar, 2003; Wetter et al., 2002; Zhu et al., 2009) will not be impacted by the market authorization of the candidate product.

7.4.2.2.4.3. Tobacco Users Who Switch from Other Commercially Marketed Tobacco Products to the Candidate Product

The relative percentage change among current cigarette smokers who switched to exclusive MRTP use increased by 20.8% (Table 7.4.2-20).

Since the would-be smoking quitter transition to the candidate product cannot be measured in the CCI Study, we made the assumption that +5.0 percentage points "would-be smoking quitters" would initiate MRTP instead of quitting cigarette smoking with the proposed modified risk claim. We characterize *would-be smoking quitters* as cigarette smokers who would otherwise quit cigarette smoking but switch to the MST instead.

7.4.2.2.4.4. Tobacco Users Who Opt to Use the Proposed Product Rather than Cease Tobacco Use Altogether

Among current cigarette smokers, the relative percentage who switched to dual use increased by 24.0% (Table 7.4.2-20).

7.4.2.2.4.5. Tobacco Users Who Use the Product in Conjunction with Other Tobacco Products

We estimate the relative percentage change among current dual users who switched to exclusive MRTP use is increased by 5.7%.

7.4.2.2.5.　Plausible Scenarios

There is an infinite array of scenarios that could potentially play out with a marketing market authorization of the proposed claim. ALCS classifies these scenarios into one of three categories:

1. Base Case is a composition of non-tobacco users, cigarette smokers, and MST users with transitions between these states as they currently exist, without a reduced risk claim on it (i.e., the status quo).

2. Modified Cases, as explained in Section 7.4.2.2.4, represent a range of scenarios that would be possible with an authorization of the modified risk claim. While ALCS has sought to identify the most likely modified case (i.e., the Master Case described below) using reasonable assumptions and best research, we are sensitive to the potential vulnerabilities of the model predictions if the input transitions deviate from expectations. To account for this, we present sensitivity analysis on each of the transitions in Section 7.4.2.1.9.

3. The Master Case is considered our most likely modified case. In this scenario, the inputs reflect a combination of our best estimates for each of the transition rates. In addition the outcome represents our most likely outcome of allowing an MRTP claim on an already marketed MST product (i.e., the candidate product). For the Master Case, we estimated the percent difference between the relevant response of the test condition (exposed to the advertisement with the modified risk claim) and control condition (exposed to the advertisement without the modified risk claim) in the CCI Study and then applied the percent difference to the nationally representative base case transition rates. Table 7.4.2-

20 shows the percentage change for the seven relevant transitions in the Master Case scenario. The Master Case scenario is discussed throughout Section 7.4.2.2.5.

We compare Base Case outputs to various Modified Case outputs to investigate the variability of model predictions through uncertainty and sensitivity analyses for each individual transition Section 7.4.2.3.3 and Section 7.4.2.2.4. We only propose one Master Case, which simultaneously incorporates the changes in all transitions of interest based on our assumptions and best findings from our research. The Master Case will provide our most-likely expected outcome if marketing of MST product with an MRTP claim is allowed.

7.4.2.2.6. Transition Probabilities and Starting Cohort Data from Published Scientific Literature and Publicly Available Databases Used in the Multiple-Cohort Analysis

As discussed in Section 7.4.2.1.10, a multiple-cohort modeling approach was used to group multiple cohorts, allowing for stronger inferences and the ability to extend inferences to the populations of interest. Data used in this analysis were obtained from published literature and publicly available databases.

- Validation of multiple-cohort approach

  - Each single cohort used to build the multiple-cohort models required a starting cohort size corresponding to number of U.S. males of age group 0 to 4 years. The U.S. Census bureau has population data for males aged 0 to 4 years from 1900 to 2010 in 5-year intervals (U.S. Census Bureau, 2016).

  - Initiation and cessation rates for each single-cohort model are obtained from Anderson et al. and Tam et al. (Anderson et al., 2012; Tam et al., 2015). Anderson et al. reported yearly initiation and cessation rates by age for 5-year birth cohorts of males born between 1910 and 1980. Given that our age groups are in 5-year intervals, initiation and cessation rates were calculated to reflect this same time frame by averaging the yearly values across 5 years. For initiation and cessation rates of males born after 1980, data from Tam et al. (Section 7.4.2.2.2) were used. Transition probabilities of MST and DU were also obtained from Tam et al. (2015). The same mortality model was employed across all single cohorts.

- Extending validation to future projections

  - The starting cohort size corresponding to number of native-born U.S. males of age group 0 to 4 years (i.e., under 5 years) from 2015 to 2060 at 5-year increments was obtained from the U.S. Census Bureau (U.S. Census Bureau, 2014), (Table 4). Future projections for comparison with the model results were also obtained from this source.

- Multiple-cohort scenario

  - Starting cohort populations at age 0 to 4 years were obtained from the U.S. Census Bureau as stated above.

- − Model inputs for Base Case and Modified Case scenarios are the same as described in Section 7.4.2.2.2 and Section 7.4.2.2.4. Similar ERRs are used as defined in Section 7.4.2.2.1.

7.4.2.2.7. ALCS Cohort Model Assumptions and Limitations

At each step of the model development and analysis, efforts were made to use both reasonable assumptions and model parameter estimates. Also, at each juncture in the ALCS Cohort Model's development, quality control measures, sensitivity analyses, uncertainty analyses, model verification, and model validation were used to ensure the model's fit for use and prediction ability. While some assumptions in the model are explicit (such as ERR values and transition probabilities), others are implicit and are summarized below:

- A key assumption is that the Kaiser-Permanente data set used to create the mortality models is representative of the general population. However, the study participants had health insurance, short follow-up periods, and their age-specific mortality rates were lower than those for the U.S. population (Friedman et al., 1997). We, therefore, have taken appropriate steps in adjusting the data set by assigning weights that reflect mortality rates in the U.S. population. Note that, apart from the Kaiser-Permanente data set, very few publicly available data of this nature exist in the literature, especially with the attributes of "number of years smoked" and "years since cessation." A similar approach has been published in peer-reviewed literature (Bachand & Sulsky, 2013).

- We assume that the mortality risks associated with the model's variables (i.e., age, years of smoking, years since quitting, and relevant interaction terms) are appropriately specified. Although these models seem to fit the data rather well, there is some evidence of overfitting, which is not unexpected with complex models.

- Although numerous transitions states can possibly occur, we assume that the 29 states are sufficiently specified to account for all reasonable paths of use over time. These 29 states in the model allow for people to switch between products, as well as to cease product use.

- We assume that the changes to transition rates from the ALCS Consumer Comprehension and Intent to Use (CCI) Study will remain approximately constant over the modeling period. Similarly we also assume that the product-specific initiation, cessation, and other transition rates do not change over the modeling time period and that age- and product use state–specific mortality rates remain constant over the modeling time period.

- (United States Department of Health and Human Services et al., 2017), have observed that poly-tobacco use (e.g., e-cigarette use) is common amongst many adult tobacco consumers; however in the order to limit the transitions to a manageable number, we did not include all the other tobacco products. Furthermore, we assume that much of the poly-tobacco use is occasional; thereby not impacting the health effects as much as regular use of cigarettes.

Three limitations identified in the ALCS Cohort Model:

- The temporal resolution of the compartmental model is five years. Hence, it cannot adequately account for participant transitions occurring within a five-year period (e.g., an individual who initiates cigarette smoking in the first year, quits smoking, and switches to MST in the second year, quits MST and returns to cigarette smoking in the fourth year, and quits smoking in the fifth year). The model will assign this participant the same risk as someone who smoked almost the entire five-year span and stopped using cigarettes right before the next transition (Section 7.4.2.2.7). We believe that this limitation should not impact the mortality outcomes significantly as most tobacco-related diseases manifest from chronic use of the product over several decades.

- Two subpopulations – "Would-be Smoker" and "Would-be Smoking Quitter"– that may be impacted by authorization of a modified risk claim could not be studied in the ALCS CCI Study (Appendix 7.3.2-1) because of the impracticality of assessing these transitions in a pre-market survey setting. Therefore, we conduct a sensitivity analysis using a wide range 0%-100% (Case 3, Table 7.4.2-39 for Would-be Smoker and Case 5, Table 7.4.2-43 for Would-be Smoking Quitter) of transition probabilities and determined that the assumptions were reasonable.

- Also limiting the single cohort approach is that the inferences are somewhat tied to the homogeneous cohort group, which limits generalizability to the population, which is inherently more heterogeneous in nature. The multiple-cohort modeling approach discussed below helps address this limitation.

7.4.2.3. Population Model Outcomes

Modeling results predict that there will be a positive net health benefit to the population if marketing of an MST product with an MRTP claim is allowed. In the single-cohort approach, we follow survival of a hypothetical cohort of 1,000,000 males through their lives, starting at age 13 years, under a series of defined scenarios. In the multiple-cohort approach, a series of cohorts, which, in their totality, represent the U.S. born male population, are modeled to determine the impact of authorization of the modified risk claim. Our results are presented as differences between a Base Case Scenario (current market where cigarette and MST coexist) and a Master Case Scenario (our most-likely expected outcome if marketing of MST product with an MRTP claim was allowed). The differences are expressed using the follows outputs of interest:

- Number of Base Case survivors ($l_{x(b)}$) and the Number of Master Case survivors ($l_{x(m)}$)

- The Base Case cumulative number of years to be lived ($Tx(b)$) and the Master Case cumulative number of years to be lived ($Tx(m)$)

The results are presented as point estimates with posterior credible intervals to address model input parameter uncertainty. The model uses a Bayesian framework that employs MCMC

(Markov Chain Monte Carlo) techniques as described in Section 7.4.2.1 and the inputs and assumptions of the model are discussed in Section 7.4.2.2.7.

We also present results from sensitivity analyses conducted based on a systematic adjustment of input parameters obtained from the ALCS Claim Comprehension and Intention Study. Finally, results from the multiple-cohort approach analysis performed using the methodology described in Section 7.4.2.1.10 are presented. The multiple-cohort approach allows us to extend inferences from the single-cohort approach to a more heterogeneous population of interest, the U.S. male population.

As previously stated in Section 7.4.2.1.10, our justification for selecting U.S.-born males as our population of interest for our MRTPA is based on historical data that shows that the candidate product and similar products in this category have very low prevalence among females in the U.S., a trend that has been reported over a long period of time [NSDUH (2016)]. Furthermore, although the ALCS CCI core focus was on males, females were not excluded from the study. Female quotas were included in the study in order to balance demographic traits. The quotas were based on population proportions in the 2013-2014 Population Assessment of Tobacco and Health Public Use File data. Of the study respondents in the main sample, there was a low incidence of females in the exclusive MST user group (3.4%). After exposure to an ad with a claim, we see expressed intentions to use the candidate product differ between males and females. On a 6-point scale, ranging from "*Strongly Agree* to *Strongly Disagree,*" among current tobacco users (includes exclusive smokers, dual users, and exclusive MST users) the average intention score post-exposure is 3.59 for males and 2.31 for females. In the overall study population, the average post-exposure intention to use the candidate product is 3.03 for males and 1.78 females. If we consider those who have never used tobacco, the average intention score post-exposure is 1.37 for males and 1.22 for females. Among former tobacco users, the average intention score post-exposure is 1.28 for males and 1.22 for females. Overall, we see higher intention scores among males compared to females across user and non-user groups. Given the information presented, focusing solely on females who are non-users, we do not see women gravitating to the candidate product. When we compare expressed intention to use results in the test condition to the control condition at post-exposure, we do not see statistically significant differences in their expressed intentions to use the candidate product at pre and post-exposure to an ad. When we compare pre-exposure to post-exposure expressed intention to use, we do not see statistically significant differences among non-users. These findings indicate that an ad with or without a claim would not have an effect on female non-users' intention to use the candidate product.

We provide evidence that the modeling estimates herein come from applying valid and reliable modeling approaches and are based on reasonable data and assumptions.

7.4.2.3.1. Life Table Measurements: MST and Cigarette Use

Life tables are mathematical constructs that provide models of mortality (or more generally, "decrements" of any type). They are straightforward when dealing with overall all-cause mortality, but they become more complex when all-cause mortality estimates are differentiated by use-state parameters such as never-tobacco use, smoking, MST use, and

dual use. The additional complexity is valuable, as our goal is to examine the effect on life expectancy of adding an MRTP claim to an already marketed MST product. We believe our proposed MRTP will facilitate transitions from one tobacco product (i.e., cigarettes) to a less risky alternative (i.e., MST). In our model, we consider the differential impact of cigarette smoking and MST use on all-cause mortality, driven by estimated changes in transition rates that can occur upon market authorization of the proposed claim.

7.4.2.3.2. Estimating Differences in Outcomes of Interest Between Base and Master Case Scenarios

Estimating differences in outcomes of interest (all-cause mortality and cumulative additional years lived) between the Base Case and Master Case scenarios required us to estimate the change in transition probabilities that would occur in the Master Case compared with the Base Case. As discussed in Section 7.4.2.2.4, to estimate relative percent change in transition rates, we evaluated the percent difference between the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without modified risk claim) from pre- to post-ad exposure in the ALCS CCI Study. The estimated relative percent change was then applied to the transition rates used in the Base Case model to create the transition rates for the Master Case model. A detailed explanation is provided in Section 7.4.2.2.4.

Using the probabilities estimated from the Claim Comprehension & Intentions Study described in Section 7.3.2, we developed a Master "most-likely" Case to evaluate the effect of marketing MST with an MRTP claim on it.

The relative percent changes in transition rates estimated from the CCI Study and applied to the Base Case transition probabilities to produce the transition rates[6] used in the Master Case (i.e., our most likely scenario upon authorization of the modified risk claim) are listed below:

- probability of "Never-Tobacco Users" initiating use of the candidate product decreases by 5 percent from its Base Case value;

- probability of "Former MST Users" initiating use of the candidate product remains constant (i.e., 0 percent change from its Base Case value);

- probability of "Current MST Users" switching to Cigarette Smoking remains constant to its Base Case value.);

- probability of "Current Cigarette Smokers" initiating exclusive candidate product use increases by 21 percent from its Base Case value;

- probability of "Current Cigarette Smokers" initiating candidate product use but also continuing cigarette smoking (i.e., a Dual User) increases by 24 percent from its Base Case value;

- probability of "Dual User" switching to exclusive candidate product use increases by 6 percent from its Base Case value; and

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[6] Transition probabilities were rounded to the nearest percentage point.

- probability of "Dual User" switching to exclusive Cigarette Smoking remains constant to its Base Case value.

The impacts on two additional transition rates could not be estimated from the CCI Study, and reasonable assumptions were made in these instances:

- probability of "Would-be Cigarette Smokers" initiating candidate product use is assumed to be 1 percent in the Master Case (it is 0 percent in the Base Case); and

- probability of "Would-be Smoking Quitters" initiating candidate product use instead of completely quitting all tobacco use is assumed to be 5 percent in the Master Case (it is 0 percent in the Base Case).

As 'Would-be Cigarette Smokers' and 'Would-be Smoking Quitters' are two populations whose behavioral changes could not be estimated from the CCI Study, we conduct additional sensitivity analyses in Section 7.4.2.3.4 and Section 7.4.2.3.6 to study the effect the transitions for these populations. Based on the sensitivity analyses results, we determined the percent increases of 1 percent for 'Would-be Cigarette Smokers' and 5 percent for 'Would-be Smoking Quitters' were appropriate for the Master Case.

Using the aforementioned estimated and assumed changes, we constructed two abridged life tables, one for the Base Case scenario (Table 7.4.2-21) and one for the Master Case scenario (Table 7.4.2-22).

For the single-cohort approach, the two life tables provide the net effect of incorporating all the changes in transition probabilities described above on survival of our initial cohort of 1,000,000 males, who are followed through their life course, starting at age 13 years. We follow them using life table functions, which are described in Section 7.4.2.1.6 and, for our purposes, include:

l_x: The number of survivors reaching age x

$_nd_x$:   Deaths between age x and $x+n$

$_nq_x$:   Probability of dying between age x and $x+n$

$_nL_x$:   Expected person-years lived between age x and $x+n$

T_x: Expected remaining person-years at age x

e_x: Life expectancy at age x ($e_x = T_x/l_x$)

$_nm_x$ Age-specific death rate

The key function is $_nq_x$ is derived from the age-specific death rate ($_nm_x$) observed in the population from which a life table is constructed. The remaining functions ($_nL_x$, T_x, and e_x) are all derived from $_nq_x$. In our analysis of the modeling results, we compare results, namely, l_x and T_x, at selected ages between the Base Case and the Master Case in order to examine the impact of market authorization of the proposed modified risk claim.

Both the Base Case and Master Case life tables that we constructed represent "multiple decrements" because they represent deaths associated with the risks of different behaviors (Yusuf et al., 2014). In addition, because both the Base Case and Master Case life tables

allow movement into various "nonterminal" states, they are multistate life tables (i.e., life tables that allow multiple increments and multiple decrements) (Yusuf et al., 2014). For example, a person can transition out of the cigarette-use state at one point in time and, at a later point in time, can transition back into the cigarette-use state.

Table 7.4.2-21 is the life table for the Base Case. It serves as the reference to which the Master Case Scenario is compared. That is, the Base Case scenario provides the impact of survival in the face of the behaviors, risks, and transitions described previously, but in the absence of an MRTP claim on the MST product. Table 7.4.2-22 is the life table for the Master Case scenario, in which the candidate product has an MRTP claim.

As shown in Table 7.4.2-21 and for the single-cohort approach, there are 676,903 survivors at age 73 years from the initial cohort of 1,000,000 males, followed from age 13 years in the Base Case scenario. In the Master Case Scenario (Table 7.4.2-22), there are 678,023 survivors at age 73 years from the initial cohort of 1,000,000 males, followed from age 13 years.

Table 7.4.2-23 provides a comparison of the Base Case and Master Case outcomes from the single-cohort approach and demonstrates that there will be a net health benefit from authorization of the proposed modified risk claim. In Table 7.4.2-23, for example, there are 1,120 more survivors at age 73 years from the original 1,000,000-male cohort when marketing of MST with an MRTP claim. In addition, for the Base Case scenario, the initial cohort of 1,000,000 males is expected to live 59,914,223 person-years, while for the Master Case scenario, there are 59,881,367 person-years expected for the same initial cohort. This demonstrates that 32,856 more person-years are expected in the scenario where the proposed claim is authorized.

Table 7.4.2-21:   **Base Case Life Table for the Single-Cohort Approach**

AGE	l_x	$_nm_x$	$_nd_x$	$_nq_x$	$_nL_x$	T_x	e_x
13	1,000,000	0.002683	2,683	0.0026831	1,001,342	59,881,367	59.88
18	997,317	0.000674	3,354	0.003363424	4,978,194	58,880,026	59.04
23	993,963	0.000994	4,926	0.004956223	4,957,487	53,901,832	54.23
28	989,036	0.001511	7,442	0.007524396	4,926,553	48,944,346	49.49
33	981,594	0.002247	10,967	0.011172946	4,880,502	44,017,793	44.84
38	970,627	0.003313	15,947	0.016429792	4,813,157	39,137,291	40.32
43	954,680	0.004826	22,760	0.023840768	4,716,269	34,324,134	35.95
48	931,920	0.006407	29,382	0.031528152	4,585,751	29,607,864	31.77
53	902,538	0.008416	37,192	0.041207803	4,419,058	25,022,113	27.72
58	865,346	0.011258	47,367	0.054737052	4,207,204	20,603,055	23.81
63	817,980	0.015539	61,149	0.074755523	3,935,048	16,395,852	20.04

AGE	l_x	$_nm_x$	$_nd_x$	$_nq_x$	$_nL_x$	T_x	e_x
68	756,831	0.022323	79,929	0.105609415	3,580,618	12,460,804	16.46
73+	676,903	0.033604	104,693	0.154664326	3,115,456	8,880,185	13.12

Note that the life table underlying this extends to a final open-ended age group of 103+ years. The values shown above in this table for T73+ years and e73 years are calculated from the underlying life table. n=5 for this analysis.

Table 7.4.2-22:   Master Case Scenario Life Table for the Single-Cohort Approach

AGE	l_x	$_nm_x$	$_nd_x$	$_nq_x$	$_nL_x$	T_x	e_x
13	1,000,000	0.002683	2,683	0.0026831	1,001,342	59,914,223	59.91
18	997,317	0.000674	3,354	0.003363324	4,978,194	58,912,882	59.07
23	993,963	0.000993	4,921	0.004951293	4,957,499	53,934,688	54.26
28	989,041	0.001509	7,436	0.007518393	4,926,593	48,977,188	49.52
33	981,605	0.002244	10,953	0.011157744	4,880,594	44,050,596	44.88
38	970,653	0.003303	15,899	0.016379185	4,813,408	39,170,002	40.35
43	954,754	0.004799	22,638	0.023710501	4,716,950	34,356,594	35.98
48	932,117	0.006368	29,210	0.031337285	4,587,170	29,639,644	31.80
53	902,907	0.008363	36,978	0.040954185	4,421,444	25,052,474	27.75
58	865,929	0.011195	47,137	0.054435198	4,210,702	20,631,030	23.83
63	818,792	0.015471	60,950	0.074439201	3,939,619	16,420,329	20.05
68	757,842	0.022259	79,819	0.105323475	3,585,961	12,480,710	16.47
73+	678,023	0.033440	104,394	0.153968228	3,121,861	8,894,749	13.12

Note that the life table underlying this extends to a final open-ended age group of 103+ years. The values shown above in this table for T73+ years and e73 years are taken from the underlying life table. n=5 for this analysis.

Table 7.4.2-23:   Base Case and Master Case lx and Tx for the Single-Cohort Approach

Age (y)	Master Case Scenario Life Table		Base Case Life Table		Difference (Master Case – Base Case)	
	$l_{x(m)}$	$Tx(m)$	$l_{x(b)}$	$Tx(b)$	$l_{x(m-b)}$	$Tx(m-b)$
13	1,000,000	59,914,223	1,000,000	59,881,367	0	32,856
18	997,317	58,912,882	997,317	58,880,026	0	32,856
23	993,963	53,934,688	993,963	53,901,832	0	32,856
28	989,041	48,977,188	989,036	48,944,346	5	32,843
33	981,605	44,050,596	981,594	44,017,793	11	32,803
38	970,653	39,170,002	970,627	39,137,291	26	32,711

Age (y)	Master Case Scenario Life Table		Base Case Life Table		Difference (Master Case – Base Case)	
	$l_{x(m)}$	$Tx(m)$	$l_{x(b)}$	$Tx(b)$	$l_{x(m-b)}$	$Tx(m-b)$
43	954,754	34,356,594	954,680	34,324,134	74	32,461
48	932,117	29,639,644	931,920	29,607,864	197	31,780
53	902,907	25,052,474	902,538	25,022,113	369	30,361
58	865,929	20,631,030	865,346	20,603,055	583	27,975
63	818,792	16,420,329	817,980	16,395,852	812	24,477
68	757,842	12,480,710	756,831	12,460,804	1,010	19,906
73+	678,023	8,894,749	676,903	8,880,185	1,120	14,564

Note: The underlying life tables extend to a final open-ended age group of 103+ years. The values shown in this table for T73+ and e73 are taken from the underlying life table.

$l_{x(b)}$ = number of survivors at each age cohort in the Base Case; $Tx(b)$ = cumulative number of years of life remaining for the survivors in the Base Case; $l_{x(m)}$ = number of survivors at each age cohort in the Master Case; $Tx(m)$ = cumulative number of years of life remaining for the survivors in the Master Case; $l_{x(m-b)}$ = number of additional survivors at each age cohort; $Tx(m-b)$ = cumulative number of additional years of life lived by the additional survivors.

As the cohort in each scenario progressively ages, the differences (a net health benefit in our simulations) between the Base Case and the Master Case in persons surviving progressively increase from the 33- to 37-year group to the 68- to 72-year group. A key driver of the net accumulation of more years lived by those in the Master Case scenario is the years of life gained by being in a lower relative risk state (i.e., switching from cigarette smoking to use of the candidate product) compared with being in a higher relative-risk state (i.e., cigarette smoker). Although not shown here, if we followed the two cohorts beyond age 73 years, we would see a declining trend of differences between the Base Case and Master Case. This trend is similar to that observed in literature, Rostron reported that mortality HRs associated with smoking in males increase with age from 45 to 74 years before declining somewhat at older ages (Rostron, 2011). Since the outcome of interest for the ALCS cohort model is difference in all-cause mortality (measured by number of survivors between our Base Case and Master Case), for our scenario analysis, we focus our attention on the age group where the greatest cumulative difference in mortality between the Base Case and the Master Case would likely be observed (i.e., the age group starting at age 73 years).

7.4.2.3.3. Uncertainty Analysis and Understanding Impact of Varying Individual Transitions on Outcomes of Interest in the Single-Cohort Model

The model results are quantified as the mean difference and its corresponding 95% posterior credible interval that is formed from the 2.5% and 97.5% quantiles of 10,000 samples drawn from the posterior distribution of the parameters of interest (i.e., difference in number of survivors between the Base Case and the Master Case). The distributions of the mean differences are also presented.

Table 7.4.2-24 summarizes the differences in number of survivors between the Base Case and Master Case (Master Case - Base Case). The 95% credible interval is 958 to 1,301 additional survivors on a base of 676,903 at age 73 years. The 95% credible interval not containing zero presents a degree of statistical certainty to the modeling outcome, because it shows that incorporating uncertainty analyses still produces positive results and bounds the estimated mean difference of 1,120 additional survivors between our Master Case and the Base Case, between values of 958 and 1,301 additional survivors (i.e., run to run variability will not impact our modeling conclusions). The outcomes for each age group through age 73 years are shown in Table 7.4.2-24. The distribution of the estimated difference between the Master Case and Base Case scenarios at age 73 years, obtained from running the 10,000 posterior samples runs, is shown in Figure 7.4.2-11.

Table 7.4.2-24:   Base Case and Master Case Scenarios with 95% Credible Intervals

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Master Case)	Mean Difference in Number of Survivors [Master - Base] Case	Credible Interval
43	954,680	954,754	74	(64, 85)
48	931,920	932,117	197	(174, 221)
53	902,538	902,907	369	(324, 417)
58	865,346	865,929	583	(507,665)
63	817,980	818,792	812	(700, 936)
68	756,831	757,842	1,010	(866, 1169)
73	676,903	678,023	1,120	(958, 1301)

Note: Results are reported for ages 43 through 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.

Figure 7.4.2-11: **Distribution of "Difference in Number of Survivors at Age 73 Years" Between Master Case and Base Case Scenarios (n = 10,000)**
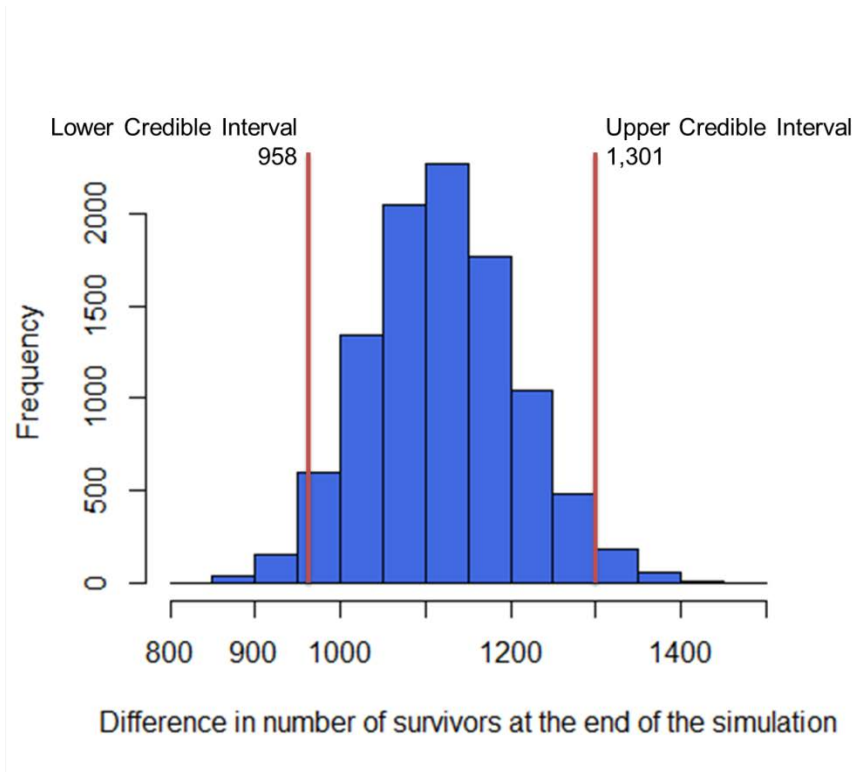
To demonstrate the contribution of each of the key individual transitions (identified from ALCS CCI study and the estimated subpopulations) probability on the overall net benefit observed (i.e., 1,120 additional survivors at age 73 years for the 1,000,000-male cohort followed from age 13 years), we present results from simulations comparing Base Case outcomes with a series of Modified Case scenarios. These seven Modified Case scenarios were constructed by varying one of the key individual transitions of interest at a time, while keeping all other transitions the same as those used in the Base Case (Table 7.4.2-25). Such an exercise is valuable in understanding the contribution, whether positive or negative, of each individual transition intervention to the additional survivors observed in the comparison between the Base Case and the Master Case scenarios.

The parameters applied to create the seven Modified Case scenarios discussed below are shown in Table 7.4.2-25. The second column shows all percentage changes as they are run in the Master Case model. In the third column "Never-Tobacco to MRTP," the percent change of -5% is isolated, with the remaining transitions unaltered (i.e., no change from their Base Case value). Similarly, in the fifth column, the "CIG to MRTP" transition of 21% to the Base Case value is isolated, with the remaining transitions controlled to 0%, and so forth.

Table 7.4.2-25: Parameters Used to Generate the Master Case Scenario and Seven Additional Modified Case Scenarios Where Only One Individual Transition Was Varied at a Time

State Transitions	Percent Changes Applied to the Base Case Transition Rates							
	Master Case	Modified Case 1: Never Tobacco → MRTP	Modified Case 2: FMST → MRTP	Modified Case 3: Would-be Smoker → MRTP	Modified Case 4: CIG → MRTP	Modified Case5: Cig Smoking Quitter → MRTP	Modified Case 6: CIG → DUAL	Modified Case 7: DUAL (MST + CIG) → MRTP
Never Tobacco → MRTP	-5%	-5%	0%	0%	0%	0%	0%	0%
FMST → MRTP	0%	0%	0%	0%	0%	0%	0%	0%
NS Would-be Smoker → MRTP	1%	0%	0%	1%	0%	0%	0%	0%
CIG → MRTP	21%	0%	0%	0%	21%	0%	0%	0%
Cig Smoking Quitter → MRTP	5%	0%	0%	0%	0%	5%	0%	0%
CIG -> DUAL	24%	0%	0%	0%	0%	0%	24%	0%
DUAL (MST + CIG) → MRTP	6%	0%	0%	0%	0%	0%	0%	6%

Analyzing the impact of individual transitions on the difference in number of survivors enables us to identify the transitions that have the greatest impact on the model's results. Table 7.4.2-26 and Table 7.4.2-27 summarize the results obtained by comparing the survival of the cohorts at age 73 years in each of the seven Modified Cases generated using the values in Table 7.4.2-25 with survival of the cohort at age 73 years in the Base Case. Since each of these transitions is altered individually and not simultaneously (as in the Master Case), the sum of these point estimates (1,116) differs slightly from the Master Case finding of 1,120 additional survivors.

Table 7.4.2-26: **Individual Transitions for Modified Cases based on the ALCS Claim Comprehension & Intentions Study Inputs: Point Estimates and 95% Credible Intervals**

Transitions	Percent Change in Transition Rates between Base Case and Modified Case	Model Estimate of Difference in Survivors (Modified Case – Base Case) at Age 73 y	Credible Interval for Modeling Estimates
Modified Case 1: Never-tobacco →MRTP	-5%	10	(-14, 36)
Modified Case 2: FMST → MRTP	0%	0	-
Modified Case 4: CIG → MRTP	+21%	425	(366, 489)
Modified Case 6: CIG → DUAL (MRTP + CIG)	+24%	282	(210, 363)
Modified Case 7: DUAL (MST + CIG) → MRTP	+6%	69	(60, 76)

ALCS = Altria Client Services LLC; CIG = cigarette smoker; DUAL = current cigarette smoker and current MRTP or MST user; FMST = former MST; MRTP = modified risk tobacco product; MST = moist smokeless tobacco.
Note: The MRTP transitions are intended to reflect transitions to MST at the category levels upon authorization of the proposed modified risk claim.

Table 7.4.2-27: **Individual Transitions That Cannot Be Estimated from the ALCS Claim Comprehension and Intention Study for Modified Cases: Point Estimates and 95% Credible Intervals**

Transitions	Absolute Percent Increase between Base Case and Modified Case	Model Estimate of Difference in Survivors (Modified Case – Base Case) at Age 73 y	Credible Interval for Modeling Estimates
Modified Case 3: Would-be Smoker → MRTP "Hypothetical"	+1%	393	(343, 443)
Modified Case 5: Would-be Smoking Quitter → MRTP "Hypothetical"	+5%	-63	(-101, -26)

MRTP = modified risk tobacco product.
These two subpopulations do not exist in the base case; hence, the percentages increase from zeros in the base case to the percentages reported in the table.

The results obtained by comparing the survival of the cohorts to age 73 years in each of the seven Modified Cases generated by varying individual transitions one at a time with survival of the cohort in the Base Case to age 73 years are discussed in the following sections.

7.4.2.3.3.1. Initiation: Nonusers Who Initiate Tobacco Use with the Proposed Product

7.4.2.3.3.1.1.   Modified Case 1: Transition from Never-User of Tobacco to Candidate Product User

As summarized in Table 7.4.2-5 and discussed in Section 7.4.2.2.4, we estimate a 5% relative percentage reduction in transition rate between the Base Case and Modified Case 1. We derive this value by comparing the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without the modified risk claim) from the CCI Study.

Modeling outputs obtained by comparing survivors in the Base Case with survivors in Modified Case 1, in which only the never-tobacco to MRTP transition rate was decreased by 5% while all other transition rates were held constant, averaged 10 additional survivors at age 73 years, with a credible interval of -14 to 36 (Table 7.4.2-28). Figure 7.4.2-12 shows the distribution of the mean differences and credible intervals from 10,000 runs.

We do not include a discussion for Modified Case 2 because the transition from Former MST Users to the candidate product user was estimated as zero.

Table 7.4.2-28:   **Mean Difference in Number of Survivors between Modified Case 1 and Base Case: Impact of Varying Only the Never-Tobacco to MRTP Transition**

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 1)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
43	954,680	954,686	6	(3, 10)
48	931,920	931,923	3	(-4, 10)
53	902,538	902,539	1	(-10, 13)
58	865,346	865,348	2	(-14, 18)
63	817,979	817,983	4	(-17, 25)
68	756,831	756,838	7	(-16, 32)
73	676,903	676,913	10	(-14, 36)

Note: Results are reported for ages 43 to 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.
MRTP = modified risk tobacco product.

Figure 7.4.2-12: Distribution of "Difference in Number of Survivors Between Modified Case 1 and Base Case At Age 73 Years" (N = 10,000): Impact of Varying Only the Never-Tobacco to MRTP Transition

Mean Difference in number of survivors at the end of the Simulation
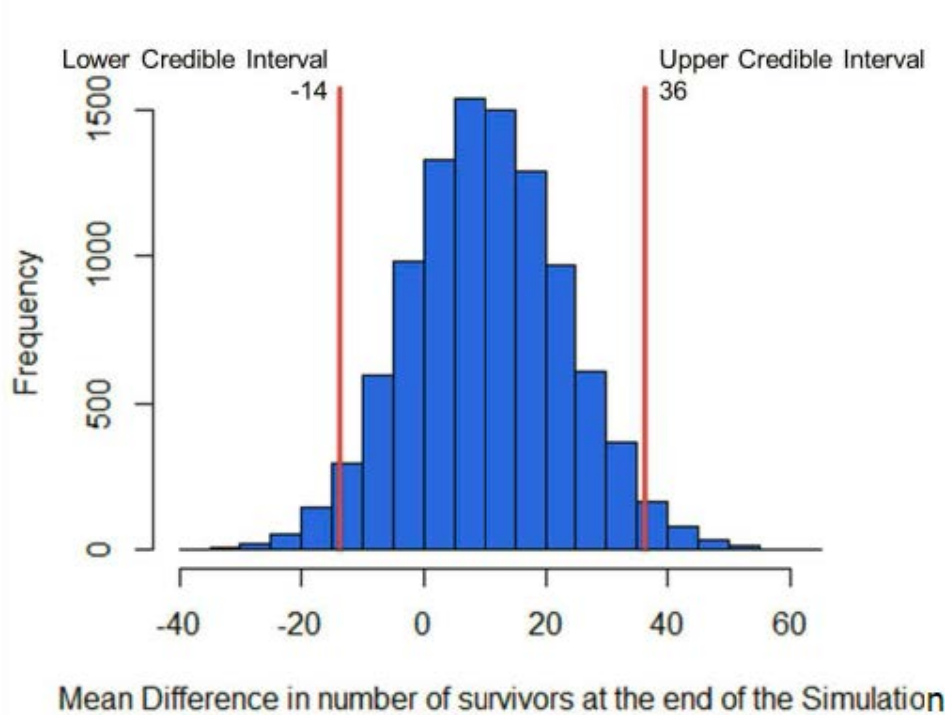
MRTP = modified risk tobacco product.

7.4.2.3.3.1.2. Modified Case 3: Transition from Would-Be Cigarette Smoker to MST User

"Would-be cigarette smokers" are adult never-users of tobacco who would otherwise initiate cigarette smoking, but in the Modified Case 3 initiate use of the candidate product instead of initiating smoking. Since this parameter is one that cannot be estimated from the CCI Study, we assume that the probability of initiating MRTP among would-be cigarette smokers is 1% upon market authorization of the proposed claim. Table 7.4.2-29 shows an average increase of 393 in the number of survivors at age 73 years, with a credible interval of 343 to 442 between the Modified Case 3 and Base Case scenarios. Figure 7.4.2-13 shows the distribution of the mean differences and credible intervals from 10,000 runs.

Table 7.4.2-29: **Mean Difference in Number of Survivors between Modified Case 3 and Base Case at Age 73 Years: Impact of Varying only the Would-Be Smoker to MRTP Transition**

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 3)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
43	954,680	954,765	85	(75, 95)
48	931,920	932,070	150	(133, 167)
53	902,538	902,760	222	(196, 246)
58	865,346	865,637	290	(256, 324)
63	817,980	818,327	348	(305, 389)
68	756,831	757,216	385	(337, 432)
73	676,903	677,295	393	(343, 442)

Note: Results are reported for ages 43 to 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.
MRTP = modified risk tobacco product.

Figure 7.4.2-13: **Distribution of "Difference in Number of Survivors between Modified Case 3 and Base Case at Age 73 Years" (n = 10,000): Impact of Varying only the Would-Be Smoker to MRTP Transition**
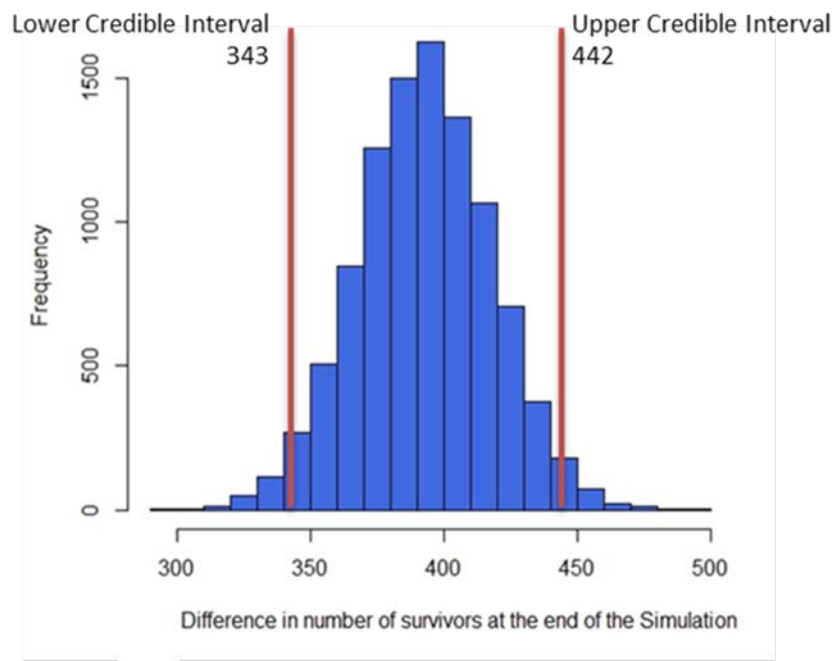
MRTP = modified risk tobacco product

7.4.2.3.3.2. Modified Case 4: Transition from a Smoker to an MST User

As summarized in Table 7.4.2-20 and discussed in Section 7.4.2.2.4, comparing the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without modified risk claim) from the CCI Study results in an estimated 21% relative percentage increase in the transition rate between the Base Case and the Modified Case 4.

Modeling outputs obtained by comparing survivors in the Base Case with survivors in the Modified Case 4, in which only the CIG to MRTP transition rate was increased by 21% while all other transition rates were held constant, averaged 425 more survivors at age 73 years with a credible interval of 366 to 489 (Table 7.4.2-30). Figure 7.4.2-14 shows the distribution of the mean differences and credible intervals from 10,000 runs.

Table 7.4.2-30:   **Mean Difference in Number of Survivors between Modified Case 4 and Base Case at Age 73 Years: Impact of Varying Only the CIG to MRTP Transition**

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 4)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
43	954,680	954,691	12	(9, 14)
48	931,920	931,965	46	(39, 52)
53	902,538	902,645	107	(92, 121)
58	865,346	865,540	194	(168, 221)
63	817,980	818,273	293	(254, 335)
68	756,831	757,211	380	(327, 435)
73	676,903	677,328	425	(366, 489)

Note: Results are reported for ages 43 to 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.
CIG = cigarette; MRTP = modified risk tobacco product.

Figure 7.4.2-14: **Distribution of "Difference in Number of Survivors between Modified Case 4 and Base Case at Age 73 Years" (n = 10,000): Impact of Varying only the CIG to MRTP Transition**

Mean Difference in number of survivors at the end of the Simulatio
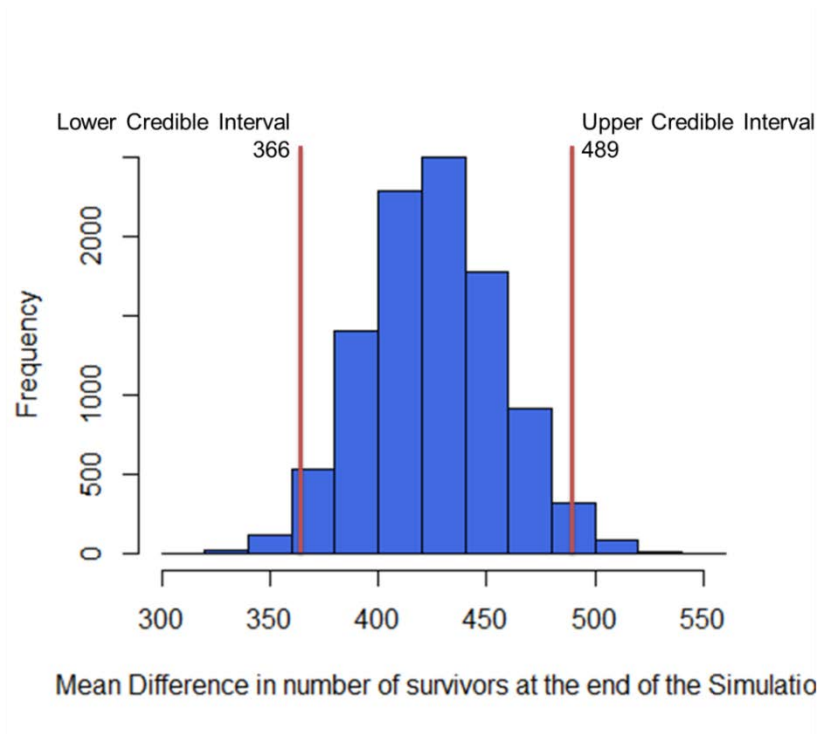
CIG = cigarette; MRTP = modified risk tobacco product.

7.4.2.3.3.3. Modified Case 5: Transition from a Would-Be Smoking Quitter to MST User

"Would-be Smoking Quitters" are adult cigarette smokers who would otherwise quit cigarette smoking, but in the Modified Case 5 initiate use of the candidate product instead of quitting all tobacco use. Since this parameter is one that is not estimable from the CCI Study, we assume that the probability of initiating MRTP among cigarette smoking quitters would be 5% upon authorization of the proposed claim. Figure 7.4.2-15 shows the distribution of the mean differences and the credible intervals. The number of survivors decreases by an average of 63, with credible interval of -99 to -26 at age 73 years (Table 7.4.2-31).

Table 7.4.2-31: **Mean Difference in Number of Survivors between Modified Case 5 and Base Case at Age 73 Years: Impact of Varying Only the CIG Smoking Quitter to MRTP Transition**

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 5)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
43	954,680	954,643	-37	(-43, -30)

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 5)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
48	931,920	931,886	-34	(-40, -28)
53	902,538	902,503	-35	(-45, -25)
58	865,346	865,307	-39	(-59, -20)
63	817,980	817,933	-47	(-75, -18)
68	756,831	756,775	-56	(-91, -20)
73	676,903	676,840	-63	(-99, -26)

Note: Results are reported for ages 43 to 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.
CIG = cigarette; MRTP = modified risk tobacco product.

Figure 7.4.2-15: **Distribution of "Difference in Number of Survivors Between Modified Case 5 and Base Case At Age 73 Years" (N = 10,000): Impact of Varying Only the CIG Smoking Quitter to MRTP Transition**
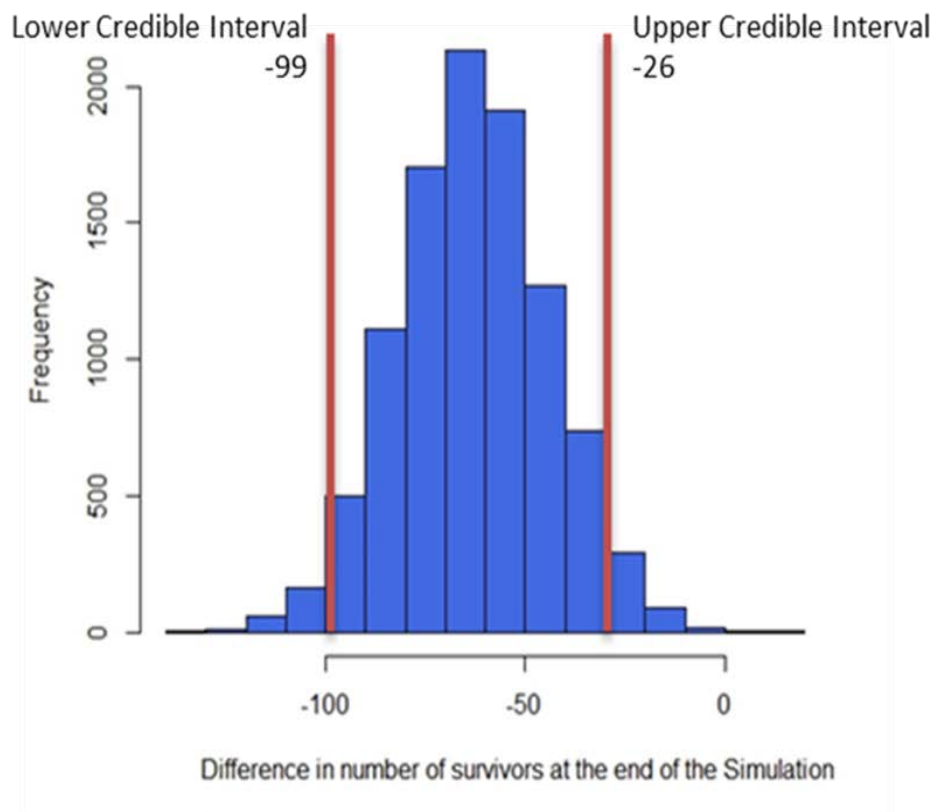
CIG = cigarette; MRTP = modified risk tobacco product.

7.4.2.3.3.4. Modified Case 6: Transition from Cigarette Smoker to Dual User

As summarized in Table 7.4.2-5 and discussed in Section 7.3.2, comparing the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without modified risk claim) in the CCI Study showed a 24% relative percentage increase in the transition rate between the Base Case and the Modified Case 6.

Modeling outputs obtained by comparing survivors in the Base Case to survivors in the Modified Case 6, in which only the CIG to DUAL Use (MRTP + CIG) transition rate was increased by 24% while all other transition rates were held constant, averaged 282 more survivors at age 73 years with a credible interval of 210 to 363 (Figure 7.4.2-16). Table 7.4.2-32 shows the distribution of the mean differences and credible intervals from 10,000 runs.

Table 7.4.2-32: **Mean Difference in Number of Survivors between Modified Case 6 and Base Case at Age 73 Years: Impact of Varying Only the CIG to DUAL Use (MRTP + CIG) Transition**

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 6)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
43	954,680	954,686	6	(3, 8)
48	931,920	931,944	24	(17, 32)
53	902,538	902,595	57	(41, 75)
58	865,346	865,451	105	(76, 138)
63	817,980	818,145	165	(120, 217)
68	756,831	757,060	229	(168, 299)
73	676,903	677,185	282	(210, 363)

Note: Results are reported for ages 43 to 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.
CIG = cigarette; MRTP = modified risk tobacco product.

Figure 7.4.2-16: **Distribution of "Difference in Number of Survivors Between Modified Case 6 and Base Case At Age 73 Years" (N = 10,000): Impact of Varying Only the CIG to DUAL Use (MRTP + CIG) Transition**
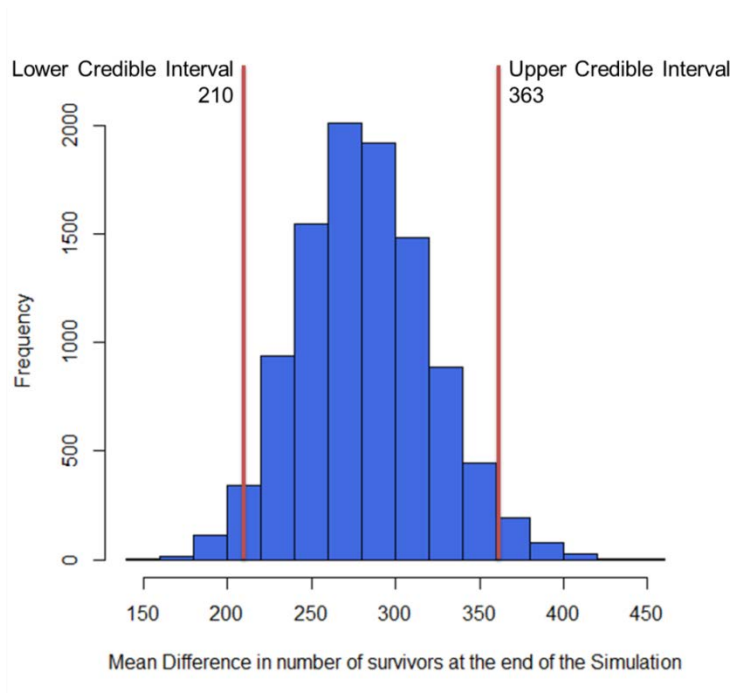
CIG = cigarette; MRTP = modified risk tobacco product.

7.4.2.3.3.5. Dual Use: Tobacco Users Who Use the Product in Conjunction with Other Tobacco Products

7.4.2.3.3.5.1. Modified Case 7: Transition from Dual User to Exclusive MRTP User

As summarized in Table 7.4.2-20 and discussed in Section 7.4.2.2.4, comparing the relevant responses of the test condition (exposed to the modified risk claim) and control condition (exposed without modified risk claim) from the CCI Study (Section 7.3.2), we estimate a 6% relative percentage increase in the transition rate between the Base Case and the Modified Case 7.

Modeling outputs obtained by comparing survivors in the Base Case to survivors in the Modified Case 7, in which only the Dual Use (MST + CIG) to MRTP transition rate was increased by 6% while all other transition rates were held constant, averaged 68 more survivors at age 73 years with a credible interval of 60 to 76 (Table 7.4.2-33). Figure 7.4.2-17 shows the distribution of the mean differences and credible intervals from 10,000 runs.

Table 7.4.2-33: **Modified Case 7: Mean Difference in Number of Survivors between Modified Case 7 and Base Case at Age 73 Years: Impact of Varying Only the Dual Use (MST + CIG) to MRTP Transition**

Age (y)	Mean Number of Survivors (Base Case)	Mean Number of Survivors (Modified Case 7)	Mean Difference in Number of Survivors [Modified – Base] Case	Credible Interval
43	954,680	954,681	2	(1, 2)
48	931,920	931,925	6	(5, 7)
53	902,538	902,552	15	(13, 16)
58	865,346	865,374	28	(25, 31)
63	817,980	818,024	45	(39, 50)
68	756,831	756,891	60	(52, 67)
73	676,903	676,971	68	(60, 76)

Note: Results are reported for ages 43 to 73 years. In the model, survival of the initial cohort of 1,000,000 males is followed in 5-year intervals, starting from age 13 years.
CIG = cigarette; MRTP = modified risk tobacco product; MST = moist smokeless tobacco.

Figure 7.4.2-17: **Distribution of "Difference in Number of Survivors Between Modified Case 7 and Base Case At Age 73 Years" (N = 10,000): Impact of Varying Only the DUAL Use (MST + CIG) to MRTP Transition**
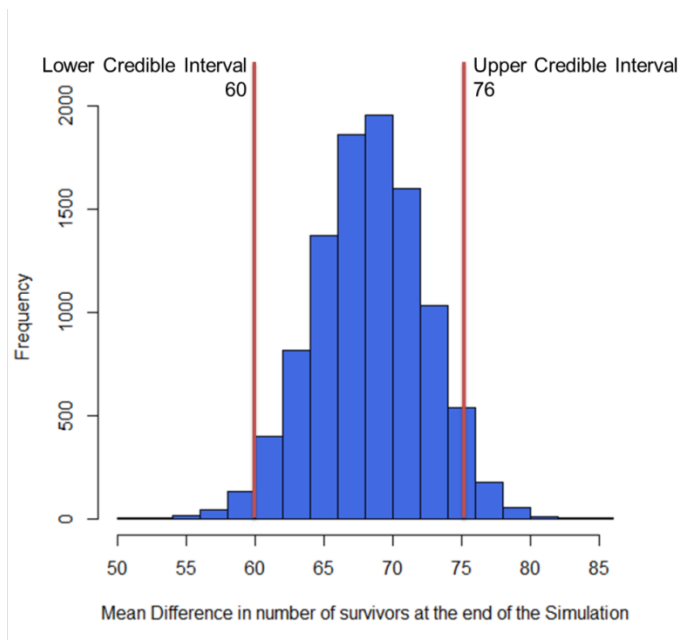
CIG = cigarette; MRTP = modified risk tobacco product; MST = moist smokeless tobacco.

7.4.2.3.3.6. Summarizing Contributions of Varying Individual Transitions to Overall Net Benefit

Sorting the individual point estimates in order of ascending benefit (i.e., increasing number of additional survivors between Modified Cases and Base Case scenarios at age 73 years) in Figure 7.4.2-18 allows us to understand the contribution of varying transitions related to individual populations of interest described in the MRTPA Draft Guidance to the overall net benefit of 1,120 additional survivors observed between the Master and Base Case scenarios at age 73 years.

Figure 7.4.2-18: **Mean Difference in Number of Survivors between Modified Cases and Base Case Scenarios at Age 73: Point Estimates and Credible Interval**
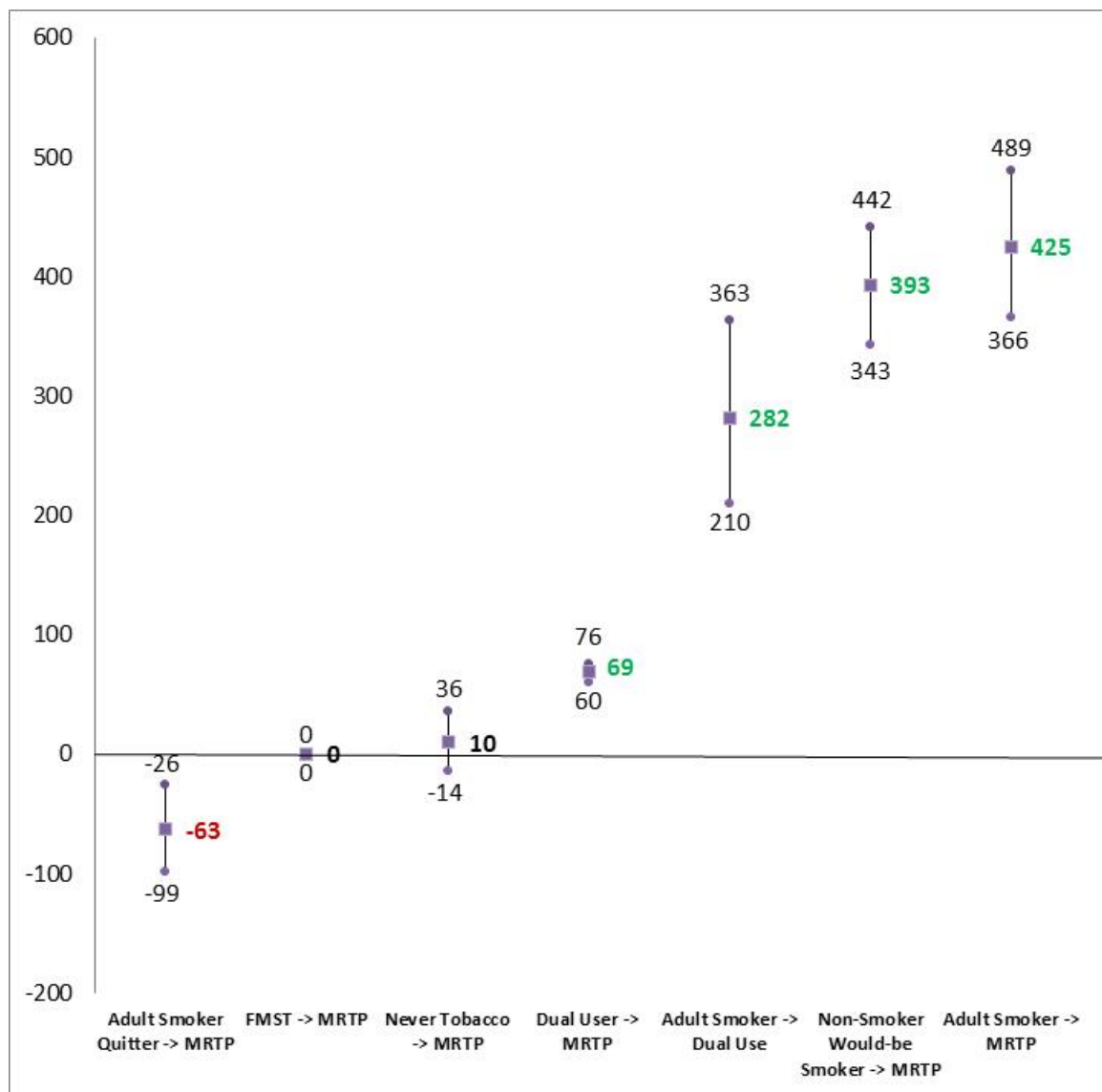
FMST = former moist smokeless tobacco user; MRTP = modified risk tobacco product

Under the conditions employed for scenario analyses with the model, the largest detrimental impacts (Figure 7.4.2-18) come from cigarette smokers who were intending to quit but decided to use the MRTP instead (63 fewer survivors).

The greatest benefits are realized (Figure 7.4.2-18) by moving members within the population from higher relative risks states, such as cigarette smoking and dual use, to lower relative risk states, such as MST use. As seen in Figure 7.4.2-18, under the conditions employed for scenario analyses with the model, the highest positive impact (425 additional survivors) arose from cigarette smokers switching to exclusive candidate product use. The benefits of intercepting smoking initiators and transitioning them to initiating the candidate product instead (393 additional survivors) and transitioning exclusive cigarette smokers to dual use (282 additional survivors) are of comparable magnitudes.

The next highest contribution to the net benefit comes from varying the dual users to exclusive candidate product use (69 additional survivors). As previously indicated, this transition rate increases by 6% with the market authorization of the modified risk claim. Although dual use and cigarette smoking states have comparable relative risks in the model, the benefit is probably realized due to changes in transition behavior. As indicated by the transition rates summarized from Tam et al. (2015) and other sources in Section 7.4.2.2.2, once a person is in dual use state, the probability of transitioning to the exclusive MST use state (i.e., lower relative risk state) is much higher compared with an exclusive smoker transitioning to exclusive MST use. For example, the 4-year adult transition rate from dual use to exclusive ST use is 17.4% as compared with the 4-year adult 1.4% transition rate from exclusive smoking to exclusive ST use (Table 7.4.2-18).

As seen in Figure 7.4.2-18, the changes in transition rates between the Base Case and the Modified Cases for both the (1) former MST users adopting the MRTP and (2) the rate for never tobacco users initiating the candidate product are very small and have minimal impact on the net benefit estimates (i.e., 0 and 10 additional survivors, respectively).

7.4.2.3.4. Sensitivity Analysis

The ALCS Cohort Modeling requires multiple input parameters, with assumptions concerning each of them (Section 7.4.2.2). Understanding how variations in input parameters could influence the model outcomes is important for understanding and interpreting the results. A commonly used approach to evaluate the effects of varying input parameters, and thus evaluate the underlying assumptions, is to conduct sensitivity analyses.

For the populations estimated within the CCI Study, we conducted the sensitivity analyses by varying the percentage change estimates of those who would switch from a candidate product *without* a claim (control condition) to a candidate product *with* a modified risk claim (test condition). The breadth of the sensitivity analysis is from 0 (assuming no change was observed between the pre-test to post-test populations) to 2 times the estimated percentage change (i.e., twice as big of a change as the actual percentage change value estimated from the CCI Study). It is important to note that, because the estimated percent change parameters estimated from the CCI Study vary in magnitude, the associated ranges considered in the

sensitivity analyses also vary (e.g., estimated percent changes that are small in magnitude will have a small range in the corresponding sensitivity analysis).

For the two untestable transitions (1) "Would-be Cigarette Smokers" initiating candidate product use instead of initiating smoking and (2) "Would-be Smoking Quitters" initiating candidate product use instead of completely quitting all tobacco use, which do not have a pre-claim to post-claim measurements in the CCI Study, the sensitivity analyses were conducted by varying the proportion of the population who may undergo these transitions.

A summary of the sensitivity analysis results obtained by varying the transition rates on seven individual transitions is shown in Table 7.4.2-34 and Table 7.4.2-35. The modeling results presented as point estimates are the same as the ones in Table 7.4.2-26 and Table 7.4.2-27 and discussed in detail in Section 7.4.2.3.4. The low and high estimates from the sensitivity analysis are presented in the corresponding columns.

Table 7.4.2-34: **Sensitivity Analysis: Mean Difference in Number of Survivors between Modified Cases based on Claim Comprehension & Intentions Study Inputs and Base Case at age 73 Years**

Transitions	Percentage Change Point Estimate (Percentage Change Range)	Mean Difference in Number of Survivors between Modified Case and Base Case at Age 73 y Point Estimate (Outcome Range based on Percentage Change Range)
Modified Case 1: Never-Tobacco → MRTP	-5% (-10% - 0%)	10 (-0, 21)
Modified Case 2: FMST → MRTP	0	-
Modified Case 4: CIG → MRTP	21% (0% - 42%)	425 (0, 844)
Modified Case 6: CIG → DUAL (MRTP + CIG)	24% (0% - 48%)	282 (0, 556)
Modified Case 7: DUAL (MST + CIG) → MRTP	6% (0% - 12%)	68 (0, 135)

CIG = cigarette; FMST = former MST; MRTP = modified risk tobacco product; MST = moist smokeless tobacco.

Table 7.4.2-35:   **Sensitivity Analysis: Mean Difference in Number of Survivors Between Modified Cases That Cannot Be Estimated from the ALCS Claim Comprehension & Intentions Study and Base Case at Age 73 Years**

Transitions	Absolute Percentage Increase Between Base Case and Modified Case[1] (Absolute Percentage Increase Range)	Mean Difference in Number of Survivors Between Modified Case and Base Case at Age 73 y Point Estimate (Outcome Range Based on Absolute Percentage Increase Range)
Modified Case 3: Would-be Smoker → MRTP "Hypothetical"	1% (0% - 5%)	393 (0, 1,963)
Modified Case 5: Would-be Smoking Quitter → MRTP "Hypothetical"	5% (0% - 10%)	-63 (-126, 0)

[1]These two hypothetical populations do not exist in the base case so the percentages increase from zeros in the base case to the percentages reported in the table.
CIG = cigarette; FMST = former MST; MRTP = modified risk tobacco product; MST = moist smokeless tobacco.

The results obtained by comparing the survival of the cohorts at age 73 years in the Modified Cases generated by varying individual transitions one at a time with survival of the cohort in the Base Case at age 73 years are discussed in detail below.

7.4.2.3.4.1. Sensitivity Analysis of Modified Case 1: Never-Users of Tobacco Initiating MST

In this sensitivity analysis for the Never-Tobacco to MRTP transition, we generated multiple Modified Case scenarios by varying the percent change factor that is applied to the Base Case transition rate to generate a range of potential transition rates for the Modified Case scenarios.

As shown in Table 7.4.2-36 and discussed in detail in Section 7.4.2.2.4, the percent change factor estimated for this transition from the CCI Study was -5% over the Base Case value. For this sensitivity analysis, the potential values over which the percent change factor was varied ranged from -10% to 0% (i.e., 2 times the value estimated from the CCI Study). The results are presented in Figure 7.4.2-19 and Table 7.4.2-36. The solid line in Figure 7.4.2-19 represents the point estimates, and the dashed lines represent the 95% credible intervals.

In this case, the estimated relative percent change factor of -5% results in 10 additional survivors at age 73 years as indicated by the vertical line at -5% on the x-axis of Figure 7.4.2-19. Sensitivity analysis shows that if we vary the percent change factor by ±1% (i.e., make it -6% or -4%), it would vary the model outcomes minimally, with number of survivors ranging from 8 to 12 additional survivors. Doubling the percent change factor to -10% results in approximate doubling of the outcome (i.e., 21 additional survivors, as shown by the second vertical line at -10% on the x-axis in Figure 7.4.2-19).

The results in Table 7.4.2-37 as discussed below are reasonable to support what is expected under the full potential range of these transition probabilities. If the transition probability did not decrease at all, the difference in survivors at age 73 years between the Modified Case and Base Case scenarios would still be an additional 1,109 additional survivors. If the transition probability is decreased by 5%, the difference increases to 1,120 and if decreased by 10%, the difference increases to 1,132.

Figure 7.4.2-19: **Sensitivity Analysis of Modified Case 1 Never-Tobacco Users Initiating Candidate Product**
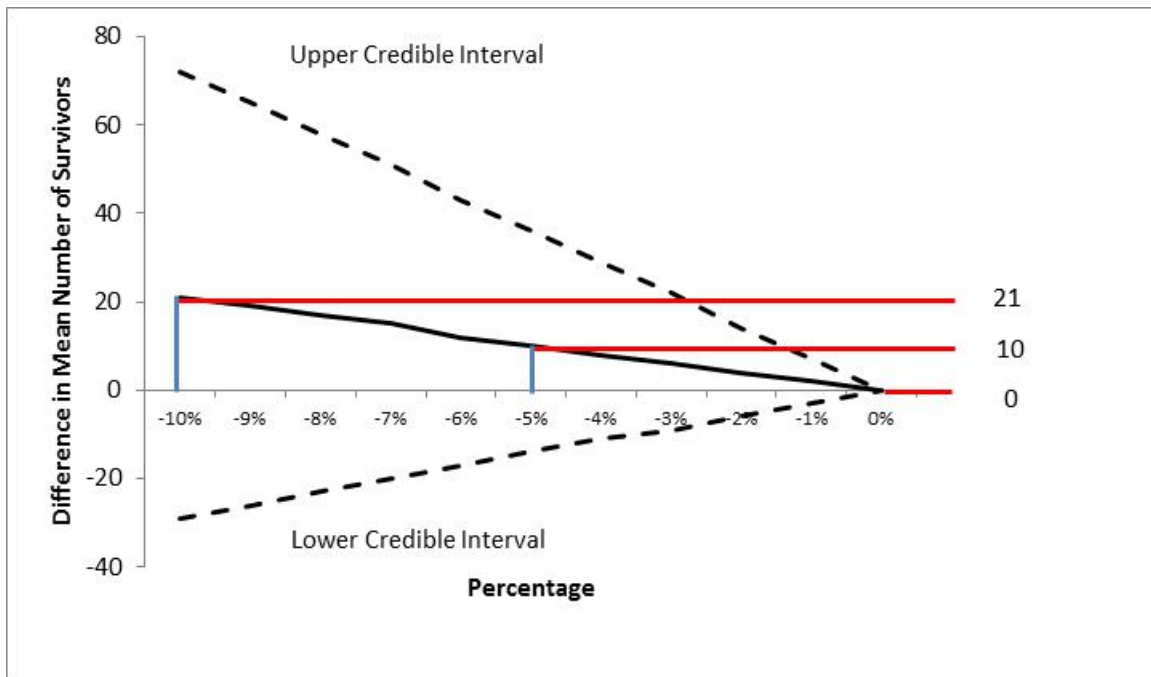
MRTP = modified risk tobacco product.

Table 7.4.2-36: **Sensitivity Analysis of Modified Case 1 Never-Tobacco Users Initiating Candidate Product**

Percentage Change from Base Case	Change in Number of Survivors
-10%	21
-9%	19
-8%	17
-7%	15
-6%	12

Percentage Change from Base Case	Change in Number of Survivors
-5%	10
-4%	8
-3%	6
-2%	4
-1%	2
0%	0

MRTP = modified risk tobacco product; MST moist smokeless tobacco.

Table 7.4.2-37: **Sensitivity Analysis of Modified Case 1: Never-Tobacco Users Initiating Candidate Product: Varying Transition Probability for Never-Tobacco Users to MRTP Transition, While Keeping All Other Transitions the Same as Those in Used in the Master Case**

Percentage Increase	Mean Difference in Number of Survivors between Modified Case 1 and Base Case Scenarios at age 73
-10%	1,132
-9%	1,129
-8%	1,127
-7%	1,125
-6%	1,123
-5% (Master Case)	1,120
-4%	1,118
-3%	1,116
-2%	1,114
-1%	1,111
0%	1,109

MRTP = modified risk tobacco product; MST = moist smokeless tobacco

7.4.2.3.4.2. Sensitivity Analysis of Modified Case 3: Would-Be Smokers Initiating MST Use Instead of Initiating Smoking

Since the Would-Be Smoker to MRTP transition is an unmeasurable transition (i.e., from a research perspective, it would not be possible to accurately sample and study people with a hypothetical future behavior), we do not have pre-claim to post-claim estimates for this

transition from the CCI Study. For the Master Case scenario (i.e., our estimate of the most likely scenario), we assumed a value of 1% for this transition.

The results from sensitivity analysis are presented in Figure 7.4.2-20 and Table 7.4.2-38. The solid line in Figure 7.4.2-20 represents the point estimates and dashed lines represent the 95% credible intervals. In this case, our estimated 1% percent change results in 393 additional survivors at age 73 years as indicated by the vertical line corresponding to 1% on the x-axis in Figure 7.4.2-20. Sensitivity analysis shows that a 1% point increase in this transition rate from 1% to 2% would impact the model outcomes substantially, with number of survivors increasing to 785, and an increase to 5% would result in 1,963 additional survivors at age 73 between the Modified Case and the Base Case as shown by the second vertical line at 5% on the x-axis in Figure 7.4.2-20.

We observed that varying the rates for this transition provides the largest gain amongst all other transitions (Table 7.4.2-38) and, consequently, subjected it to further review. In an alternate sensitivity analysis approach, we developed multiple Modified Case scenarios by varying the Would-be Smoker to MRTP transition, while keeping all other transitions the same as those in used in the Master Case, described in Section 7.4.2.3.2. For the Master Case scenario, we estimated a value of 1% for this transition. For this sensitivity analysis, we varied the potential value for this transition rate over the entire range from 0% (worst-case scenario) to 100% (best-case scenario). The results are presented in Table 7.4.2-39.

The results in Table 7.4.2-39, as discussed above, are reasonable to support the assumption that was made for this scenario shows what is expected under the full potential range of these transition probabilities. If the transition probability did not increase at all, the difference in survivors at age 73 years between the Modified Case and Base Case scenarios would still be an additional 1,074 survivors. If the transition probabilities are increased to 1%, the difference increases to 1,120 and so on to a hypothetical increase to 100%, which results in a difference of 39,466 additional survivors at age 73 years.

Figure 7.4.2-20: **Sensitivity Analysis of Modified Case 3: Would-Be Smokers Initiating to Candidate Product Use, Instead of Smoking: Varying Transition Probability for Would-Be Smoker to MRTP Transition, While Keeping All Other Transitions the Same as Those in Used in the Base Case.**
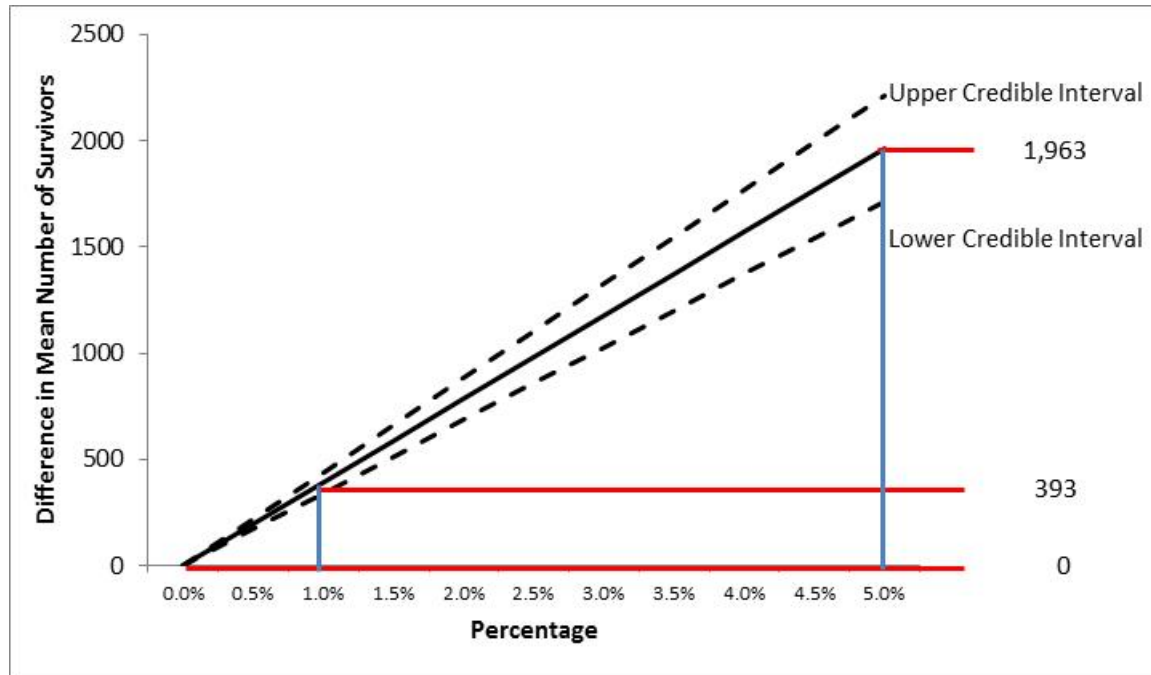
MRTP = modified risk tobacco product.

Table 7.4.2-38: **Sensitivity Analysis of Modified Case 3: Would-be Smokers Initiating Candidate Product**

Percentage Increase	Change in Number of Survivors
0.0%	0
0.5%	196
1.0%	**393**
1.5%	589
2.0%	785
2.5%	981
3.0%	1,178
3.5%	1,374
4.0%	1,570

Table 7.4.2-38: **Sensitivity Analysis of Modified Case 3: Would-be Smokers Initiating Candidate Product (Continued)**

Percentage Increase	Change in Number of Survivors
4.5%	1,767
5.0%	1,963

Table 7.4.2-39: **Sensitivity Analysis of Modified Case 3: Would-Be Smokers Initiating Candidate Product Instead of Smoking: Varying Transition Probability for NS Would-Be Smoker to MRTP Transition, While Keeping All Other Transitions the Same as Those in Used in the Master Case**

Percentage Increase	Mean Difference in Number of Survivors between Modified Case 3 and Base Case Scenarios at age 73
0%	733
1% (Master Case assumption)	1,120
5%	2,670
10%	4,606
20%	8,480
40%	16,226
60%	23,973
80%	31,719
100%	39,466

MRTP = modified risk tobacco product; NS = Nonsmoker

7.4.2.3.4.3. Sensitivity Analysis of Modified Case 4: Current Cigarette Smokers Switching to MST Use

In this sensitivity analysis for the CIG to MRTP transition, multiple Modified Case scenarios were generated by varying the percent change factor that is applied to the Base Case transition rate to generate a range of potential transition rates.

As shown in Table 7.4.2-40 and discussed in detail in Section 7.4.2.2.4, the percent change factor estimated for this transition from the CCI Study was 21% from the Base Case transition rate. For this sensitivity analysis, the potential values over which the percent change factor was varied from 0% to 42% (i.e., 2 times the value estimated from the CCI Study). The results are presented in Figure 7.4.2-21 and Table 7.4.2-40. The solid line in the figure represents the point estimates, and the dashed lines represent the 95% credible intervals.

In this case, the estimated relative percent change factor of 21% results in 425 additional survivors at age 73 (see vertical line corresponding to 19% on the x-axis in Figure 7.4.2-21).

Sensitivity analysis shows that if we vary the percent change factor by ±1% (i.e., make it 22% or 20%), it would vary the number of survivors by +20 or -20, respectively. Doubling the percent change factor to 42% results in an approximate doubling of the outcome (i.e., 844 additional survivors, as shown by the second vertical line at 42% on the x-axis in Figure 7.4.2-21).

The results in Table 7.4.2-41 as discussed below are reasonable to support what is expected under the full potential range of these transition probabilities. If the transition probability did not increase at all, the difference in survivors at age 73 years between the Modified Case and Base Case scenarios would still be an additional 620 additional survivors. If the transition probability is increased by 21%, the difference increases to 1,120 and to 1,611 if increased by 42%.

Figure 7.4.2-21:   Sensitivity Analysis of Modified Case 4: Current Cigarette Smokers Switching to Candidate Product Use
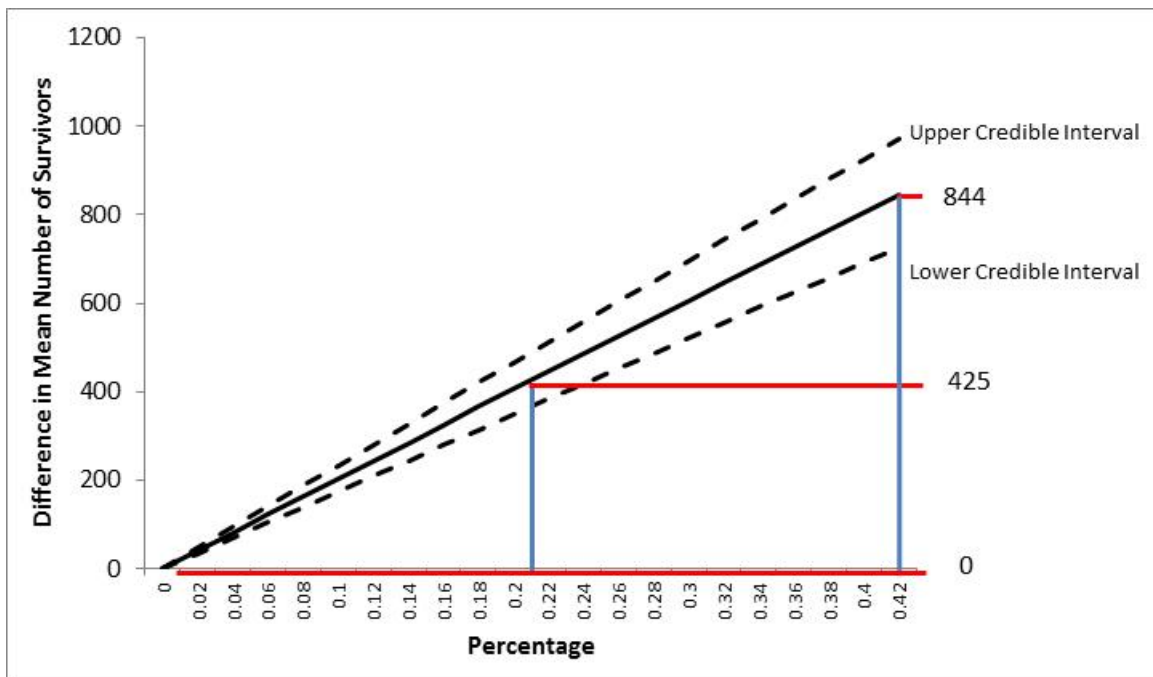
Table 7.4.2-40: **Sensitivity Analysis of Modified Case 4: Current Cigarette Smokers Switching to Candidate Product Use**

Percentage Change from Base Case	Change in Number of Survivors
0%	0
2%	41
4%	82
6%	122
8%	163
10%	203
12%	244
14%	284
16%	325
18%	365
20%	405
21%	425
22%	445
24%	486
26%	526
28%	566
30%	606
32%	646
34%	685
36%	725
38%	765
40%	804
42%	844

Table 7.4.2-41: **Sensitivity Analysis of Modified Case 4: Current Cigarette Smokers Switching to Candidate Product Use: Varying Transition Probability for Current Cigarette Users to MRTP Transition, While Keeping All Other Transitions the Same as Those in Used in the Master Case**

Percentage Increase	Mean Difference in Number of Survivors between Modified Case 4 and Base Case Scenarios at age 73
0%	620
6%	764
12%	907
18%	1,049
21% (Master Case)	1,120
24%	1,191
30%	1,332
36%	1,472
42%	1,611

MRTP = modified risk tobacco product

7.4.2.3.4.4. Sensitivity Analysis of Modified Case 5: Would-Be Smoking Quitters Initiating the Candidate Product

The CIG Smoking Quitter to MRTP transition is the second unmeasurable transition rate (i.e., from a research perspective, it would not be possible to accurately sample and study people with a hypothetical future behavior), for which we do not have pre-claim to post-claim estimates from the CCI Study. For the Master Case scenario (i.e., our estimate of the most likely scenario), we assumed a value of 5% for this transition.

The results from sensitivity analysis are presented in Figure 7.4.2-22 and Table 7.4.2-42. The solid line in the figure represents the point estimates, and the dashed lines represent the 95% credible intervals. In this case, our estimated 5% change results in 63 fewer survivors at age 73 years as indicated by the vertical line at 5% on the x-axis in Figure 7.4.2-22. Our sensitivity analysis shows that a 1% point increase or decrease in this transition rate, i.e. varying between 6% and 4%, results in the number of survivors decreasing or increasing by 13, respectively. An increase to 10% would result in 126 fewer survivors at age 73 years as shown by the second vertical line at 10% on the x-axis in Figure 7.4.2-22.

We observed that varying the rates for this transition provides the largest loss amongst all other transitions (Table 7.4.2-42) and subjected it to further review. In an alternate sensitivity analysis approach, we developed multiple Modified Case scenarios by varying the NS Would-be Smoker to MRTP transition while keeping all other transitions the same as those in used in the Master Case described in Section 7.4.2.3.2. For the Master Case scenario, we had estimated a value of 5% for this transition (i.e., our estimate of the most likely scenario). For

this sensitivity analysis, we varied the potential value for this transition rate over the entire range from 0% to 100%. The results are presented in Table 7.4.2-43. By presenting the full range of hypothetical transition probabilities, we again establish a level of transparency for the assumption that was made for the Master Case scenario.

Because the scenario is hypothetical, we look again at an extreme case, which, in this case, is a transition probability of 100% (i.e., assuming every smoker who was intending to quit switched to the candidate product use instead). The results indicate that, even under this extreme scenario, addition of an MRTP label claim to the candidate product would still yield a net positive benefit of 368 additional survivors due to positive contributions from other favorable changes in transition rates.

Figure 7.4.2-22:   Sensitivity Analysis of Modified Case 5: Would-Be Smoking Quitters Initiating the Candidate Product, Instead of Quitting All Tobacco Use: Varying Transition Probability for CIG Smoking Quitter to MRTP Transition While Keeping All Other Transitions the Same as Those Used in the Base Case
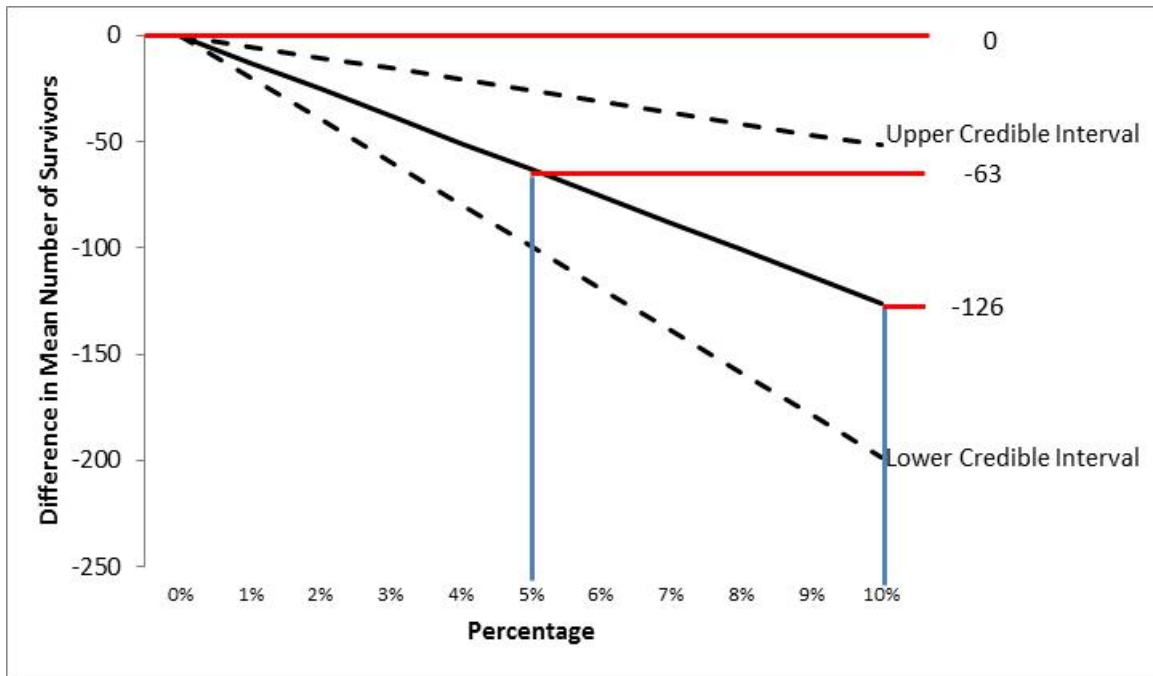
CIG=Cigarette; MRTP = modified risk tobacco product.

Table 7.4.2-42: **Sensitivity Analysis of Modified Case 5: Would-be Smoking Quitters Initiating the Candidate Product, Instead of Quitting all Tobacco Use**

Percentage Increase	Change in Number of Survivors
0%	0
1%	-13
2%	-25
3%	-38
4%	-50
5%	**-63**
6%	-76
7%	-88
8%	-101
9%	-113
10%	-126

Table 7.4.2-43: **Hypothetical Population Sensitivity Analysis of Modified Case 5: Smoking Quitters Initiating Candidate product: Varying Transition Probability for CIG Smoking Quitter to MRTP Transition, while Keeping All Other Transitions the Same as Those Used in the Master Case**

Percentage Increase	Mean Difference in Number of Survivors
0%	1,177
5% (Master Case assumption)	1,120
10%	1,063
20%	949
40%	721
60%	493
80%	265
100%	37

CIG = cigarette; MRTP = modified risk tobacco product

7.4.2.3.4.5. Sensitivity Analysis of Modified Case 6: Current Cigarette Smoking to Dual Use Transition

In this sensitivity analysis for the CIG to DUAL use (MRTP + CIG) transition, multiple Modified Case scenarios were generated by varying the percent change factor that is applied

to the Base Case transition rate to generate a range of potential transition rates for the Modified Case scenarios.

As shown in Table 7.4.2-44 and discussed in detail in Section 7.4.2.2.4, the percent change factor estimated for this transition from the CCI Study was 24% from the Base Case value. For this sensitivity analysis, the potential values over which the percent change factor was varied ranged from 0% to 48% (i.e., 2 times the value estimated from the CCI Study). The results are presented in Figure 7.4.2-23 and Table 7.4.2-45. The solid line in Figure 7.4.2-23 represents the point estimates, and the dashed lines represent the 95% credible intervals.

In this case, the estimated relative percent change factor of 24% results in 282 additional survivors at age 73 years as indicated by the vertical line at 24% on the x-axis in Figure 7.4.2-23. Sensitivity analysis shows that if we vary the percent change factor by ±1% (i.e., make it 25% or 23%), it would vary the number of survivors by +12 or -12, respectively. Doubling the percent change factor to 48% results in an approximate doubling of the outcome (i.e., 556 additional survivors, as shown by the second vertical line at 48% on the x-axis in Figure 7.4.2-23).

The results in Table 7.4.2-45 as discussed below are reasonable to support what is expected under the full potential range of these transition probabilities. If the transition probability did not increase at all, the difference in survivors at age 73 years between the Modified Case and Base Case scenarios would still be an additional 762 additional survivors. If the transition probability is increased by 24%, the difference in number of lives saved increases to 1,120 and if increased by 48%, the number of lives saved increases to 1,465.

Figure 7.4.2-23: **Sensitivity Analysis of Modified Case 6: Varying Transition Rate of Current Cigarette Smoking Transiting to Dual Use**
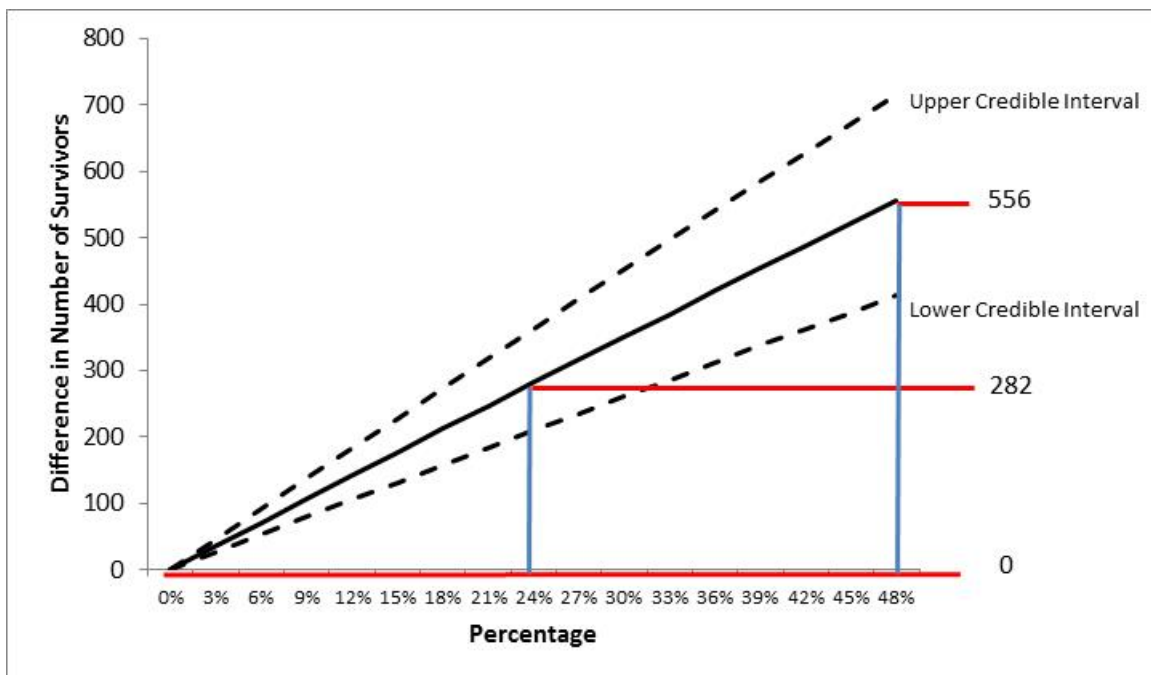
Table 7.4.2-44: **Sensitivity Analysis of Modified Case 6: Mean Survivors: Varying Transition Rates of Current Cigarette Smokers Transitioning to Dual Use**

Percentage Change from Base Case	Change in Number of Survivors
0%	0
3%	36
6%	71
9%	107
12%	142
15%	177
18%	212
21%	247
23%	270
24%	282
25%	294
27%	317
30%	351
33%	385
36%	420
39%	454
42%	488
45%	522
48%	556

Table 7.4.2-45: **Sensitivity Analysis of Modified Case 6: Current Cigarette Smokers Switching to Dual Use: Varying Transition Probability for Current Cigarette Smokers to Dual Use Transition, While Keeping All Other Transitions the Same as Those Used in the Master Case**

Percentage Increase	Mean Difference in Number of Survivors between Modified Case 6 and Base Case Scenarios at age 73
0%	762
3%	808
6%	853

Percentage Increase	Mean Difference in Number of Survivors between Modified Case 6 and Base Case Scenarios at age 73
9%	898
12%	943
15%	988
18%	1,032
21%	1,076
24% (Master Case)	1,120
27%	1,164
30%	1,208
33%	1,251
36%	1,294
39%	1,337
42%	1,380
45%	1,423
48%	1,465

7.4.2.3.4.6. Sensitivity Analysis of Modified Case 7: Dual Use to Exclusive MST Use

In this sensitivity analysis for the DUAL Use (MST + CIG) to MRTP transition, multiple Modified Case scenarios were generated by varying the percent change factor that is applied to the Base Case transition rate, to generate a range of potential transition rates for the Modified Case scenarios.

As shown in Table 7.4.2-46 and discussed in detail in Section 7.4.2.2.4, the percent change factor estimated for this transition from the CCI Study was 6% from the Base Case value. For this sensitivity analysis, the potential values over which the percent change factor was varied ranged from 0% to 12% (i.e., 2 times the value estimated from the ALCS Claim Comprehension and Intention Study). The results are presented in Figure 7.4.2-24 and Table 7.4.2-46. The solid line in Figure 7.4.2-24 represents the point estimates, and the dashed lines represent the 95% credible intervals.

In this case, the assumed estimated percent change factor of 12% results in 68 additional survivors at age 73 years as indicated by the vertical line at 6% on the x-axis in Figure 7.4.2-24. Sensitivity analysis shows that if we vary the percent change factor by ±1% (i.e., make it 7% or 5%), it would vary the number of survivors by +11 or -11, respectively. An extreme increase driven by doubling the percent change factor to 12% would result in approximately 135 additional survivors compared with to the assumed value of 6% (i.e., see second vertical line corresponding to 12% on the x-axis and 135 additional survivors on the y-axis in Figure 7.4.2-24).

The results in Table 7.4.2-47 as discussed below are reasonable to support what is expected under the full potential range of these transition probabilities. If the transition probability does not increase at all, the difference in survivors at age 73 years between the Modified Case and Base Case scenarios would still be an additional 1,033 additional survivors. If the transition probability is increased by 6%, the difference increases to 1,120 and if increased by 12%, the difference increases to 1,204.

Figure 7.4.2-24: **Sensitivity Analysis of Modified Case 7: Dual Use to Exclusive Candidate Product Use**
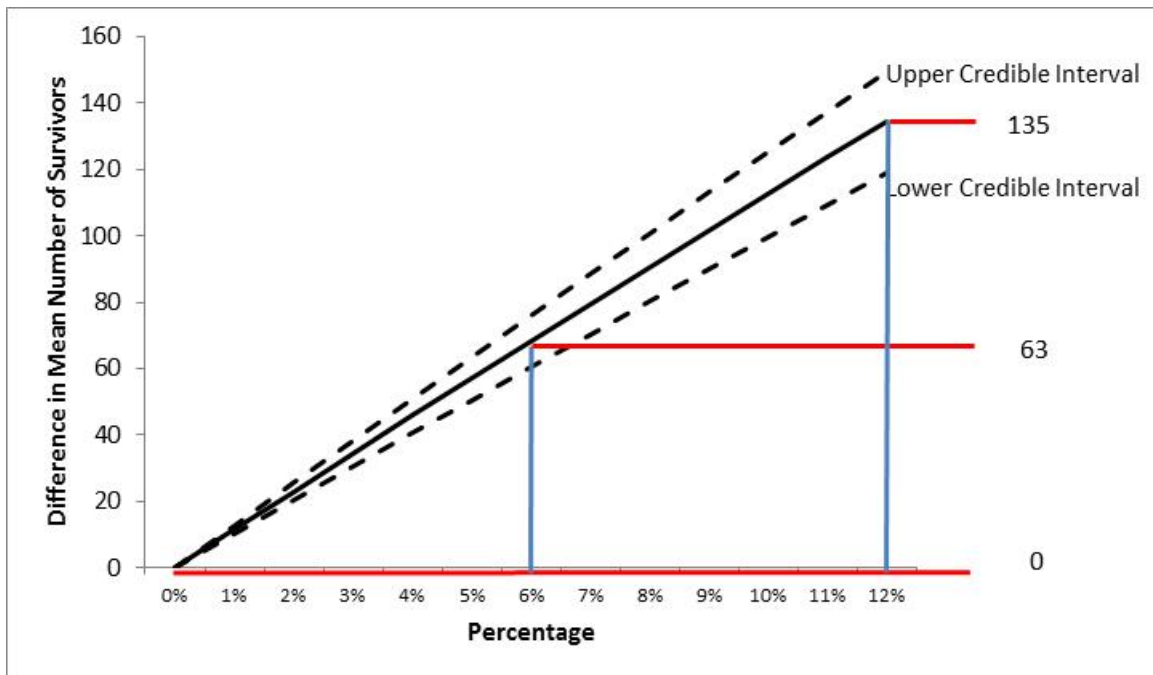
Table 7.4.2-46: **Sensitivity Analysis of Modified Case 7: Dual Users Switching to Candidate Product Use**

Percentage Change from Base Case	Change in Number of Survivors
0%	0
1%	12
2%	23
3%	34
4%	46
5%	57
6%	68
7%	80

Percentage Change from Base Case	Change in Number of Survivors
8%	91
9%	102
10%	113
11%	124
12%	135
68%	663
72%	695

Table 7.4.2-47:   **Sensitivity Analysis of Modified Case 7: Dual Users Switching to Candidate Product Use: Varying Transition Probability for Dual Users to MRTP Transition, While Keeping All Other Transitions the Same as Those Used in the Master Case**

Percentage Increase	Mean Difference in Number of Survivors between Modified Case 7 and Base Case Scenarios at age 73
0%	1,033
2%	1,063
4%	1,092
6% (Master Case)	1,120
8%	1,149
10%	1,177
12%	1,204

MRTP = modified risk tobacco product

7.4.2.3.5. Multiple-Cohort Analysis

As demonstrated in the previous sections, single-cohort models are a feasible and justifiable tool for understanding the impact of behavioral changes resulting from market authorization of the proposed claim. Following well-defined cohorts allows us to monitor the impact of these behavioral changes on specific health outcomes, such as all-cause mortality and years of lives saved, and to infer causation. In the single-cohort approach, we followed survival of a hypothetical cohort of 1,000,000 males from age 13 years through their life course under a Base Case scenario (representative of the current market, where cigarette and MST coexist) and a Master Case scenario (representative of the market after FDA authorization of the proposed claim). An additional 1,120 survivors existed in the Master Case scenario at age 73 years, demonstrating a net beneficial impact from authorization of the proposed claim. A major limitation of the single-cohort approach, however, is the inability to translate the net

benefit of 1,120 survivors to our population of interest, which, in the context of this MRTPA, is the U.S.-born male population.

As discussed and validated in Section 7.4.2.1.10, we implemented a multiple-cohort approach as a way to extend inferences from a single-cohort approach to a heterogeneous population. In the multiple-cohort approach, a series of individual cohorts, whereby each individual cohort is considered homogeneous, is used to construct the full population. This allows for the heterogeneity in the overall group to be maintained via a collection of individual, homogenous groups. We believe that grouping via multiple cohorts will allow for stronger inferences and provide the ability to extend these inferences to our population of interest.

This multiple-cohort modeling approach employs a single-cohort model in a multiple-cohort setting with a staggered time structure. The multiple-cohort modeling approach was validated on the U.S. native-born male population by comparing population estimates for the U.S. male native-born population over an extended time period (up to year 2060) against U.S. Census estimates for the same population. Validation details are discussed in Section 7.4.2.1.10.

In the multiple-cohort modeling approach, each cohort starts at age 0 to 4 years, and the ALCS Cohort Model is used to follow survival of the cohort, moving forward through time in 5-year intervals. We implemented this approach multiple times, starting from 1990, to populate the number of people alive in all age categories from ages 0 to 84 years in 2075. The initial U.S. male native-born population for age 0 to 4 years was acquired from U.S. Census data for the initial cohorts (1990-2010) and from U.S. Census estimates for future cohorts beyond 2015 (U.S. Census Bureau, 2016), (U.S. Census Bureau, 2014) (Table 4), respectively.

We implemented the above-mentioned modeling analysis in the Base Case scenario and in the Master Case scenario, described in Section 7.4.2.3.2, where it was assumed that a market authorization of proposed claim was allowed in 2015. Additional input parameters described in Section 7.4.2.2.6 were also used in this analysis. Two simplifying assumptions were made: (1) product-specific initiation, cessation, and other transition rates do not change over the modeling time period; and (2) age- and product use state–specific mortality rates remain constant over the modeling time period.

Under the specific modeling scenario of authorization of the proposed claim in 2015, we followed multiple cohorts until the year 2075, under both Base Case and Master Case scenarios. Comparing the difference in the number of people alive in all age categories from ages 0 to 84 years between the Base Case and Master Case scenarios in the year 2075 allows us to make inferences about the impact of authorization of the proposed claim on the overall health of the population of interest. Results of the Master Case and Base Case scenarios across age groups for year 2075 and the difference in the number of survivors between the two scenarios for males alive in all age categories from ages 0 to 84 years are shown in Table 7.4.2-48.

Results in Table 7.4.2-48 show that, in the Master Case scenario, there are an additional 93,323 people alive in all age categories from ages 0 to 84 years in the year 2075 compared to the Base Case scenario. Note that minimal differences are observed before age 40 years.

This is not surprising, as smoking related health impacts are minimal at young ages. The difference in the number of people alive in the Master Case scenario compared to the Base Case scenario increases from ages 40 to 74 years before beginning to decline. This is in alignment with discussions presented in Section 7.4.2.1.2 and the observation by Rostron (2011) that mortality ratios associated with smoking in males increase with age from 45 to 74 years before somewhat declining at older ages.

Table 7.4.2-48: **Results in Year 2075 of the Master Case and Base Case Scenarios for All Age Groups and the Differences Between the Two Scenarios in the Number of People Who Are Alive**

2075			
Age Group	**Master Scenario**	**Base Scenario**	**Difference**
0-4	11,659,500	11,659,500	0
5-9	11,503,227	11,503,227	0
10-14	11,343,808	11,343,808	0
15-19	11,384,863	11,384,863	0
20-24	11,210,354	11,210,354	0
25-29	10,975,495	10,975,342	153
30-34	10,691,665	10,691,192	473
35-39	10,398,367	10,397,394	973
40-44	10,101,332	10,099,412	1,920

Table 7.4.2-48: **Results in Year 2075 of the Master Case and Base Case Scenarios for All Age Groups and the Differences Between the Two Scenarios in the Number of People Who Are Alive (Continued)**

2075			
Age Group	**Master Scenario**	**Base Scenario**	**Difference**
45-49	9,787,295	9,783,564	3,731
50-54	9,355,425	9,348,637	6,788
55-59	8,757,301	8,747,530	9,771
60-64	8,050,922	8,038,615	12,307
65-69	7,691,177	7,676,364	14,813
70-74	6,889,508	6,873,894	15,614
75-79	5,774,009	5,759,539	14,470
80-84	4,761,915	4,749,605	12,310

2075	
Total additional people alive in the Master vs. Base Case	**93,323**

The outcomes of the multiple-cohort modeling approach exercise allow us to extend the inference of an additional 1,120 survivors within a 1,000,000-male cohort from the single-cohort modeling approach to a larger and heterogeneous population of interest. The multiple-cohort results demonstrate that, under the conditions employed for the defined modeling scenarios, the approval of this proposed claim could result in approximately 93,000 more native-born U.S. males being alive 60 years after a market authorization is given for the candidate product (i.e., Master Case scenario), compared with the status quo (i.e., the Base Case scenario).

Finally, the current market share of the candidate product allows us to scale the results of the multi-cohort approach to more realistically estimate the net benefit to the U.S. native-born male population if the proposed claim is authorized for the candidate product. The US current market of the candidate product is approximately 8%, therefore 7,500 of the 93,000 additional lives resulting from the multiple cohort modeling approach represents the net benefit of our candidate product. We are making a conservative assumption that the market share of the candidate product remains the same over the 60 years after the candidate product is given a market authorization. Though it is quite reasonable to expect that if a modified risk claim is authorized for the candidate product, as users begin to better understand the lower risks of using MST compared to cigarette smoking, additional users may switch over from smoking or dual use to exclusive use of MST, thereby further increasing this projected net benefit.

7.4.2.3.6. Conclusions

In this section, we present the results of the ALCS Cohort Model and examine the impact of FDA authorization of the proposed claim. By comparing results of our model's Master Case (i.e., the most likely outcome from authorization of the proposed claim) and Base Case (i.e., the status quo) scenarios, we demonstrate that a market authorization of the proposed claim provides a net health benefit to the population. Our conclusions are supported by the validation, uncertainty, and sensitivity analyses and   based on reasonable data and assumptions.

In summary, we believe that our model's results are justified, well-supported, and representative of potential outcomes in the real world for several reasons, including but not limited to (1) The input data come from robust external and internal sources, such as national databases and surveys, transition probabilities derived from the CCI Study based specifically on the candidate product, and the ALCS Linked Mortality analyses ; (2) the results come from a validated model; and (4) the validity and impact of assumptions were evaluated via uncertainty and sensitivity analyses.

The single-cohort modeling approach showed that, out of a cohort of 1,000,000 males, the Master Case scenario yielded 1,120 additional survivors with 32,856 additional expected years of life compared to the Base Case scenario. We employed a multiple-cohort modeling

approach to extend our single-cohort modeling predictions to the U.S.-born male population. Results suggest that market authorization of the proposed claim would lead to approximately 93,000 more U.S.-born males being alive between the ages of 0 and 84 years in 2075, after a maximum follow-up period of 60 years, compared with the status quo. Moreover, when factoring the current market share of the candidate product, the expected net benefit to the U.S. native-born male population is that an additional 7,500 people will be alive after a follow-up period of 60 years, when compared with the status quo.

In summary, we believe that our model's results are justified, well-supported, and representative of potential outcomes in the real world for several reasons, including but not limited to (1) the input data come from robust external and internal sources, such as national databases and surveys, transition probabilities derived from the CCI Study based specifically on the candidate product, and the ALCS Linked Mortality analyses ; (2) the results come from a validated model; and (4) the validity and impact of assumptions were evaluated via uncertainty and sensitivity analyses.

7.4.2.4. Literature Cited

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