DEVELOPMENT AND VALIDATION OF A DISCRETE EVENT SIMULATION MODEL TO EVALUATE THE LONG TERM USE OF ELECTRONIC CIGARETTES IN US POPULATION

Kunal Saxena

Follow this and additional works at: https://scholarscompass.vcu.edu/etd

Part of the Epidemiology Commons, and the Pharmacy Administration, Policy and Regulation Commons

© The Author

Downloaded from
https://scholarscompass.vcu.edu/etd/3919

This Dissertation is brought to you for free and open access by the Graduate School at VCU Scholars Compass. It has been accepted for inclusion in Theses and Dissertations by an authorized administrator of VCU Scholars Compass. For more information, please contact libcompass@vcu.edu.
DEVELOPMENT AND VALIDATION OF A DISCRETE EVENT SIMULATION MODEL TO EVALUATE THE LONG TERM USE OF ELECTRONIC CIGARETTES IN US POPULATION

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

By

Kunal Saxena,
BSPharm, Manipal University, 2009
MS, Manipal University, 2011
PhD candidate,
Department of Pharmacotherapy and Outcomes Science
School of Pharmacy
Virginia Commonwealth University

Academic Advisor:
David A. Holdford, R.Ph., M.S., Ph.D., FAPhA
Professor
Department of Pharmacotherapy and Outcomes Science
School of Pharmacy

Virginia Commonwealth University
Richmond, Virginia
May 2015
Dedication

This dissertation is dedicated to my mother, “Poonam Saxena”, who taught me to dream big, and that no dream is impossible to achieve if I pursue it with hard work, honesty and perseverance. The dream of her son getting the utmost education is now realized. This is for you, Mamma!
Acknowledgments

This study would not have been completed without the support of many people. I would like to start by thanking God for being so kind and generous to bless me with amazing opportunities in life, and guiding me through good and bad times.

Second, I am very grateful to my family; my mother, sister and father. They were brave and selfless enough to let me leave home to pursue my pharmacy and graduate education, and live away from them for all these years. I want to especially thank my sister, Keya, who took great care of my parents in times when I was needed at home. It is because of their numerous sacrifices and continuous motivation that I was able to focus on my education and achieve this milestone.

Third, I want to thank my adviser, Dr. David Holdford, for showing faith and accepting me as his graduate student. It has been an incredible journey of five years and he has done a great job in training me as an independent researcher and a competent professional. Thanks for teaching me to stretch my limits and go out of the comfort zone to complete challenging tasks. I hope to practice this in my professional career and make him proud.

Fourth, I wish to express my thanks to my PhD committee; Dr. Norman Carroll, Dr. Edward Boone, Dr. Mohamadi Sarkar, and Dr Pramit Nadpara. I will always be thankful and indebted to them for sharing their expertise, experience, knowledge and most of all their valuable guidance and encouragement extended to me for finishing this project. In addition, I would like to thank all the teachers I had the honor of learning from, at Virginia
Commonwealth University. Their teachings have helped me gain skills and expertise required to progress through the program and complete my PhD.

Fifth, I would like to show my deepest appreciation to my friends and colleagues in graduate school. They have been an indispensable source of professional and personal advice, and provided all the help I could have asked for. I was fortunate to have a great support system in them and I wish everyone the best of luck in their future endeavors.

Sixth, I would like take this opportunity to express my gratitude to the highly efficient administrative staff of the Pharmacy School Graduate program, Department of Pharmacotherapy and Outcomes Science, and Phar-Tech. They have been extremely helpful at various stages of my graduate program.

Finally, I would like to thank the Altria Regulatory Health Science Group for their extremely generous financial support granted through the 2 years pre-doctoral fellowship.
# Table of Contents

List of Figures ......................................................................................................................... viii
List of Tables ................................................................................................................................. x
Abstract ........................................................................................................................................ xi

Chapter 1: Introduction .................................................................................................................. 1
  Background ................................................................................................................................. 2
  Rise in the use of e-cigs and related effects ................................................................................. 5
  Regulatory Perspective to the use of e-cig .................................................................................... 7

Chapter 2: Literature Review ......................................................................................................... 9
  Conceptual framework .................................................................................................................. 13
  Impact on public health ............................................................................................................... 15
    *Survey studies* ......................................................................................................................... 17
    *Experimental studies* .............................................................................................................. 25
    *Cohort studies* ......................................................................................................................... 27
    *Physiological studies* .............................................................................................................. 29
  Gaps in literature ....................................................................................................................... 34

Chapter 3: Methods .................................................................................................................... 36
  Overview ....................................................................................................................................... 37
  What is simulation modeling? ..................................................................................................... 38
    *Simulation Modeling Applications in Healthcare* ................................................................... 38
  Model Selection Process ............................................................................................................ 39
  Discrete Event Simulation and its components .......................................................................... 47
  The E-cig model ........................................................................................................................... 52
  Model parametrization ............................................................................................................... 59
  Assigning baseline probabilities and distributions ..................................................................... 62
  Simulation Pathway ..................................................................................................................... 63
  Outcome Measures .................................................................................................................... 67
  Simulation runs ............................................................................................................................ 68
  Model validation ........................................................................................................................ 70
  Model assumptions .................................................................................................................... 73

Chapter 3: Results ....................................................................................................................... 75
List of Figures

Figure 1. Model selection flowchart (Barton et al., 2004) ................................................................. 40
Figure 2. Flow diagram of the computation process for a discrete event simulation (Caro et al., 2010) ....................................................................................................................... 47
Figure 3. Working flowchart of the model structure ........................................................................... 72
Figure 4. E-cig use simulation model .................................................................................................. 86
Figure 5. Projected estimate of e-cig prevalence among initial current cigarette smokers .......... 87
Figure 6. Projected e-cig prevalence by age group among initial current cigarette smokers in the US. .................................................................................................................... 88
Figure 7. Projected e-cig prevalence by gender among initial current cigarette smokers in the US. 89
Figure 8. Projected e-cig prevalence by race among initial current cigarette smokers in the US. .... 90
Figure 9. Projected e-cig prevalence by education among initial current cigarette smokers in the US. .................................................................................................................... 91
Figure 10. Projected estimate of e-cig prevalence among initial recent former cigarette smokers ... 92
Figure 11. Projected e-cig prevalence by age group among initial recent former cigarette smokers in the US..................................................................................................................... 93
Figure 12. Projected e-cig prevalence by gender among initial recent former cigarette smokers in the US.......................................................... ........................................................................ 94
Figure 13. Projected e-cig prevalence by race among initial recent former cigarette smokers in the US..................................................................................................................... 95
Figure 14. Projected e-cig prevalence by education among initial recent former cigarette smokers in the US..................................................................................................................... 96
Figure 15. Projected estimate of e-cig prevalence among late former cigarette smokers in the US. . 97
Figure 16. Projected e-cig prevalence by age group among initial late former cigarette smokers in the US..................................................................................................................... 98
Figure 17. Projected e-cig prevalence by gender among initial late former cigarette smokers in the US..................................................................................................................... 99
Figure 18. Projected e-cig prevalence by race among initial late former cigarette smokers in the US. ..................................................................................................................... 100
Figure 19. Projected e-cig prevalence by education among initial late former cigarette smokers in the US..................................................................................................................... 101
Figure 20. Projected estimate of e-cig prevalence among initial never cigarette smokers in the US. ..................................................................................................................... 102
Figure 21. Projected e-cig prevalence by age groups among never cigarette smokers ................. 103
Figure 22. Projected e-cig prevalence by gender among never cigarette smokers ....................... 104
Figure 23. Projected e-cig prevalence by race among never cigarette smokers ............................ 105
Figure 24. Projected e-cig prevalence by education level among never cigarette smokers .......... 106
Figure 25. Projected estimate e-cig prevalence in the US population over the simulation period... 107
Figure 26. Comparison of projected e-cig use and conventional cigarette use over the simulation period .......................................................................................................................... 108
Figure 27. Projected e-cig prevalence by age groups in the US population ........................................ 109
Figure 28. Projected e-cig prevalence by gender in the US population ............................................. 110
Figure 29. Projected e-cig prevalence by race in the US population .................................................. 111
Figure 30. Projected e-cig prevalence by education level in the US population ................................. 112
List of Tables

Table 1. Main differences between Decision trees, Markov models and DES ...........................................46
Table 2(a). Demographic attributes of the national sample of current cigarette smokers. ..................76
Table 3. Demographic attributes of the national sample of recent former cigarette smokers ..........78
Table 4. Demographic attributes of the national sample of late former cigarette smokers ............79
Table 5. Demographic attributes of the national sample of never cigarette smokers .......................80
Table 6. E-cig initiating probabilities and assigned distribution for current smokers ..........................82
Table 7. Baseline attributes, corresponding probabilities and assigned distribution for recent former smokers ........................................................................................................83
Table 8. Baseline attributes, corresponding probabilities and assigned distribution for late former smokers ........................................................................................................84
Table 9. Baseline attributes, corresponding probabilities and assigned distribution for never smokers ................................................................................................................85
Table 10. Prevalence estimates at the end of 15 years for different scenarios in sensitivity analyses in current smokers ........................................................................................................113
Table 11. Model Population descriptive results: ................................................................................143
Table 12. Projected e-cig prevalence for each year in the simulation period within different demographic categories of current cigarette smokers ..................................................................................147
Table 13. Projected e-cig prevalence for each year in the simulation period within different demographic categories of recent former cigarette smokers ........................................................................149
Table 14. Projected e-cig prevalence for each year in the simulation period within different demographic categories of late former cigarette smokers ........................................................................152
Table 15. Projected e-cig prevalence for each year in the simulation period within different demographic categories of never cigarette smokers ........................................................................154
Abstract

DEVELOPMENT AND VALIDATION OF A DISCRETE EVENT SIMULATION MODEL TO EVALUATE THE LONG TERM USE OF ELECTRONIC CIGARETTES IN US POPULATION

By Kunal Saxena, BSPharm, MS

A dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Virginia Commonwealth University.

Virginia Commonwealth University, 2015

Academic Advisor:
David A. Holdford, R.Ph., M.S., Ph.D., FAPhA
Professor
Department of Pharmacotherapy and Outcomes Science
School of Pharmacy

Introduction

Cigarette smoking is associated with lung cancer, cardiovascular disease, and chronic respiratory conditions. It is responsible for high mortality and morbidity risk in the US population. Smokers find sudden quitting difficult and it is reported that a large number of unassisted quitting attempts are eventually unsuccessful. Electronic cigarette or e-cig is a novel battery-driven, nicotine delivery product, currently being used as a smoking cessation tool by current and former smokers. Since its resemblance to a conventional cigarette, and its non-combustible nature, e-cig use has risen exponentially in the last few years. To address such public health issues, the US FDA is working on formulating
regulations to manufacture, market, and distribute e-cigs has called for research evidence on the long term use of e-cig use.

**Objective**

The objective of this study was to develop and validate a Discrete Event Simulation model to simulate the electronic cigarette (e-cig) use behavior, and to estimate the long term e-cig use prevalence, in different groups of the US population.

**Methods**

The model population was generated from analyzing the National Health Interview Survey data from 2011-2013. The population was categorized into current, recent former, late former and never smokers. Population birth rates and death rates were applied using the 2012 US Census Bureau data. Model parametrization, transition probabilities and e-cig related risks were obtained and applied using cross sectional survey and longitudinal e-cig studies done on US population. The model was run for the period of 15 years and e-cig use prevalence at the end of the simulation period was estimated. Each simulation was replicated 100 times using Monte Carlo simulation approach. Model validation was performed by the use of null and extreme input values (internal validation), examining programing codes (debugging), verification by tobacco science and system analysis experts (structural and technical validation), comparison of model’s first year results with CDC reports (external validation).
Conclusion

Total projected e-cig prevalence in the US population at the end of simulation of period was found to be around 19%. The results showed a gradual reduction in the number of conventional cigarette smokers and an increase in the e-cig users over the simulation period. Highest e-cig users were <21 years old, male, white and had less than high school level education. Sensitivity analyses of various model parameters showed that the e-cig prevalence was most sensitive to the impact and timing of policy implementation.

As a novel nicotine delivery system, e-cigs are rapidly gaining acceptance in the US and recent reports have shown an exponential rise in the popularity of e-cig among minors and young adults. Our research provides empirical evidence that can be used by the scientific community and regulatory bodies to formulate regulations for marketing and sales of e-cigs in various sections of the population, where the prevalence is expected to rise in future. Our study can also guide the policy makers to introduce relevant policies at specific time points when the e-cig use is expected to rise.
Chapter 1

Introduction
Background

Cigarette smoking is an important and preventable cause of morbidity in the US associated with lung cancer, cardiovascular disease, and chronic respiratory conditions. Recent US health care reports (How tobacco smoke causes disease. 2010; Health consequence of smoking: US surgeon general report. 2014) have shown that smokers are at greater risk than non-smokers for diseases that affect the heart and blood vessels (cardiovascular disease), eventually leading to stroke and coronary heart disease. Further, smoking can cause lung diseases by damaging the airways and the small air sacs (alveoli) found in the lungs. This leads to COPD, which includes emphysema and chronic bronchitis (Health consequence of smoking: US surgeon general report. 2014). Cigarette smoking also causes most cases of lung cancer in the country (How tobacco smoke causes disease. 2010; Health consequence of smoking: US surgeon general report. 2014). In terms of mortality, the US Centers for Disease Control and Prevention (CDC) reports that approximately 443,000 deaths occur annually in the US due to smoking, including those from secondhand smoke (Agaku, King, Husten, & Bunnell, 2014).

Along with negative health effects, smoking also results in a high economic burden. Annual smoking-attributable economic costs in the United States estimated for the years 2009–2012 were more than $289 billion, which included approximately $133 billion for direct medical care of adults and more than $156 billion for indirect costs due to lost productivity (Health consequence of smoking: US surgeon general report. 2014).
Although cigarette smoking is declining among U.S. adults over the past five decades, there is still a high proportion of population smoking cigarettes and other tobacco products (Agaku et al., 2014). During 2012–2013, the US surgeon general report identified approximately one in five U.S. adults (total of 50 million persons) used any tobacco product every day or some days, and an estimated 60 million people used tobacco products every day, some days, or rarely (How tobacco smoke causes disease.2010; Health consequence of smoking: US surgeon general report.2014). The majority of the smoking population consisted of young adults and teenagers. A report from the Center of disease control and prevention (CDC) indicated that the prevalence of current tobacco product use among middle and high school students was 6.7% and 23.3%, respectively (CDC morbidity and mortality report.2013).

Offering help to quitting tobacco use in people addicted to nicotine is one of the most important policies identified by the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) to expand the fight against the tobacco epidemic (WHO.2012). However, due to the addictive nature of nicotine, most of the smokers are biobehaviorally addicted. That is, not only they are dependent on the biological constituents of tobacco, but are also dependent on the behavior aspect of using tobacco products like holding and puffing on cigarettes.

Quitting smoking can be very difficult and is often accompanied by variety of withdrawal symptoms (Benowitz, 1991). Approximately, 70% of smokers try to quit, but less than 5% of unassisted attempts are successful (Benowitz, 1991). Sudden quitting may also result in fatigue, dizziness, nicotine withdrawal, irritability, anger, frustration, sad mood, anxiety,
decreased concentration, hunger, insomnia, restlessness, decreased heart rate, weight gain and an eventual relapse of smoking (Benowitz, 1991; Siegel, Tanwar, & Wood, 2011). Many smokers intending to quit take help of pharmacotherapy as well as patient counselling but smokers using these approaches have shown a high rate of an eventual relapse (Bell & Keane, 2012).

The latest addition to the existing tools for smoking cessation and abstinence is electronic cigarettes (e-cigs). Launched in China in 2003, e-cigs are hand-held battery-powered nicotine delivery devices which enable users to inhale doses of vaporized nicotine (Barbeau, Burda, & Siegel, 2013). A basic model of an e-cig consist of a mouthpiece comprising of a liquid-filled cartridge mainly filled with variable concentration of nicotine, concentrated flavors, and a humectant substance such as propylene glycol, vegetable glycerin or polyethylene glycol (Besaratinia & Tommasi, 2014). An atomizer equipped with an electronic controller, sensor, and battery powered heater converts the liquid inside the cartridge into vapor that mimics the cigarette smoke, with a colored LED simulating a burning cigarette tip. Used e-cig cartridges can be replaced or refilled with a new cartridge, which is readily available in any e-cig store (Besaratinia & Tommasi, 2014). Since no tobacco is burned, inhaling nicotine via e-cigs provides a potentially safer alternative to smoking regular cigarette since it eliminates the harmful tars and carbon monoxide (Dawkins, Turner, Hasna, & Soar, 2012). E-cigs therefore are often perceived to help in cigarette smoking cessation and reduction (Dawkins et al., 2012). It also reduces the problems of second hand and third hand smoke. (Barbeau et al., 2013; Siegel et al., 2011; Zhu et al., 2013).
Rise in the use of e-cigs and related effects

As a novel nicotine delivery system, e-cig are rapidly gaining acceptance in the US and many parts of the world. Currently, the global e-cig market is worth $6 billion and in the US alone, the estimated e-cig retail sales approached $2 billion at the end of 2013, and is estimated to rise to $10 billion by 2017 (Herzog, 2013). It is anticipated that e-cig sales will surpass that of conventional tobacco cigarettes by 2023 (Herzog, 2013). According to a study by the Centers for Disease Control and Prevention (CDC), nearly 6% of all U.S. adults have used e-cig, and approximately 21% of American adult smokers (i.e., an estimated population of 45 millions) have tried e-cig in the past (CDC morbidity and mortality report.2013). The Tobacco Vapor Electronic Cigarette Association claims that around 4 million Americans are e-cig users (TVECA, 2013). This increasing trend for e-cig use also extends to minors as the number of U.S. middle and high school students who tried e-cig more than doubled between 2011 and 2012, rising from 4.7% to 10% (CDC morbidity and mortality report.2013). In 2012, around 1.78 million middle and high school students nationwide admitted to using e-cig. Along with that, 76.3% of youth who used e-cig within the past 30 days also smoked regular tobacco cigarettes in the same period, giving rise to dual use (CDC morbidity and mortality report.2013).

Although e-cigs has been portrayed as a less harmful substitute for smokers who are unable to quit, the counter-argument to the use of e-cig is that it may cause nicotine dependence in smokers and long term use may cause health complications (Dutra & Glantz, 2014; Tomar, 2007). Despite the fact that the e-cigs deliver fewer amounts of nicotine vapors than tobacco cigarettes, they nevertheless have showed long term nicotine
dependency in e-cig users (Tomar, 2007). Also, recent studies done on chemical analysis of e-cig vapor/liquid has shown the presence of toxins and carcinogens, generally at lower levels, in various e-cig products (Goniewicz, Kuma, Gawron, Knysak, & Kosmider, 2013; Kim & Shin, 2013; McAuley, Hopke, Zhao, & Babaian, 2012).

The rising popularity of e-cig among minors and young adults is particularly concerning because these products may serve as a ‘gateway’ to using conventional tobacco products. In other words, e-cigs use has potential unintended consequences, such as becoming “starter products” for non-smokers, especially young adults, leading to increased smoking initiation and derailing the potential for ultimate smoking abstinence (Pepper et al., 2013; Riker, Lee, Darville, & Hahn, 2012). Because the vast majority of smokers pick up the habit as teenagers (Pearson, Richardson, Niaura, Vallone, & Abrams, 2012), the excessive use of e-cig by teenagers and young adults is a critical concern because it may ultimately lead to long lasting smoking habits.

The use of e-cig also draws attention to the increasing trend of dual use claiming that smokers may use e-cig to temporarily alleviate their craving for tobacco cigarettes, especially in settings where smoking is prohibited. Under such assumption, dual users may take advantage of e-cig as a ‘quick fix’, and maintain their smoking status without feeling the need to quit smoking (Pepper et al., 2013).
**Regulatory Perspective to the use of e-cig**

The WHO stated that the efficacy of e-cig in aiding smoking cessation had not been demonstrated scientifically, and recommended that consumers should be advised not to use e-cig until the recognized regulatory bodies have found them safe and effective (WHO.2012). Since then, several countries such as Australia and Canada have restricted the sale of e-cigs until pending review by their regulatory agencies (WHO.2012). At present, the FDA is formulating regulations for the sale and marketing of e-cig as a smoking cessation product. However, the nature of the regulation procedure is yet to be determined as there is a lack of research evidence on the health impact of using e-cigs (WHO.2012; Henningfield & Zaatari, 2010).

In the US, with the enactment of the Family Smoking Prevention and Tobacco Control Act (FSPTCA) in 2009, the FDA was granted authority to regulate the manufacture, marketing, and distribution of tobacco products to protect the public health and to reduce tobacco use by minors (Family smoking prevention and tobacco control act (FSPTCA).2014). Within the framework of the FSPTCA, the FDA and the National Institutes of Health (NIH) have formed an interagency partnership to foster research relevant to tobacco regulatory science, and identified multiple research opportunities, including e-cig initiation, use (including transition to other tobacco products and multiple use), perceptions, dependence, and toxicity (Tobacco regulatory science program (TRSP).2014).

The ongoing and future research on these topics is expected to provide empirical evidence that can be used to inform the general public, scientific community, and regulatory
authorities of the health risks and benefits associated with e-cig use. Not only will this information help generate further interests for scientists in the field of tobacco regulatory research, but it will also assist the regulatory agencies in making scientifically based decisions on the development and evaluation of regulations on novel tobacco products such as e-cigs to ensure safety of public health.
Chapter 2

Literature Review
Tobacco use is a global phenomenon, affecting an estimated 1.2 billion people, which poses substantial health burden and costs. With approximately 5 million tobacco-related deaths annually, cigarette smoking is the leading cause of preventable premature mortality in the world (World health organization.1997). The risk of serious disease diminishes rapidly after quitting and permanent abstinence is known to reduce the risk of lung cancer, heart disease, chronic lung disease, stroke, and stroke (Health consequence of smoking: US surgeon general report.2014; Lightwood & Glantz, 1997).

Existing treatments for smoking cessation includes various methods, from simple medical advice to pharmacotherapy. However, the potential addictive nature of nicotine creates a huge obstacle for those who desire to quit smoking. It has been shown that approximately 80% of smokers who attempt to quit on their own relapse within the first month of abstinence and only about 3-5% remain abstinent at 6 months (Hughes, Keely, & Naud, 2004).

Smokers often take help of drug therapies to help them quit their smoking habit. The latest treating tobacco use and dependency guidelines of US Department of Health and Human Services (How tobacco smoke causes disease.2010)categorizes pharmacotherapy for treatment of tobacco dependence into first-line (nicotine replacement therapy [NRT], bupropion, and varenicline) and second-line medications (include nortriptyline and clonidine). Most of the first line medications have established efficacy profiles but the FDA has not approved the second line medications for tobacco dependence treatment indication and there are concerns about their potential side effects (Hays, Ebbert, & Sood, 2009a).
NRT is the most common existing medication used to assist tobacco cessation. It acts by partially replacing the nicotine formerly obtained from tobacco smoking and aids smoking cessation by weakening the reinforcing effects of nicotine delivered via tobacco, and therefore reducing the severity of withdrawal symptoms and cravings (Gross & Stitzer, 1989). Despite the first line treatment, NRT does not completely eliminate all symptoms of withdrawal because the delivery system does not reproduce the rapid and high levels of nicotine achieved through regular tobacco use (Benowitz, 1991). Differences in formulations (lozenge, gum, patch, nasal spray, and inhaler) may provide some relief to the withdrawal symptoms or urges to smoke, but there is little direct evidence that one nicotine product is more effective than another (Benowitz, 1991). In general, NRT is considered to be safe for most patients, with a relatively low rate of discontinuation due to adverse events (Tonnesen & Mikkelsen, 2000).

Bupropion hydrochloride (brand names: Zyban, Wellbutrin), another first line smoking cessation drug is found to be effective as a smoking-cessation aid, with sustained-release (SR) oral formulations as well as immediate release. The mode of action of bupropion in smoking cessation is not clearly explained but inhibition of neuronal reuptake of dopamine and a weak nAChR antagonist effect are thought to contribute to the reported reduction in the severity of nicotine cravings and withdrawal symptoms (Jorenby, 2002). Pooled analyses of studies with bupropion generally show quit-rates similar to those observed with NRT (Hughes, Stead, Hartmann-Boyce, Cahill, & Lancaster, 2014). However, bupropion have been commonly associated with insomnia and dry mouth (Hughes et al., 2014).
Varenicline (brand names: Chantix/Champix), launched in 2006, became the first new prescription drug for smoking cessation in 10 years. Varenicline acts by dual effects: partial stimulation of nAChRs, without creating the full effect of nicotine (agonist action), and blocking nAChRs, which prevents the nicotine from tobacco from reaching them (antagonist action) (Tonstad et al., 2006). These effects provide relief from the cravings and withdrawal symptoms experienced during smoking cessation (Tonstad et al., 2006). Varenicline is generally well tolerated, however it is still associated with adverse effects including nausea, insomnia, gastrointestinal upsets and headache (Hughes et al., 2014). The prescribing information for varenicline also carries a black-box warning highlighting an increased risk of psychiatric symptoms and suicidal ideation in patients reporting any history of psychiatric illness (Tonstad et al., 2006).

Both nortryptiline and clonidine are second-line medications for treatment of tobacco dependence but they do not have approval from the US FDA for this indication, as there are concerns about potential side effects (Fiore, 2000). Combinations of smoking-cessation medications such as nicotine patch plus a more rapid release NRT such as gum, lozenge or spray, or bupropion plus NRT, have shown to increase efficacy in smoking cessation compared to monotherapy (Fiore, 2000).

The use of e-cigs, also referred to as vaping, is a relatively new phenomenon that is rapidly gaining the interest of many long-time tobacco users and health care professionals. E-cigs are becoming a preferred alternative for nicotine delivery among many smokers because of their realistic look, feel, and taste compared to traditional cigarettes. Furthermore, many
cigarette smokers have turned to vaping because e-cigs vendors are marketing their product as a cheaper and safer smokeless alternative to traditional cigarettes, and a possible smoking cessation tool (Herzog, 2013). Awareness and vaping of e-cigs has increased exponentially in recent years. Data obtained from surveys and smoking reports showed that in the US, awareness of e-cigs rose from 40.9–57.9% from 2010 to 2011, with e-cigs use rising from 3.3–6.2% over the same time period [King et al. 2013].

**Conceptual framework**

The substitution of conventional tobacco products by newer e-cigs draws similarity from effective patient behavior changes, which are required to help maintain and improve
health, reduce disease risks, and control illnesses. Most of the successful health programs and interventions are based on an understanding of patient’s health behaviors with respect to different contexts. Several different approaches or interventions are currently observed to be practiced by health care providers to modify patient behavior. The most commonly targeted behaviors are tobacco use, diet and physical activity patterns, alcohol consumption, medication adherence, unsafe sexual behavior, and preventive behavior such as screening and vaccinations (Ashenden, Silagy, & Weller, 1997; Grol & Grimshaw, 2003).

Literature shows it is highly difficult for patients to completely quit a long-term habit at once, such as smoking or alcoholism (Hays, Ebbert, & Sood, 2009b). It is observed that counseling patients to completely stop smoking or consuming alcohol does not deter patients’ habits and results in withdrawal symptoms and other stressful conditions. Clinicians and therapists are observed to offer alternative pharmacotherapies (nicotine replacement therapy), substitute but less harmful products or group and individual counseling to patients wanting to quit. It is a proven fact that offering these alternatives and less harmful products (substitute products) ends up being more successful in reaching eventual abstinence than asking them to completely quit their habit (Ashenden et al., 1997). Along with offering substitute products, exposing patients to threats and benefits of a particular behavior also helps to achieve a health related action (Grol & Grimshaw, 2003).

In context of the behavior of tobacco use or cigarette smoking, it is an addiction that is difficult to break. Smokers trying to quit have to cope simultaneously with the psychological and pharmacologic aspects of tobacco dependence (Polosa & Benowitz,
2011). Along with the pharmacological effects of nicotine which results in symptoms like nausea, insomnia, fatigue, restlessness and increased cardiovascular rhythm, it is crucial to note the importance of behavioral aspects of tobacco dependence. The rising popularity of e-cigs can be attributed to their ability to deal with both the pharmacological (i.e. nicotine) and the behavioral component (similar shape, mechanism and pleasure) of smoking addiction. Most of the drug therapies do not deal with the behavioral aspects of smoking cigarettes. E-cigs, on the other hand, provide simulation of smoking behavior with its physical similarity with a conventional cigarette and the feeling of inhaling and exhaling smoke, which are important determinants of its effectiveness in reducing or substituting cigarette smoking.

Along with pacifying the withdrawal symptoms of nicotine, the action of using an e-cig is also perceived to protect the smokers from getting smoking-related diseases and overcome other negative effects such as social unacceptability among family and friends. The potential benefit of an e-cig in addition to lower barriers associated with the use of e-cigs which include experiencing the same pleasure as tobacco cigarette, habitual of inhaling smoke, price-difference between e-cig and regular cigarette, and handling and carrying issues results in high acceptability of e-cigs among the youth and adult smoking population. The high awareness of e-cig via media advertising, observing other people using it and easy accessibility and availability of e-cig also contributes to its successful initiation among different sections of the population.

**Impact on public health**
Despite the fact that the e-cigs deliver fewer amounts of nicotine vapors than tobacco cigarettes, they nevertheless have showed long term dependency in e-cig users (Tomar, 2007). To counter this, the proponents of e-cigs claim that use of e-cigs is safer because tobacco is not combusted and there is no inhalation of the toxins found in cigarette smoke (Barbeau et al., 2013). However, the FDA has reported that e-cig cartridges and solutions contain nitrosamines, diethylene glycol, and other contaminants potentially harmful to humans (Westenberger, 2009). Based on this, the FDA wants the sale of e-cigs to be prohibited or regulated as dangerous nicotine delivery systems that should comply with the safety standards of the Federal Food Drug and Cosmetic Act (FDCA.2013).

Studies conducted by Foulds et al. (Foulds, Veldheer, & Berg, 2011) believe that more research needs to be conducted to determine the safety and efficacy of e-cigs as a smoking cessation tool. However, they also stated that individuals who have successfully quit smoking in favor of vaping should continue to use e-cigs as a healthier alternative to conventional cigarettes. E-cigs could play an important role in the future of smoking cessation, but their use is currently under scrutiny by a complicated legal and political issues. It is evident that there is a need to conduct more research on the long-term effect and net benefits of e-cigs, to be able to formulate the control measures which will streamline the legal and political ramifications surrounding these products.

The potential health hazards of nicotine addiction from other smokeless tobacco products have been previously published by the American Heart Association and include hemodynamic effects, endothelial dysfunction, thrombogenesis, systemic inflammation, and other metabolic effects (Piano et al., 2010). Because of that, there is a concern that
increased availability of e-cigs could increase worldwide nicotine dependence, especially among the young as they are enticed by the various flavor options e-cigs have to offer. Also, since vaping does not produce smoke from burning tobacco, the opponents of e-cigs fear that traditional smokers will substitute vaping for smoking in settings where smoking is not permitted without any real intention of quitting conventional cigarettes. Furthermore, vaping in public places could possibly undermine or weaken current antismoking regulations.

In order to face these challenges, it is very important to become more familiar with the available scientific evidence-based literature concerning e-cig and vaping. Currently, the literature is limited, but it is growing fast and more studies are getting published in the areas of e-cig based surveys studies, chemical analysis of e-cigarette cartridges, nicotine content, delivery, and clinical and physiological studies, and evaluating long term effect of vaping. We attempt to comprehensively review the literature published till date on aforementioned areas and try to address the gap in the current literature. The studies discussed are categorized on the basis of their study designs including survey design, experimental, cohort and physiological studies.

**Survey studies**

The biggest survey study done on e-cig users was done by Adkison et al, to examine the e-cig related awareness, use, and product-associated beliefs among current and former cigarette smokers in the U.S., Canada, Australia, and the UK (Adkison et al., 2013). The survey was conducted via telephonic interviews from July 2010 to June 2011 and the data were analyzed to explore changes in smoking behavior between e-cig users and non-users.
Results indicated that e-cig awareness ranged from 73% in the U.S. to 20% in Australia. Among those aware, 16% had tried e-cigs (7.6% of the total sample), and among those who had tried e-cigs, 39% (2.9% of the sample) were current users. Across countries, awareness of these relatively new products was higher among younger, non-minority populations with higher incomes. Trial and use of e-cigs was associated with smoking status and frequency of smoking, with nondaily smokers being the most likely to try e-cigs, although there were few non-daily smokers in the sample. Current use was associated with a greater reduction in cigarettes per day over time, compared to non-e-cig users (among cohort participants, where data were available); however, users were not more likely to quit smoking than non-users.

Another four country survey conducted by Etter et al in France, Belgium, Switzerland and Canada reported the usage patterns of e-cigs, reasons for use, and users’ opinions of these products (Etter, 2010). The results of the study suggested that e-cigs were marketed to current smokers either for enjoyment or for use in smoke-free places, and most people who bought these products were current and former smokers, who used e-cigs to help quit smoking, just as they would use NRT. The survey also showed that e-cigs were used quite intensively by almost all respondents daily and the number puffs per day was substantial. The studied showed that the users reported more positive than negative effects with e-cigs and many reported perceived positive effects on the respiratory system (breathing better, coughing less), compared to regular cigarette smoking. The study also reported that many respondents reported that the e-cigs helped them quit smoking, and several compared it favorably with either nicotine patch or bupropion. The respondents
also reported that e-cigs relieved craving and withdrawal, which was an added benefit over nicotine patches. It was also reported that dry mouth and throat was a frequent adverse effect of the e-cigs.

A longitudinal survey study done by Etter and Bullen reported the change over time in the behavior of e-cig users (Etter & Bullen, 2014). Data were collected at the baseline and after 12 months. The study reported information on the natural behavior of an international cohort of vapers over 12 months outside clinical settings or efficacy trials. The results reported that most of the e-cig users were former smokers, who used e-cigs much like nicotine medications, to assist quitting, but with a longer duration of use. Among e-cig users, a low proportion of former smokers and recent quitters relapsed to smoking. Dual users of e-cigs and conventional cigarettes were shown to reduce their cigarette consumption after they started to vape, and about half had stopped smoking at 1-year follow-up.

Another survey study conducted by Pearson et al, addressed the knowledge gap by using cross-sectional data from 2 separate surveys conducted in 2010, exclusively on the US population of e-cig users to estimate e-cig awareness, use, and harm perceptions in the adult US population (Pearson et al., 2012). The first survey was a nationally representative survey (Knowledge Networks’ Knowledge Panel) and the second one was from the follow-up of a large cohort of current smokers and recent former smokers (Legacy Longitudinal Smoker Cohort (LLSC). The study reported that national estimates of e-cigs ever-use prevalence was 11.4% for smokers, 2.0% for former smokers, and 0.8% for never smokers.
It also reported that roughly 5 million smokers and more than 1 million former and never smokers reported to have used e-cigs. Ever use was mostly concentrated among current smokers, young adults, and non-Hispanic Whites. It was also indicated that the use was popular among those with a college degree. Current e-cig use was most common among current smokers (4.1%) and former smokers (0.5%).

A face-to-face survey was conducted by Foulds et al on experienced e-cig users attending a meeting for e-cig aficionados (e-cig experts), described the e-cig products they used and discussed the public health issues raised by these products and implications for clinicians (Foulds et al., 2011). The results of this study were mostly consistent with previous online or e-mail based surveys of e-cig users and found out that a high proportion had completely replaced cigarette smoking with e-cig use. Among 3000 ever users of e-cigs, 77% used e-cigs to quit smoking or avoid relapsing and 20% stated that they used e-cigs to reduce tobacco consumption with no intention of quitting smoking. Most of the ex-smokers in that study (79%) feared that they might relapse to smoking if they stopped using the e-cig.

A more recent 1 year longitudinal e-cig analysis was conducted by Grana et al on a national sample of current US smokers to determine whether e-cig use predicted successful quitting or reduced cigarette consumption (Grana, Popova, & Ling, 2014). The participants were current smokers recruited from the Knowledge Networks probability-based web enabled panel who completed baseline (November 2011) and follow-up (November 2012) surveys. The study reported that significantly more women, younger adults, and individuals with less education used e-cigs. At baseline, a greater proportion of e-cig users reported
smoking their first cigarette less than 30 minutes after waking compared with non-users. Also, baseline e-cig use was not shown to be significantly associated with greater intention to quit smoking. E-cig use at baseline did not significantly predict quitting 1 year later. A second model including intent, consumption, and dependence covariates found that intention to quit and cigarettes smoked per day significantly predicted quit status while past 30-day e-cigarette use did not. Among participants who reported smoking at both baseline and follow-up, e-cigarette use at baseline was not associated with a change in cigarette consumption, controlling for baseline cigarette consumption.

Siegel et al reported the results of a survey conducted using a non-convenience sampling frame of all first-time purchasers of a particular brand of e-cigs (Siegel et al., 2011). The survey was done to determine the effectiveness of e-cigs for smoking cessation. The results of this study showed a 6-month point prevalence of smoking abstinence among the current e-cig users as 31.0%. Respondents who were not smoking at the 6-month point, or past e-cig users, around one-third of them were reported as nicotine-free. Around 67% of respondents reported a reduction in the number of cigarettes they smoked and around 49% of respondents reported abstinence from smoking.

Dutra et al used the National Youth Tobacco Survey, which recently started to capture the information related to e-cig use among the youth population, to further examine the relationship between e-cig use and conventional cigarette smoking and smoking cessation among US adolescents (Dutra & Glantz, 2014). The data analysis showed that dual use of e-cigarettes and conventional cigarettes was high among adolescents and increasing rapidly.
Adolescents who had ever used a cigarette (not even one puff) and used e-cigs, were more likely to report having smoked at least 100 cigarettes and to be current smokers than adolescents who never used e-cig. Thus, it showed that the e-cig users were becoming heavier smokers and less likely to stop smoking cigarettes. These results cast a serious doubt that e-cigs are effective as smoking cessation aids.

Similar to Dutra and his colleagues, Lee et al used a nationalized database in Korea to assess the prevalence of e-cig use as well as the relationship between e-cigarette use and current cigarette smoking, cigarettes per day, attempts to quit conventional cigarettes, and stopping smoking cigarettes (Lee, Grana, & Glantz, 2014). The findings of this study reported a high dual use of cigarettes and e-cigs, and that e-cigs were not being used as a substitute for cigarettes among Korean adolescents. Around 9.4% of Korean adolescents were found to have ever tried e-cigs and 4.7% were current users. Furthermore, a significant association between current e-cig use and higher levels of cigarette consumption was found, compared to ever and never e-cig user. Tenth graders had the highest e-cig use and 12th graders had the highest conventional cigarette use. The study also reported that among ever e-cig users, around 85% were dual users. Also, among current e-cig users, more than 75% were dual users.

Studying the willingness to use and the gateway effect of e-cigs, Pepper et al conducted a study to understand how male adolescents would respond to e-cigs (Pepper et al., 2013). The study surveyed a national sample of males ages 11-19 to explore their awareness of e-cigarettes and their willingness to try them, along with the proportion of population
showing dual use. The sample population consisted of parents with sons’ ages 11-17 years and male adolescents of ages 18-19 years. The results showed that around two thirds were aware of e-cigs, out of which older adolescents were more likely to be aware of e cigarettes than younger adolescents, while Hispanic adolescents were less likely to be aware compared to their non-Hispanic counterparts. The results also showed that nearly 1 in 5 adolescent males were willing to try either a plain or flavored e cigarette. After controlling for significant correlates, the odds of a smoker being willing to try an e cigarette were 10 times the odds of a nonsmoker.

A large cross-sectional survey of a representative sample of the English population conducted by Brown et al used data from an ongoing national surveillance program (the Smoking Toolkit Study) which has been tracking the use of e-cigs as a reported aid to cessation among the general population in England since July 2009 (Brown, Beard, Kotz, Michie, & West, 2014). The study aimed to address the question of how effective e-cig were compared with NRT bought over-the-counter and unaided quitting in the general population of smokers who were attempting to stop. The primary outcome was self-reported abstinence up to the time of the survey, adjusted for potential confounders including nicotine dependence. The results showed that the in the study population (5863 smokers), 7.9% had used e-cigarettes, 32.8% had used NRT bought over-the-counter and 59.3% had used no aid to cessation. Quitting method did not differ by sex or the number of quit attempts in the past year but was associated with age, social grade, time since the quit attempt started, CPD, smoking less than one CPD, the measures of dependence (time with and strength of urges and HSI) and whether the attempt had begun abruptly. Further
comparisons showed that those who used either e-cigs or no aid were younger than those using NRT over-the-counter, and that those who used NRT over-the-counter or no aid were more likely to hold a lower social grade than those using e-cigarettes. E-cig users smoked more cigarettes, and were more dependent by the strength of urges measure and heaviness of smoking index (HIS), than those using no aid.

A more recent study done on e-cig population in Spain by Martinez et al aimed to estimate the prevalence and analyze the correlates of current and ever use of e-cigarettes, including purchase location and satisfaction with its use, in a sample of the general population of the city of Barcelona in 2013 and 2014 (Martinez-Sanchez et al., 2014). The study utilized data from a survey of representative sample of the adult (n=1245) and asked questions on current use, ever use and experimentation with e-cigs. The results showed that the prevalence of ever e-cigarette use was 6.5%, with the population distribution as mean age of 45.1 years, 56.2% men and 58.3% with intermediate educational level. In total, 75% of e-cig users were current cigarette smokers (dual use), 22.9% were former smokers and 2.1% were never-smokers at the time of the interview. The prevalence of ever e-cig use was higher among men (8%), younger people (≤44 years old, 13.1%) and people with intermediate educational level (9.8%). There was a statistically significant association between ever e-cigarette use and current smoking (OR=54.57) and the highest prevalence (46.4%) of ever e-cig use was among current smokers with a high cigarette dependence score.
King et al from the National Center for Chronic Disease Prevention and Health Promotion at the CDC analyzed data from the 2010 and 2011 “Health Styles” surveys, a consumer panel survey, to determine estimates of the national prevalence and socio-demographic correlates of awareness and ever-use of e-cigs among U.S. adults (King, Alam, Promoff, Arrazola, & Dube, 2013). The survey results showed that the awareness and use of e-cigs were increasing rapidly. Approximately 6 in 10 adults were found to be aware of e-cigs in 2011 compared with 4 in 10 adults in 2010. Moreover, in 2011, 6.2% of all adults and 21.2% of current smokers had ever used e-cigs, representing an approximate doubling of 2010 estimates. Differences in awareness and use of e-cigs were observed across subpopulations such as adults <65 years of age, non-Hispanic Whites, and current and former smokers were most aware of e-cigs. Current smokers were significantly higher users of e-cigs than non-smokers.

Experimental studies

Since the launch of the e-cig, there have been couple of randomized controlled trials performed on the e-cig users. The randomized controlled trial conducted by Bullen et al from 2011 till 2013 in New Zealand, aimed to assess whether nicotine e-cigs were more effective for smoking cessation than nicotine patches, and included a blind comparison with e-cigs containing no nicotine (placebo e-cig) (Bullen et al., 2013). The results showed a significant reduction of the mean cigarette consumption by two cigarettes per day more in the nicotine e-cigs group than the patches group (P = 0.002). It was also observed that 57% of the e-cigs group reduced daily cigarettes by at least half at 6 months than in the nicotine patches group (41%; P = 0.0002) and in the placebo e-cig group (45%; P = 0.08). The results
also showed an abstinence at 6 months after quit day of 7.3% in the nicotine e-cig group, of 5.8% in the nicotine patches group (5.8%), and of 4.1% in the placebo e-cig group. Moreover, time to relapse in the nicotine e-cig group was observed to be 35 days, more than twice as long as in the patches group (14 days) or placebo e-cigarettes group (12 days).

The ECLAT trial (Efficiency and safety of an electronic cigarette) was a prospective 12-month, double-blind, randomized controlled trial conducted by Caponnetto and his colleagues in Italy, during the period June 2010–February 2011 (Caponnetto et al., 2013). It was designed to assess the efficacy and safety of e-cigs loaded with different strengths of nicotine (7.2 mg, 5.4 mg and no nicotine cartridges). The results of this study showed a decline in cigarette per day used in all three groups, with no consistent differences among study groups. Smoking reduction was reported documented in 22.3% and 10.3% at Weeks 12 and 52, respectively. Complete abstinence from tobacco smoking was reported as 11%, 17% and 4% in the three arms respectively, at week 12 and 13%, 9% and 4% in the three arms respectively at week 52 (P= 0.001 versus baseline).

In another smaller scale trial in terms of participants, Dawkins et al chose 86 e-cig naive smokers and randomly allocated them to either 18 mg nicotine e-cig (nicotine), 0 mg e-cig (placebo) or just hold the e-cig (just hold) groups (Dawkins et al., 2012). The study reported that desire to smoke declined over time for both nicotine and placebo groups relative to the just hold group. After using the e-cig, the mean desire to smoke score
significantly changed from 4.5 (at baseline) to 2.5, 20 min after use (P=0.05). The difference was found to be statistically significant for males and females from baseline to 20 minutes.

**Cohort studies**

Polosa et al conducted a proof-of-concept study to monitor changes in the smoking habits of a group of regular smokers in Italy, focusing on smoking reduction and smoking abstinence (Polosa et al., 2011). Eligible participants were followed up prospectively for 6 months. The study reported that in 13 of the total 40 (32.5%) participants, the use of cigarette per day was reduced by 50% at the end of the study (P= 0.001). A reduction of 80% in the number of cigarettes smoked was observed in 5 of the 40 participants (12.5%, P= 0.043).

A similar proof-of-concept study was conducted by Caponnetto et al to monitor modifications in the smoking habits of a group of regular smokers with schizophrenia experimenting a popular brand of e-cigs (Caponnetto, Auditore, Russo, Cappello, & Polosa, 2013). The study participants were followed up prospectively for 12 months. The results showed a reduction of 50% in the number of cigarette per day in 7 of the 14 participants and the median value of 30 cigarettes per day decreased significantly to 15 cigarettes per day (P =0.018). Additionally, sustained smoking abstinence at week 52 was observed in 2 of the 14 (14.3%) participants.
Farsalinos et al conducted a study to examine the profile and e-cig use patterns in a specific group of past cigarette smokers who managed to completely substitute smoking with e-cig use without using any other aid (Farsalinos, Romagna, Tsiapras, Kyrzopoulos, & Voudris, 2013). The study focused on evaluating nicotine levels used, reported side effects and benefits, and the dependency potential of e-cigs compared with tobacco cigarettes. The study reported that a significant proportion (42%) of the participants quit smoking during the first month of using e-cigs. Most participants reported increasing the nicotine concentration in their e-cigs in order to achieve complete substitution of smoking. More than 80% of e-cig users were reported to quit smoking cigarettes by using nicotine levels higher than 15 mg/mL.

Polosa et al investigated long-term efficacy of the e-cigs as a smoking-cessation tool in a cohort of current smokers followed up to 24 months (Polosa et al., 2014). The prospective observational study evaluated smoking reduction and abstinence by measuring >50% reduction in the number of cig/day from baseline, >80% reduction in the number of cig/day from baseline, and complete abstinence from smoking. The outcomes were measured at the baseline, 6 months, 18 months and 24 months. The results showed a significant overall 80% reduction in median cig/day use from 25 to 4 cigarette by the end of the study. Sustained 50% reduction in the number of cig/day at 24 months was seen in 27.5% subjects. There were 12.5% quitters by the end of the study. Overall, combined sustained 50% reduction and smoking abstinence was seen in 40% participants at 24 months, with a median of 24.5 cig/day decreasing significantly to 4 cig/day (p<0.001).
Another study conducted by Rigotti et al described the prevalence of current e-cig use among adults who were admitted to nine acute-care hospitals in five geographically dispersed U.S. cities (Birmingham, AL; Boston, MA; Kansas City, KS; New York, NY; and Portland, OR) over 3.5 years, from July 2010 to December 2013 (Rigotti et al., 2014). The study evaluated the association between self-report of having used one or more e-cigs in the 30 days before the hospital admission and covariates including enrollment date, age, sex, race/ethnicity, marital status, educational attainment, health insurance, type of admission (emergency room vs. other), number of cigarettes per day before admission, and whether the smoker planned to quit smoking after discharge. The results showed that overall 14% of all patients (n=4660) admitted between July 2010 and December 2013 reported having used an e-cig in the 30 days prior to their hospital admission. Out of all the covariates, e-cig use significantly varied by the patient characteristics of age, race/ethnicity, education and cigarettes smoked per day. The results also showed that the prevalence of e-cig use significantly increased over time, from 1.1% in 2010, to 10.3% in 2011, to 10.2% in 2012, and 18.4% in 2013 (p < .0001). Younger smokers (<45 years), heavier smokers (≥10 cigarettes/day), and those with more education (high school diploma or more) were more likely to have used an e-cigarette in the 30 days before hospital admission, controlling for other factors.

Physiological studies

Vansicket et al conducted a study to characterize e-cig users’ nicotine and CO exposure, cardiovascular response, and ratings of nicotine abstinence symptom suppression
The study involved 32 tobacco cigarette smokers and compared the effect of two e-cig brands with own brand cigarettes and placebo smoking (i.e., puffing on an unlit cigarette). The results of this acute study suggested that two 10-puff bouts with the e-cigs exposed users to no significantly measurable nicotine or CO and did not increase heart rate. The results also showed that neither of the e-cig exposed users to measurable levels of nicotine or CO, although both suppressed nicotine/tobacco abstinence symptom ratings.

Another study looking at the cardiovascular effects was conducted by Eissenberg et al and it examined how two brands of e-cigs influenced plasma nicotine levels, heart rate and cigarette craving in cigarette smokers, and compared these effects to those produced by smokers’ usual brand of cigarettes (Eissenberg, 2010). The study recruited 16 naive e-cig users who used either their own brand cigarettes, sham smoking (puffing an unlit cigarette), or two different brands of e-cigs. The results of the study showed that relative to tobacco cigarette, 10 puffs from either of the branded e-cigs delivered little to no nicotine and suppressed craving less effectively.

Vansickel et al conducted a second study to investigate an initial abuse liability assessment of an e-cig brand current regular cigarette smokers (Vansickel, Weaver, & Eissenberg, 2012). To accomplish this, the nicotine delivery profile, subjective and cardiovascular effects of an e-cig were examined following puffs of regular cigarettes and bouts of the e-cigs. Their plasma nicotine concentration, heart rate and subjective effects were measured. It was observed that tobacco abstinence symptom suppression and increased product
acceptability ratings were associated with e-cig. In terms of heart rate, there was an insignificant increase observed from a pre-administration average of 67.5 beats per minute to 75 beats per minute, 5 minutes after the first e-cig bout. No effect of e-cig administration was observed for systolic or diastolic pressure.

Flouris et al conducted a study to assess the acute impact of active and passive e-cigarette smoking on serum cotinine and lung function, as compared to active and passive tobacco cigarette smoking (Flouris et al., 2012). Fifteen current and fifteen never-smokers were asked to undergo a control session, an active tobacco cigarette smoking session and an active e-cig smoking session and their serum cotinine, lung function, exhaled carbon monoxide (CO) and nitric oxide were assessed at the baseline, immediately post and 1 hour post exposure of the sessions. The results showed a statistically significant linear association between the serum cotinine levels observed immediately after and 1 hour after the active tobacco and active e-cig sessions. Further, no statistical difference in the lung function data was observed within each individual time point (i.e. baseline, immediately post and 1 h post-exposure), in both groups. In the active control group, no significant fluctuations were observed in the lung function and serum cotinine concentration. In contrast, the lung function and CO levels changed significantly across time during the active tobacco session. During the active e-cog session, cotinine was found to be fluctuated significantly but no significant effect was observed in lung function and exhaled CO.

Another study to assess the physiological impact of e-cig was conducted by Farsanilos et al (Farsalinos, Tsiapras, Kyrzopoulou, Savvopoulou, & Voudris, 2014). They evaluated the
effects of e-cig use on cardiac function, more specifically to investigate the acute effects of using an e-cig for 7 minutes on hemodynamics parameters and myocardial function, compared to the effects of smoking a tobacco cigarette. The study population consisted of current smokers who were smoking for at least 5 years and were consuming at least 15 cigarettes per day and e-cig users who had quit smoking and were using e-cigs for at least 1 month. The results showed that after-use values of systolic BP, heart rate and pressure rate were elevated in the smoker group but not in the e-cig group. In contrast, diastolic BP increased almost equally in both groups.

Vardavas et al conducted a study to investigate whether using an e-cigarette for short period of time could affect respiratory mechanics, using the experimental vs control group study design (Vardavas et al., 2012). The study population was composed of 30 adults recruited from a community setting in Athens, Greece. All subjects were current smokers with a minimum pack-year index of 5. The results showed that with regards to pulmonary oxidative stress, exhaled nitric oxide within the experimental group decreased by 16% after the use of an e-cig, whereas it remained unchanged within the control group. According to the study, decrease in exhaled nitric oxide results in respiratory impedance and respiratory flow resistance (similar to cigarette use). The results also showed that the lung airways impedance increased significantly in the experimental group whereas no differences were noted among control group participants. After controlling for subject’s baseline’s responses, the peripheral flow resistance was found to increase significantly after use of the e-cigs.
Tzatzarakis, et al published their research in the abstracts of the 49th Congress of the European Societies of Toxicology (EUROTOX) (Tzatzarakis, Tsitoglou, & Chorti, 2013). The research was conducted to examine the acute and short term impact of active and passive tobacco and e-cig smoking on inflammatory markers. Ten smokers and 10 never-smokers completed the repeated measures controlled study. Smokers underwent a control session, an active tobacco cigarette smoking session, and an active e-cig smoking session. Never-smokers underwent a control session, a passive tobacco cigarette smoking session, and a passive e-cigarette smoking session. Several smoking-related biomarkers including Interleukins (IL) 1 alpha, 1 beta, 2, 4, 6, 8, and 10 as well as vascular endothelial growth factor, tumour necrosis factor alpha (TNFa), monocyte chemotactic protein-1, and epidermal growth factor (EGF) were assessed at baseline, immediately following smoking/control, and one hour thereafter. The results showed that neither a brief session of active e-cig smoking nor a 1 hour passive e-cig smoking significantly affected the assessed inflammatory markers. In contrast, active tobacco cigarette smoking significantly increased IL2 and EGF immediately after smoking. Also, passive tobacco cigarette smoking increased TNFa immediately after the smoking exposure.
Gaps in literature

Despite the increasing popularity of e-cigs worldwide, not much research has been done regarding the long term effects of e-cigs on the smoking behavior of the current smoking population. Most of the literature deals with survey studies, soliciting personal views on vaping, studies analyzing potential toxins and contaminants in e-cig cartridges, reports profiling nicotine content, delivery, and pharmacokinetics and very few clinical and physiological studies investigating the effects of acute vaping. Till today, only one research protocol could be found which aimed to evaluate the long-term adherence to e-cigs and the long term efficacy of e-cigarettes in reducing and/or quitting traditional cigarette smoking. However, the protocol plans to follow up subjects for 5 years and the results will most likely not be out before 2018 (Manzoli et al., 2013).

None of the studies mentioned above have tried to estimate or quantify the long term effects of e-cigs in a smoking or a non-smoking population. Most of the studies followed a cross-sectional survey design and used a snapshot of e-cig users at one point in time. Some studies observed the e-cig users for 6 months or maximum for 12 months to identify the effects of cessation. Based on the short term or cross sectional study designs, most of these studies suggest that using e-cigs or vaping could be used as a possible harm reduction tool. However, to trust e-cigs as a smoking-cessation agent, we need to have more comprehensive research evidence to make informed decisions. It is a well-known fact that smoking is a long term and a highly dynamic habit. It will be safe to say that if a person who is abstinence today, may start using e-cig tomorrow and then switch to regular cigarette in future. Keeping that in mind, it is important identify different behavior scenarios to model
the long term effects of e-cig in a population. Using the evidence from currently available literature, it will be interesting to predict the long term net effects of e-cigs.

**Study Objectives**

The primary objective of this study was to construct a Discrete Event Simulation system to model the behavior and pattern of e-cig use among different smoking groups of the US smoking population. The model was built and validated using the e-cig use behavior information available in the published literature and by seeking expert opinion from the field of Tobacco Regulatory Health Science. The secondary objective of this study was to run the simulation model to estimate the long term prevalence of e-cig use in different groups of the US smoking population.
Chapter 3

Methods
Overview

The primary purpose of this study was to develop a simulation model to simulate e-cig use behavior pattern of current smokers, former smokers and never smokers for fifteen years. We chose to use the technique of Discrete Event Simulation (DES) to model the e-cig use. The principles of good research practices for modeling studies outlined by the ISPOR task force (Karnon et al., 2012) were followed as closely as possible to build the model. The model consisted of current, former and never smokers whose behavior was simulated, based on existing data available in published literature. The model included the population attributes and the list of events that occurred over the simulated time. The states or events were continuously updated through the model simulation. The uncertainty around the literature estimates was accounted by using stochastic simulation over deterministic simulation.
**What is simulation modeling?**

The ISPOR task force put together a report for good research practices in modeling studies in health care evaluation in 2012 (Karnon et al., 2012). It defined modeling as “a logical mathematical framework that permits the integration of facts and values, which in turn link these data to outcomes that are of interest to health care decision makers.” A generalized version of the definition summarizes simulation modeling as a computerized version of the system which is run over time to study the implications of the defined interactions among the input parameters (Weinstein et al., 2003). It helps us accurately reflect the randomness and interdependence of behavior and outcomes present in reality with available data and resources. Using simulation, we can predict the future outcomes by including time related events and probability distributions into the modeling framework as they occur in real life to obtain accurate estimates (Briggs & Sculpher, 2006; Weinstein et al., 2003).

**Simulation Modeling Applications in Healthcare**

Simulation modelling approaches are now widely used to assess new health care technologies, simulate disease or treatment pathways or simulate health behaviors. Generally, the modeling is needed to study consequences of any event or intervention, beyond the direct application of observed data (Barton, Bryan, & Robinson, 2004). In research, simulation modeling generally comprises of mathematical equations and analytic methodology that account for events that occur over time (Gold, Siegel, Russell, & Weinstein, 1996). This type of modeling differs from statistical models such as regression models by allowing a combination of information from a variety of sources or synthesize
data for the purpose of making a decision (Barton et al., 2004). Simulation modeling can also be used in conditions where cost and effectiveness parameters are compared beyond the data observed in a clinical trial, intermediate clinical end-points are linked to final health outcomes, extrapolation of the results obtained in one clinical setting to other, making comparisons of alternative competing interventions where direct comparisons have not been made in clinical trials or guiding policy decisions in absence of real data (Buxton et al., 1997).

As the ISPOR definition mentioned above, simulation models structures are made up of logical framework and mathematical equations which uses the best available information about the system being studied, the outcomes of interest, and the risks and probabilities affecting each action (Stahl, 2008). Incorporating this information into the model structure helps in generating evidence for or against our hypotheses, and help researchers understand the nature of the problem under study. We also use simulation models to aid our decision making by helping us make decisions under conditions of uncertainty. We can use it to evaluate the outcomes of different strategies, to explore the consequences of changes to the system and to predict how the behavior of a system with change in time.

**Model Selection Process**

The selection of an appropriate modelling approach is an integral step for the question being considered. It is represented as a flowchart in figure 1.
Can Markov model be built without needing an excessive number of states?

No

Is interaction between individuals important?

No

Can patient pathways be adequately represented and manageable by decision tree branches?

No

Is history important in deciding the progress of individual in the model?

No

Can Markov model be built without needing an excessive number of states?

Yes

Discrete event simulation

Yes

Decision Tree

Model selection flowchart (Barton et al., 2004)
Interaction or no interaction

The selection of the appropriate model for modeling a health care intervention should be made along the lines shown in Figure 1. As mentioned above, the initial consideration is whether the individuals in the model may be regarded as independent or not. When interaction is not an important issue then the choice is between decision trees, or Markov models. Where interaction is a significant issue in modelling, models such as DES are required.

Cohort or individual

The second important aspect in the model selection process the nature of the object that is to be modeled and conceptualizing what happens to those objects. The objects can either be modeled as a population (cohort or aggregate modeling) or as individuals in the population (individual level simulation) (Brennan, Chick, & Davies, 2006). With respect to conceptualizations, the problem can be represented as a series of states that the objects can be in, or it can be represented as events the objects can experience (Brennan et al., 2006; Stahl, 2008).

There are two major concerns with a cohort approach. Firstly, the determination of proportion of population at each relevant time point. That proportion is dependent on the risk the population is exposed to, and that risk is affected by treatment the population is subject to. However in reality, the risk will also depend on patient characteristics, such as age, sex, smoking, and other risk factors. Hence, it is important to characterize the population and examine these factors individually.
Secondly, the transition from one state to another is not random. People who are at higher risk, tend to move from better to worse state earlier than the rest. However, it is difficult to characterize these patients in terms of features that may be determinants of further risk. If the future risk is dependent on the duration of the time spent in the previous state, the estimates will be inaccurate given that the arriving populations mix into a single group and do not retain any memory of when they became sick (Caro, Moller, & Getsios, 2010).

All the problems listed above in the cohort approach are readily solved by modeling individuals instead of the entire population in the aggregate. For each individual, the risk can be computed based on their characteristics, the risks can be easily updated over time, and can be recalculated based on changing history of an individual. Individual level modeling give us the freedom from restriction to analyze population as homogeneous groups with equal risks for everyone.

*State versus Event*

In a state-transition model, such as Markov models, the system is conceptualized as a series of interrelated that the population may be in. These snapshots occur at fixed, discrete time points called cycles. Trying to represent conditions with large number of states leads to different combinations of all possible outcomes, which may result in inaccuracies.

The most common types of healthcare models that do not involve interaction are decision trees and Markov models (Karnon & Brown, 1998).
**Decision Trees**

The Decision Tree has the simplest structure. All possible patient pathways are shown explicitly on decision tree branches, with associated probabilities and outcome measures. If the time frame is short and if the nature of patients’ outcome does not differ across strategies, a simple decision tree is an appropriate choice. Decision trees are usually constructed with a single decision node at the root of the tree, which then grows into a set of linked probability branches, one for each alternative. Although decision trees are simpler to understand and analyze, there is a limit to the manageable size of a tree. In case of a complex problem, such as a situation where the issue of interest is the survival time, using a decision tree becomes a cumbersome approach. To avoid an infinite number of branches in the tree, it is necessary to consider a different approach to model survival time with a different range.

**Markov Models**

Markov models are increasingly being used in complex healthcare problems. Their main advantage is the easy representation of recurrent events, but like decision trees they do not allow for interaction between individuals. Also, the transition probability depends only on the state in which the patient is at the start of the cycle. This is known as the Markov assumption. The Markov assumption does not allow the transition probability to depend either on the time a patient has spent in a given state, or the patient’s previous history before entering that state (Briggs & Sculpher, 1998). Markov models thus assume that patients in a given state can be treated as homogeneous groups and this homogeneity
assumption is inherent in Markov models. For any given alternative, the proportion of patients in each state can be calculated sequentially for each time cycle over a period of simulated time. Costs are then accumulated according to the number of patients in a given state in each cycle. Different policies may be tested by changing the costs and transition probabilities.

*Models that account for interaction between individuals*

*Discrete Event Simulation*

DES accounts for interaction between individuals. Also, when the outcome depends on the history of the patient or the continuous update of patient’s characteristics, models such as DES are required. DES works at an individual level and allows full representation of each individual’s history and the interaction between specific individuals. It can accommodate a more complex structure than Decision Trees and Markov models, and can still remain manageable in size.

DES provides the luxury of overcoming the homogeneity assumptions by attaching attributes to the individuals within a model. The transition probabilities can be made to vary according to these attributes in any way that is desired. Furthermore, attributes can be updated while the model is running. Another advantage of DES is that it allows the patient to remain in a given state for a variable length of time, unlike the fixed states of Markov models. Also, DES uses stochastic models that include probabilistic sensitivity analyses to quantify the uncertainties caused due to variability in parameters whereas
Deterministic models are mathematical models where outcomes are precisely determined through known relationships among states and events, without any room for random variation. Conducting probabilistic sensitivity analyses in stochastic models also allows some amount of generalizability over different geographical and demographic settings. In a DES, the experience of individuals is modeled over time in terms of the events that occur and the consequences of those events. Many of the limitations and inaccuracies of Markov models and decision trees are easily avoided with DES.

Another big advantage of DES over cohort-based models is that they can work relatively more efficiently with limited data availability. The quality of model is highly dependent on the data which is incorporated into it. In case of limited individual level data availability, a DES model provides a great advantage because the inadequacy of the data is not built into the structure of the model (Caro et al., 2010). The simulation can be designed to properly reflect the problem and carry out exploratory analyses with the limited data and make predictions. It can then incorporate additional data when it becomes available (Caro et al., 2010). In our case, simulation will be useful as long term observational data pertaining to e-cig use is not available yet. It will help us better understand and predict the vaping behavior (real or hypothetical) that we are trying to examine.

The differences between Decision Trees, Markov models and DES are outlined in table 1 below:
<table>
<thead>
<tr>
<th>Features</th>
<th>Decision Trees</th>
<th>Markov Models</th>
<th>Discrete Event Simulation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time horizon</strong></td>
<td>Short</td>
<td>Short and long</td>
<td>Lifetime behavior</td>
</tr>
<tr>
<td><strong># of events modeled</strong></td>
<td>Small</td>
<td>Relatively higher</td>
<td>High number of events</td>
</tr>
<tr>
<td><strong>Memory feature (Different risk factors over time)</strong></td>
<td>No</td>
<td>No</td>
<td>Accounts for risk changes</td>
</tr>
<tr>
<td><strong>Probabilistic sensitivity analysis</strong></td>
<td>Difficult</td>
<td>Difficult</td>
<td>Inherent in the model</td>
</tr>
<tr>
<td><strong>Data requirement</strong></td>
<td>Not good for limited data</td>
<td>Not good for limited data</td>
<td>Simulate large number of subjects with unique characteristics</td>
</tr>
<tr>
<td><strong>Accounts for interactions between individuals</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Update of model population</strong></td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Computational requirements</strong></td>
<td>Simple (Microsoft Excel)</td>
<td>Simple (Microsoft Excel)</td>
<td>Special software programs</td>
</tr>
</tbody>
</table>

Table 1. Main differences between Decision trees, Markov models and DES
Discrete Event Simulation and its components

The working structure of a DES closely replicates the course outlined in figure 2.

Figure 2. Flow diagram of the computation process for a discrete event simulation (Caro et al., 2010).

The model starts by setting the simulation clock to zero. The initial state is set by the user based on the system being modeled and incorporating the baseline characteristics of the
model population. Next step is to list out all the relevant events using the logical and mathematical framework of the system. This will drive the flow of the model population and decide the change in current and future states of the model. Once the initialization step is over and the model is made to run, based on the individual’s characteristics and the way it is programmed, it determines which event will the individual will go to next. Accordingly, the system jumps to the next event by bringing the individual to that particular state and advancing the simulation model clock, which in turn records the time at which the event took place. Once the event is processed in the system, the change in states of the individuals and the system as a whole is recorded and the individual characteristics are updated. Based on the updated characteristics, the future states in the path of the individual is determined. This process is repeated until all the individuals are made to go through the entire cycle or until the pre-set simulation time period ends. After the simulation has ended, final reports are generated showing the estimated outcomes of the simulation.

The fundamental components of the DES technique are described below:

1) Entities

A central component of DES is the entity. Entities are the items that flow through the simulation, smokers in our case. Smokers have attributes (e.g. age, sex, race, smoking history), with each individual having a specific value for each characteristic. These values are defined at the start of the simulation and are updated as events take places such as age increases, initiating e-cig use, or quit attempts. These updates can happen at particular points in time. The model update is decided on the basis of the structure of the problem.
2) Events

The second major element of the simulation is the events that drive the entities. An event can be defined as anything that happens during the simulation. Thus, it can be the occurrence of a quit attempt, initiation of e-cig, relapse or just aging in the model. Events can happen in any logical sequence and even simultaneously. They can recur if that happens in reality. Events change the course of individuals’ experience by influencing their attributes and occurrence of future events with no restriction on memory. For example, the initiating of e-cig can depend on previous use but can also be altered by making a quit attempt in future. The rates at which events occur can take any functional form supported by the data or assumptions. They can be dependent on any attributes or variables and these functions can change over time as appropriate.

3) Time

The third important component of a DES is time. A simulation clock keeps track of the passage of time in the model. This permits the modeler to clearly signal the start and end of the simulation and to create internal time periods such as the length of staying in a particular state. By making time explicit, a DES allows more flexibility than Markov models and Decision trees. Time moves continuously and the units can be minutes, days, months or whatever is convenient. However, since the progression of simulation depends on events, the simulation clock is advanced to the time when the next event will occur.
4) Means of Execution

The final component is the means to execute the simulation, following a desired logic and carrying out all the calculations. The execution begins by formulating the question in detail, providing a description of the system that is to be modelled, specifying the details that pertain to the condition in question. Following that, the model is designed conceptually in the form of an influence diagram. Once the concept has been validated with help from relevant experts, data are fit to the model.

5) Actual simulation

Once the model is coded in software and debugged, the analysis in a DES proceeds by specifying the initial system conditions (i.e. starting values for all attributes and variables) and simulation settings (e.g. duration, time units, number of replications). The software then carries out the simulation by applying the logic to each entity (patient) using random numbers to obtain specific values from assigned distributions and determine whether probabilistic events occur at a given time to a given patient. Thus, a DES is an individual patient, stochastic simulation (Caro et al., 2010).
As explained in the overview section of this chapter, we decided to construct a DES model to simulate the behavior of e-cig users in the US. The description of the data sources, model parametrization, simulation pathway and handling uncertainty is described as follows.
The E-cig model

Generating the model population

To generate the model population, we used publicly available data from the cross-sectional National Health Interview Survey (NHIS), a nationally representative multistage household survey of the civilian noninstitutionalized population of the United States. The National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) has conducted the NHIS annually since the 1950s to monitor the nation’s health at both the household/family level (e.g., type of living quarters, family size, and total combined family income) and the individual level (e.g., various medical/health conditions, risk factors, and access to care). The main objective of the NHIS is to monitor the health of the US population through the collection and analysis of data on a broad range of health conditions. The survey also collects current data on many demographic and socioeconomic characteristics (NCHS, 2012).

The NHIS covers the civilian population residing in the United States at the time of the interview. It is a cross-sectional household interview survey and the sampling plan follows a complex, multistage probability sample that incorporates stratification, clustering, and oversampling of some subpopulations (e.g., Black, Hispanic, and Asian) in some years (MPC, 2011; NCHS, 2012). Because of the complex sampling design of the NHIS, sampling weights are constructed so that each unit (survey respondent or household) can be inflated or expanded to represent other individuals or households in the United States (NCHS, 2012).
The NHIS questionnaire contains four major components: Household, Family, Sample Adult, and Sample Child. The Household component collects demographic information on all of the individuals living in a particular house. The Family component collects additional demographic information on each member from each family in the house and collects data on topics including health status and limitations, injuries, healthcare access and utilization, health insurance, and income and assets. The Family Core component allows the NHIS to serve as a sampling frame for additional integrated surveys as and when needed. From each family in the NHIS, one sample adult and one sample child are randomly selected and information on each is collected with the Sample Adult Core and the Sample Child Core questionnaires. Because some health issues are different for children and adults, these two questionnaires differ in some items but both collect basic information on health status, health care services, and health behaviors. Its protocol and administration have been approved by the NCHS's Research Ethics Review Board, and all NHIS participants provide informed consent (NCHS, 2012).

For the purpose of our model population, we pooled the data for 2011, 2012 and 2013 to generate a recent national estimate of the US population with specific demographic and smoking-related characteristics. Each data file contained household, family, and person record identifiers that made merging the data files possible. Once the data files were sorted by the household, family, and person record identifiers (coded as HHX, FMX and FPX in NHIS, respectively), the Household, Person, and Sample Child data files were merged, for each of the three years. Variable names were changed from one year to another when required. The data across the years were combined or concatenated to increase the number of observations or respondents and thus increase the precision of estimates. The
three years’ worth of merged data files joined one after the other (concatenation). New weights were constructed to adjust for combining data years. For three years of data, the new weights were calculated by dividing the original weights by 3 to give the final weight of every individual in the sample.

The pooled dataset had 86,402 individuals who had complete information on their demographic characteristics and smoking behavior. We classified a respondent’s cigarette smoking behavior by his/her answers to questions about cigarette smoking status and smoking cessation attempts based on an existing NHIS recoded variable with six response levels: current smoker, recent former smoker, and never smoker. Respondents that reported having smoked at least 100 cigarettes in their entire life and were currently smoking every day or some days at the time of interview, were classified as current smokers (CS). Respondents reported smoking at least 100 cigarettes during their lifetime but currently did not smoke at least for the past 12 months, were classified as former smokers (FS). FS were further classified into recent former smokers or late former smokers. Recent former smokers were those former smokers who had stopped smoking less than 12 months ago. Late former smokers were those former smokers who had stopped smoking over a year ago.

Respondents reported not having smoked at least 100 cigarettes in their life and were not currently smoking for the past 12 months, were classified as never smokers (NS). This method of smokers’ classification has been recommended by NCHS and is used in earlier studies done on smoking population (Mehta & Preston, 2012).
Descriptive analyses was run on the sample to calculate the frequency distribution of population demographic and smoking characteristics. The demographic categories included age (<21, 21-35, 36-50, 51-65, >65), gender (male, female), race (white, black, other), and education level (less than high school, high school, college). The smoking-related categories included years of regular smoking (for current smokers), at least one quit attempt in the past 12 months (for current smokers) and nicotine dependence score (for current smokers). The information on nicotine dependence had to be utilized from a different source. We used the estimates of a matched sample, from a web based survey on current and former smokers in the US (Yeomans et al., 2011).

Probability estimates related to e-cig use

The probabilities of current e-cig use associated with different demographic and smoking characteristics, among different smoking categories of the US population were derived from the prevalence estimates published in several cross-sectional and longitudinal e-cig studies done in the US.

The e-cig prevalence estimates associated with age, gender, race, education level for current, former and never smokers were utilized from the Knowledge Networks survey data, which was commissioned by the University of California, San Diego (Zhu et al., 2013). The survey collected information on smoking history and cigarette use, perceptions about different tobacco products and quitting aids, attitudes toward tobacco control efforts, and beliefs and ideation about the process of quitting smoking. The study sampled the smokers, former smokers and never smokers from the panel in a way such that the three smoking status groups were approximately equal in size. The final survey sample consisted of 3,111
current smokers, 3,676 former smokers and 3,254 never smokers. Following the same classification as our NHIS sample, current smokers (CS) were defined as those who had smoked at least 100 cigarettes in their lifetime and were still smoking some days or every day at the time of survey administration. Former smokers were defined as smokers who smoked at least 100 cigarettes in their lifetime and were not smoking at the time of survey administration. Former smokers were further classified into recent former smokers (RFS) and late former smokers (LFS). Former smokers were classified as RFS if they smoked their last cigarette within the time period of 1 year or less, and as LFS if they smoked their last cigarette over 1 year ago. Never smokers (NS) were defined as those who had not smoked 100 cigarettes in their lifetime (Zhu et al., 2013).

Use of e-cigs was also assessed in multiple questions. First, respondents were asked if they had ever heard of e-cigs. Next, those who had heard of e-cigs were asked if they had ever tried an e-cig. Those who answered yes were considered ever users. Ever users were also asked if they had used e-cig multiple times in the last 30 days. Those who answered yes, were considered current e-cig users (Zhu et al., 2013).

Along with the prevalence estimates associated with demographic characteristics, the Knowledge Networks Panel survey data also provided related standard errors and 95% confidence intervals which were used to carry out sensitivity analyses for the simulation model. We did not use the prevalence estimate for ever e-cig users as published studies have indicated that ‘ever use’ is not the accurate measure of e-cig prevalence (Adkison et al., 2013; Bell & Keane, 2012). Mostly, ever users have been known to try e-cig once and not
continue after that. Also, we wanted to use a conservative estimate in our simulation model to predict the outcomes. Hence, current e-cig use estimates were chosen over ever e-cig use.

Zhu et al did not report the prevalence associated with e-cig users below 18 years. Since the age group of 6-18 years has been associated with a high use of e-cig in the US (Agaku et al., 2014), we used another study to obtain prevalence estimates of age category 6-20 years. The study analyzed a sample of 3,912 high school and middle school students of current and recent former cigarette smokers and e-cig users (Camenga et al., 2014). The students were attending high schools in Connecticut and New York and were asked similar questions as in the Knowledge Networks survey.

For the probability associated with making a quit attempt, we used estimates from the Legacy Longitudinal Smoker Cohort (LLSC) survey data (Pearson et al., 2012). The LLSC collected data on a large cohort of current smokers and recent former smokers (n= 5616) living in the US, and was used to obtain demographic and point estimates for awareness, use, and harm perceptions associated with e-cigs.

The e-cig use associated with the nicotine dependence score and cigarette per day use, were derived from estimates obtained from the International Tobacco Control Four Country Survey (ITC-4) data, conducted between 2002 and 2011 (Kasza et al., 2014). The survey population consisted of 6,110 adult smokers in the US, Canada, UK and Australia and it examined the demographic and smoking-related predictors of use of unconventional
tobacco products (i.e., other smoked tobacco products, smokeless tobacco products, unconventional cigarettes, and e-cigs). We used the estimates reported for the US population. The prevalence estimates along with the source for current, recent former, late former and never smokers are summarized in tables 6, 7, 8 and, 9 respectively, in the results section.
Model parametrization

The model was structured in terms of the specific events that individuals experience over the course of the simulation. The events and the attributes assigned to the model population were chosen after reviewing the e-cig literature and choosing the variables which had statistically and practically significant association with the use of e-cig among current, former and never smokers. Most studies indicated that age, gender, race, education level, years of smoking, past quit attempts, and nicotine dependence showed a significant association with the use of e-cig among current cigarette smokers (Kalkhoran, Grana, Neilands, & Ling, 2015; Kasza et al., 2014; King et al., 2013; McMillen, Gottlieb, Shaefer, Winickoff, & Klein, 2014). Accordingly, each individual was assigned a set of unique attributes which were corresponding to their baseline characteristics at the start of the simulation. These attributes or characteristics, were updated throughout the simulation, depending on the subject’s course through the model. The set of events in the simulation correspond closely to the behavior of e-cig users when they switch to e-cigs.

At the beginning, 100,000 smokers were generated by using the “Create” module from the Arena toolbar. The smokers were created and an exponential distribution was assigned to their arrival in the system. Once the model population was generated, the next step was to send them into one of the four branches; CS, RFS, LFS, and NS. The percent of people sent into each depended on the real live distribution of smokers obtained from the NHIS data. Next, the smokers were assigned baseline attributes using the “Assign” module. We assigned age, gender, race, education level, nicotine dependence, years of smoking,
cigarette per day use, and past quit attempts to each initial smoker. We then recorded each smoker’s yearly progress based on these assigned characteristics.

**Age**

The age assignment was done using the frequency distribution from the NHIS survey. The attribute “Age” was categorized into 5 age groups, which matched the data available for e-cig use. A continuous probability distribution was assigned to the Age attribute. Additionally, an original age attribute “AgeOrig” was assigned in the simulation to keep the track of the smokers’ increasing age within the system. Finally, another attribute “Age Group” was assigned based on current age in the model.

**Gender**

Similar to the age assignment, the “Gender” attribute was assigned using the frequency distribution from the NHIS survey. The assignment was done at two levels; 1-Male, 2-Female, and a discrete probability distribution was assigned to this attribute.

**Race**

The smokers’ race was assigned as a 3-level attribute named “Race”. Derived from the NHIS sample, level 1 was for “white”, 2 for “black” and 3 for “others”. The Race categorization was done to match the e-cig use data. Similar to the Gender attribute, Race was assigned a discrete distribution.
**Education**

The education level was assigned as a 3-level attribute named “Education”. Derived from the NHIS sample, level 1 was for smokers who had did not have a high school diploma, 2 for smokers who had at least a high school diploma and 3 was for smokers who had at least a college degree. The Education categorization was done to match the e-cig use data. Education was also assigned a discrete probability distribution.

**Nicotine Dependence score**

The next assignment was done using the “Assign” module again and it was used to assign the nicotine dependence score attribute “FTND score” to current smokers. The 3-level attribute derived the values from the matched sample from the web-based survey of US current smokers (Yeomans et al., 2011). It was assigned a discrete probability distribution.

**Previous Quit attempts**

The assignment of previous quit attempts was done using the distribution from the NHIS sample. The 2-level attribute was named “PrevQuit” and it had 0 for smokers who did not make even a single quit attempt and 1 for smokers who had attempted to quit at least once in their life. It was assigned a discrete probability distribution. Along with the “PrevQuit” attribute, another attribute named “CountQuitAttempt” was assigned in the system. The original value of this attribute was assigned as “PrevQuit” and its value was supposed to increase with every quit attempt a smokers makes in the simulation. Essentially, this step created the history of quit attempts before the current smokers entered the simulation model. CountQuitAttempt attribute was used to add the new quit attempts to the quit
attempts already made in the past (PrevQuit) of a current smoker, and there by changed the individual risk associated with the quit attempts in the system.

Assigning baseline probabilities and distributions

The probability for each event in the simulation model was assigned using the “Variable” module. A specific probability within each level of attribute, for every attribute was assigned which was responsible for events experienced by that individual smokers through the simulation. The probabilities were derived from the e-cig prevalence estimates discussed above.

Two specific distributions were assigned to the probabilities in the model, Continuous and Discrete. The Continuous distribution in Arena returns a sample from a user-defined continuous distribution, which in this case was the age distribution. Pairs of cumulative probabilities and associated values are specified, and then the sample returned has a real number between associated values and with corresponding cumulative probabilities. The continuous empirical distribution is often used to incorporate actual data for continuous random variables directly into the model.

The Discrete function in Arena returns a sample from a user-defined discrete probability distribution. The distribution is defined by the set of n possible discrete values that can be returned by the function and the cumulative probabilities. In our study, model inputs such as gender (1, 2), race (1, 2, 3), or education level (1, 2, 3) had discrete distribution. The discrete empirical distribution is often used to incorporate discrete empirical data directly into the model.
**Simulation Pathway**

This section presents the events that determine whether or not simulated smokers will become an e-cig user or not. For current smokers, these events were:

- Using e-cig
- Making a quit attempt
- Relapse
- Quitting
- Ageing
- Leaving the model

Once the smoker entered into the model, he/she was assigned the baseline attributes, associated probabilities and the corresponding probability distributions. After that, the smokers moved ahead and were given a choice to initiate using e-cig. The decision to use or not use came from the probability equations discussed below.

If the smoker decided to start using e-cig, he or she was given a chance to quit using e-cig within that same year. Around 48% made a quit attempt after using e-cig once and did not use it again. However, 52% continued using e-cig. This estimate was used from the study conducted by Kasza et al where the smokers who became e-cig users were asked after 1 year if they had made any attempts to stop smoking after using e-cig (Kasza et al., 2014).

Smokers who made a quit attempt the same year, were evaluated if they made a relapse to using e-cig within the same year. Based on the same study, 9% smokers who attempted a quit attempt did not make a relapse and stayed a quitter (Kasza et al., 2014). These quitter
were then assigned the status of “Former smoker” and their risk of e-cig use also were changed accordingly. Smokers who continued using e-cigs (relapse) were allowed to remain the in the loop and age in the simulation process. Next year, these smokers were made to pass through quit attempt module again to see if they made a quit attempt next year. Smokers who made a relapse were evaluated for the number of quit attempts and their age.

With each failed quit attempt, the probability of using the e-cig increased by 13% according to the literature (Pearson et al., 2012). We factored this scenario by recording the new quit attempts made after initiating the e-cig to the “CountQuit” attribute. That way, the new quit attempts were added to the history of previous quit attempts, and accordingly changed the overall probability of using the e-cig again in the simulation model. We did not want the probability to cross over 100% with several quit attempts, so we limited the number of quit attempts to 4. Anyone who made 4 quit attempts in the model, was counted as a regular e-cig user and allowed to exit the model.

Finally, smokers who did not initiate e-cig in the first year were allowed to age and assigned two new risks for initiating e-cig next year. First, as they aged a new risk of using e-cig was assigned based on their new age. Second, after 7 years into the simulation, every year the overall risk was made to reduce by 1% of the preceding year. We did this because we assumed that the initiating probability of e-cig will reduce in future due to variety of reasons ranging from new policies or regulations to the launch of new unconventional tobacco products. Also, since e-cig has been launched fairly recently, currently it is not regulated by any agency. However, in a few years, perhaps the FDA will control the sale of
e-cigs to young adults, or another unconventional tobacco product will be launched, or the consumer will have enough information about e-cig to make a decision, so its prevalence will wane down (Foulds et al., 2011). Hence, we factored this in by reducing the overall risk each subsequent year. Please see figure 3 for the working structure of the DES model. We used the risk reduction of 1% from a recent study done to examine the potential impact of price-related and tax-related policies on e-cigs use by assessing the own and cross-price elasticity of demand for e-cigs (Huang, Tauras, & Chaloupka, 2014). The study reported a 10% increase in price would reduce sales of e-cigs by approximately 12% or 10%. Taking the conservative approach, we first reduced the risk by 1% each year after the 7th year, and then tested the impact by increasing it to 3% and 5% each year in sensitivity analyses. Similarly, we tested the impact of timing of the policy by applying it at 5 years, 10 years and not applying it at all.

**Cumulative probability equation**

The ideal way to calculate the probability of an event happening is to run a linear regression on the model parameters to get the relationship and mutually exclusive probabilities. According to the probability theory, events E1, E2, En are said to be mutually exclusive if the occurrence of any one of them implies the non-occurrence of the remaining n – 1 events. Therefore, two mutually exclusive events cannot occur at the same time. Formally said, the intersection of each two of them is empty (the null event): \( A \cap B = 0 \). In consequence, mutually exclusive events have the property: \( P(A \cap B) = 0 \) (Beerenwinkel & Siebourg, 2012).
However, due to unavailability of individual level data related to e-cig, we were unable to use mutually exclusive probabilities. Instead, we used non-mutually exclusive event probabilities. Non-mutually exclusive events are events in which there is some overlap. When \( P(A) \) and \( P(B) \) are added, the probability of the intersection is added twice. To compensate for that double addition, the intersection needs to be subtracted. In other words, the probability of one or both events occurring is denoted \( P(A \cup B) \) and in general it equals \( P(A) + P(B) - P(A \cap B) \) (Beerenwinkel & Siebourg, 2012). Hence, we added all the individual probabilities associated with e-cig use and subtracted the intersections from the total sum.
Outcome Measures

Structural simulation of e-cig users’ behavior

One of the broader outcome of this study was to make an exploratory model which uses the currently available literature in structurally capturing the behavior of current, former and never smokers in terms of e-cig use. The model structure accounted for change in smoking habits, temporary or permanent use of e-cig, quitting behavior and relapse to smoking.

E-cig prevalence among current, former and never smokers

Another important outcome of this study was to estimate the national prevalence of e-cig use among the population of current cigarette smokers, past cigarette smokers and never smokers, and plot the estimates against time. The prevalence was also estimated in the sub population groups, specifically within different age groups, gender, race, and education level. The model was run for the period of fifteen years and the prevalence was plotted against time for each of the fifteen years.
**Simulation runs**

The model ran several sets of analyses to introduce the variation around the estimates. Specifically, the model was run using populations of 100,000 current, former and never smokers. Every simulation was for 100 replications to obtain confidence intervals when examining changes in the smoking groups.

**Calculating smoking prevalence**

The prevalence was calculated using the formula below:

- The average number of simulated CS, recent FS, late FS and NS who were recorded as e-cig users at the end of the simulation, for each time period.
- The size of the simulated smoking population (N=100,000) which entered the model.
- Since it is a population model, each year the number of people being born and dying were taken care by implementing the equation:

\[
Population_{t+1} = Population_t + br \times Population_t - dr \times Population_t
\]

The birth rate (br) adds to and the death rate (dr) subtracts from the population at each point, and the rates were obtained from the US census bureau website (US Census Bureau, 2014).
• Prevalence was then calculated by dividing the average number of e-cig users during the specified time period by the size of the simulated population.

The formula for calculating prevalence is shown below.

\[
\text{Prevalence} = \frac{\text{E-cig users at the end of each time period}}{\text{Size of simulated population during the same time period}} \times 100
\]
Model validation

The model was validated by a variety of methods. First, the model was tested for internal validation by using null and extreme input values to test whether they produce the expected outputs. This helped in verifying that the mathematical equations were calculating the correct values. Secondly, it was checked for debugging that included getting the program code examined for syntactical errors and test of reproducibility using equivalent input values. Debugging was performed by getting the programming code verified by Dr. Jaime Carro (Evidera) and Dr. Jorgen Moller (Evidera), who are experts in DES programming and have been making DES models in healthcare evaluation for over 10 years. Thirdly, the structural validity was conducted by getting the model structure examined by experts in the area of e-cig use. It ensured that the model incorporated all the feasible behavior scenarios in the model structure. Additionally, the model structure was validated by comparing our model structure with other published DES models (Gestios et al, 2013; Howard et al, 2008) which looked at cigarette smoking behavior and smoking cessation strategies, and the scenarios applicable to smoking behavior were incorporated in our model structure. Fourth, the model was tested for internal consistency by verifying that the mathematical probability equations used in the model were correct based on the probability theory and by seeking expert opinion from professionals in modeling and systems analyses. This was done by getting model structure verified by Dr. Edward Boone (VCU) and Marc Botteman (Pharmerit), who are experts in the area of system analysis. They checked the flow of smokers through different branches and helped in authenticating the output of our model.
We believe that getting our model verified by external DES and system analysis experts also increased the face validity of the model. Face validation helped to ensure that the model was constructed and used in accordance with the most current scientific and best available evidence. This enhanced the credibility and the acceptance of results. Moreover, we were able to perform limited amount of external validity which means comparing the model’s results to actual information in the real world. It involved comparing our model’s first year’s results with the most recent CDC reports on e-cig prevalence in the US population. Due to data limitation, we could not perform an independent validation whereby data used to validate comes from a source other than the one used to build the model.
Create smokers → Assign baseline characteristics → Assign FTND score and previous quit attempts → Use E-cig?

- No
- Yes → Make a quit attempt within 12 months?
  - No
  - Yes → Record the quit attempt
  - No → Relapse to e-cig?
    - Yes → Record the e-cig prevalence
    - No → Stay a quitter and become a former smoker

- Yes → Go into the loop again
- No → Wait for next year to quit and try quitting again

Figure 3. Working flowchart of the model structure.
Model assumptions

- The proportion of smokers using e-cigs in each sub-group was assumed as probabilities associated with the use of e-cig.
- The decision to use or not to use an e-cig each year in the model, depended only upon their baseline demographic and smoking characteristics and associated probabilities.
- The probability associated with making a quit attempt toward e-cig were assumed to be similar to the probability associated with quitting regular cigarette.
- Smokers inside the simulation model were not all allowed to use any external smoking cessation source such as primary or secondary smoking cessation treatments. Also, they were assumed to be willing to try e-cig as a smoking cessation tool.
- The quit attempt made inside the simulation model was assumed to be associated only with the use of e-cig and not because of external factors such as smoker’s intention, health risks, or cost changes.
- In never smokers, a person was assumed to not initiate using e-cig after 35 years of age.
- The nicotine dependence score derived from the matched sample of the web based survey smokers’ profile were assumed to be the nicotine dependence score of current smoker population created from NHIS.
- The effect of e-cig policies and regulations which will come into place in future was assumed to be 1% and was factored in the model by structuring a branch for non e-
cig users which reduced the overall probability of using e-cig by 1% each subsequent year.

- It was assumed that the smoking environment will not have any drastic change which will affect the initiation and the use of e-cig for the next 15 years.
- Smokers over 85 years were assumed to die and allowed to exit the model.
- The number of maximum quit attempts a person could make in the simulation was capped at 4.
- All e-cig users were assumed to be using a nicotine containing e-cigs.
Chapter 3

Results
Model Population Descriptive Analyses

<table>
<thead>
<tr>
<th>Demographic attributes</th>
<th>N</th>
<th>Weighted N</th>
<th>Weighted %</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21 years</td>
<td>60</td>
<td>839069</td>
<td>1.825</td>
<td>0.257</td>
</tr>
<tr>
<td>21-35 years</td>
<td>1209</td>
<td>15951411</td>
<td>34.701</td>
<td>1.063</td>
</tr>
<tr>
<td>36-50 years</td>
<td>1184</td>
<td>15583632</td>
<td>33.901</td>
<td>0.808</td>
</tr>
<tr>
<td>51-65 years</td>
<td>944</td>
<td>10921864</td>
<td>23.760</td>
<td>0.898</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>376</td>
<td>2671325</td>
<td>5.811</td>
<td>0.449</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2179</td>
<td>25536741</td>
<td>55.554</td>
<td>1.089</td>
</tr>
<tr>
<td>Female</td>
<td>1594</td>
<td>20430560</td>
<td>44.445</td>
<td>1.089</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1813</td>
<td>31386247</td>
<td>68.279</td>
<td>2.521</td>
</tr>
<tr>
<td>Black</td>
<td>944</td>
<td>6412197</td>
<td>13.949</td>
<td>1.385</td>
</tr>
<tr>
<td>Other</td>
<td>1016</td>
<td>8168857</td>
<td>17.771</td>
<td>1.603</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No high school diploma</td>
<td>391</td>
<td>2958378</td>
<td>9.615</td>
<td>0.692</td>
</tr>
<tr>
<td>High school diploma</td>
<td>1079</td>
<td>13470898</td>
<td>43.781</td>
<td>1.400</td>
</tr>
<tr>
<td>Any college</td>
<td>1032</td>
<td>14339077</td>
<td>46.603</td>
<td>1.504</td>
</tr>
</tbody>
</table>

Table 2(a). Demographic attributes of the national sample of current cigarette smokers.
### Table 2b. Smoking related attributes of the national sample of current cigarette smokers.

<table>
<thead>
<tr>
<th>Smoking related attributes</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>CPD (Means, SD)</td>
<td>11.87 (8.80)</td>
</tr>
<tr>
<td>Years of regular smoking (Means, SD)</td>
<td>27.02 (15.69)</td>
</tr>
<tr>
<td>At least 1 quit attempt in past 12 months (%)</td>
<td>46.97</td>
</tr>
</tbody>
</table>

Table 2(a) presents the baseline characteristics of the current cigarette smokers’ population in the US. The weighted N and the weighted percent indicate the nationally representative sample. The age-wise distribution indicated that most of the current smokers were in the age-group 21-35 years old (34.70%), followed by the age group of 36-50 years old (33.90%). Around 55.56% of CS were males, 68.28% white and 46.60% had a college degree. Table 2(b) presents the distribution with respect to the smoking related attributes. Mean (SD) cigarette per day (CPD) use and mean (SD) years of regular smoking were found to be 11.87(8.8) and 27.02(15.69), respectively. Around 46.97% of current smokers had attempted at least 1 quit attempt in the past 12 months.
Table 3 presents the baseline characteristics of the recent former cigarette smokers’ population in the US. Most of the smokers were in the age group 51-65 years old (32.03%) followed by smokers in the age group >65 years old (28.61%). The age group of <21 years old had the least proportion of smokers (0.52%). Around 55.32% of recent FS were males, 78.27% white and 51.91% had a college degree.
Table 4 presents the baseline characteristics of the late former cigarette smokers’ population in the US. Similar to recent FS, most of the late FS were in the age group 51-65 years old (33.35%) followed by smokers in the age group >65 years old (30.84%). The age group of <21 years old had the least proportion of smokers (0.32%). Around 55.32% of late FS were males, 78.82% white and 51.28% had a college degree.
<table>
<thead>
<tr>
<th>Demographic attributes</th>
<th>N</th>
<th>Weighted N</th>
<th>Weighted %</th>
<th>Standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;21 years</td>
<td>231</td>
<td>3340197</td>
<td>2.771</td>
<td>0.403</td>
</tr>
<tr>
<td>21-35 years</td>
<td>2679</td>
<td>35530624</td>
<td>29.484</td>
<td>0.940</td>
</tr>
<tr>
<td>36-50 years</td>
<td>2574</td>
<td>37034518</td>
<td>30.732</td>
<td>0.880</td>
</tr>
<tr>
<td>51-65 years</td>
<td>2199</td>
<td>27546725</td>
<td>22.859</td>
<td>0.662</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>1980</td>
<td>17053907</td>
<td>14.151</td>
<td>0.507</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3907</td>
<td>50751366</td>
<td>42.115</td>
<td>0.598</td>
</tr>
<tr>
<td>Female</td>
<td>5756</td>
<td>69754605</td>
<td>57.884</td>
<td>0.598</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White NH</td>
<td>3637</td>
<td>76205275</td>
<td>63.237</td>
<td>2.208</td>
</tr>
<tr>
<td>Black NH</td>
<td>2125</td>
<td>14735580</td>
<td>12.228</td>
<td>1.090</td>
</tr>
<tr>
<td>Other NH</td>
<td>3901</td>
<td>29565116</td>
<td>24.534</td>
<td>1.249</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No high school diploma</td>
<td>1189</td>
<td>7503846</td>
<td>11.060</td>
<td>0.755</td>
</tr>
<tr>
<td>High school diploma</td>
<td>2023</td>
<td>24466045</td>
<td>36.061</td>
<td>1.052</td>
</tr>
<tr>
<td>Any college</td>
<td>2681</td>
<td>35875006</td>
<td>52.878</td>
<td>1.173</td>
</tr>
</tbody>
</table>

Table 5. Demographic attributes of the national sample of never cigarette smokers.

Table 5 presents the baseline characteristics of the never smokers’ population in the US. Most of the NS were in the age group 36-50 years old (30.73%), followed by smokers in the age group 21-35 years old (29.48%). The age group of <21 years old had the least proportion of smokers (2.78%). Around 57.88% of NS were females, 63.23% white and 52.88% had a college degree.
Tables 6, 7, 8 and 9 show the results of the literature review done to obtain demographic and smoking behavior related risks associated with the initiation of e-cig. The tables list the assignment of probabilities associated with initiating of e-cig use, based on each level of population attribute for current, recent former, late former and never smokers, respectively. Along with that, the columns show the assigned probability distributions, data source and the studies which analyzed the data and reported those estimates.
Model Input Parametrization

<table>
<thead>
<tr>
<th>Parameters</th>
<th>E-cig use probability</th>
<th>Assigned probability distribution</th>
<th>Data</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>Continuous</td>
<td>School students survey in NY and CT, Knowledge</td>
<td>Camenga et al, Zhu et al</td>
</tr>
<tr>
<td>&lt;21</td>
<td>0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-35</td>
<td>0.072</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>36-50</td>
<td>0.059</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-65</td>
<td>0.082</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Discrete</td>
<td>Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>Male</td>
<td>0.049</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.086</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>Discrete</td>
<td>Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>White</td>
<td>0.075</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.062</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.014</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td>Discrete</td>
<td>School students survey in NY and CT, Knowledge</td>
<td>Camenga et al, Zhu et al</td>
</tr>
<tr>
<td>less than high school</td>
<td>0.088</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than high school</td>
<td>0.066</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>any college</td>
<td>0.045</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FTND Score</td>
<td></td>
<td>Discrete</td>
<td>International Tobacco</td>
<td>Kasza et al</td>
</tr>
<tr>
<td>Low</td>
<td>0.016</td>
<td></td>
<td>Control Four Country</td>
<td></td>
</tr>
<tr>
<td>Medium</td>
<td>0.014</td>
<td></td>
<td>Survey (ITC-4) data</td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>0.021</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quit attempts within past 12 months</td>
<td></td>
<td>Discrete</td>
<td>Legacy Longitudinal</td>
<td>Pearson et al</td>
</tr>
<tr>
<td>None</td>
<td>0.013</td>
<td></td>
<td>Smoker Cohort (LLSC)</td>
<td></td>
</tr>
<tr>
<td>At least 1</td>
<td>0.037</td>
<td></td>
<td>survey data</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. E-cig initiating probabilities and assigned distribution for current smokers.

Table 6 presents the mutually unexclusive probabilities associated with the initiation of e-cig based on different attributes, in current smokers. The highest probability of
initiation was found to be in the age group of <21 years (0.35) compared to other age groups. Females (0.56), whites (0.48), and those who had less than high school education (0.49) had a higher probability than their counterparts. With respect to smoking-related attributes, smokers having a high nicotine dependence (0.52) and those who had at least one quit attempts in the past (0.64) had a higher probability than their counterparts.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>E-cig use probability</th>
<th>Assigned probability distribution</th>
<th>Data</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>Continuous</td>
<td>School students survey in</td>
<td>Camenga et al</td>
</tr>
<tr>
<td>&lt;21</td>
<td>0.100</td>
<td></td>
<td>NY and CT, Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>21-35</td>
<td>0.073</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>36-50</td>
<td>0.059</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-65</td>
<td>0.082</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.026</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Discrete</td>
<td>Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>Male</td>
<td>0.049</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.076</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>Discrete</td>
<td>Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>White</td>
<td>0.076</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.062</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.028</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td>Discrete</td>
<td>School students survey in</td>
<td>Camenga et al</td>
</tr>
<tr>
<td>less than high school</td>
<td>0.088</td>
<td></td>
<td>NY and CT, Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>more than high school</td>
<td>0.066</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>any college</td>
<td>0.045</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Baseline attributes, corresponding probabilities and assigned distribution for recent former smokers.
Table 7 presents the probabilities associated with the initiation of e-cig in recent former smokers. Similar to current smokers, the highest probability of initiation was found to be in the age group of <21 years (0.31), females (0.51), whites (0.44), and those who had less than high school education (0.51).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>E-cig use probability</th>
<th>Assigned probability distribution</th>
<th>Data</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td>Continuous</td>
<td>School students survey in NY and CT, Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>&lt;21</td>
<td>0.039</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-35</td>
<td>0.011</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>36-50</td>
<td>0.004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>51-65</td>
<td>0.032</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td>Discrete</td>
<td>Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>Male</td>
<td>0.002</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.008</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>Discrete</td>
<td>Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>White</td>
<td>0.008</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.003</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td>Discrete</td>
<td>School students survey in NY and CT, Knowledge</td>
<td>Zhu et al</td>
</tr>
<tr>
<td>less than high school</td>
<td>0.002</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>more than high school</td>
<td>0.001</td>
<td></td>
<td>Networks Panel Survey</td>
<td></td>
</tr>
<tr>
<td>any college</td>
<td>0.007</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 8. Baseline attributes, corresponding probabilities and assigned distribution for late former smokers.
Table 8 presents the probabilities associated with the initiation of e-cig in late former smokers. The highest probability of initiation was found to be in the age group of 21-35 years (0.36), females (0.51), whites (0.41), and those who had college level education (0.43).

Table 9 presents the probabilities associated with the initiation of e-cig in never smokers. Since we assumed that never smokers will not initiate e-cig use after 35 years, we only used probabilities of <21 years and 21-35 years age groups. The age group <21 years (0.58), females (0.53), whites (0.47), and those who had college level education (0.45) had a higher probabilities than their counterparts.
Creating smokers and assigning baseline characteristics based on the NHIS population data

Assigning use of e-cig based on population attributes and incorporating different e-cig use scenarios

Recording e-cig prevalence, aging of the population, going back into the loop and population exodus

Figure 4. E-cig use simulation model
**E-cig Prevalence in Current Cigarette Smokers**

Figure 5 presents the projected e-cig use for the overall population of current cigarette smokers in the US. The prevalence was found to increase steadily from around 2% in the first year to around 6.7% in the eight years. From there onwards, the increase was found to slow down and found to be 7.9% at the end of the simulation period.
Figure 6 presents the projected estimates of e-cig use by age group among current cigarette smokers. The highest prevalence at the end of the simulation period was found in smokers in the age group of 6-20 years. It was followed closely by smokers in the age group of 21-35 years. The highest number of e-cig users after those two categories were found to be in 51-65 years, 36-50 years and lowest in over 65 years.

Figure 6. Projected e-cig prevalence by age group among initial current cigarette smokers in the US.
Figure 7 presents the projected estimates of e-cig use by gender among current cigarette smokers.

Males and females showed approximately the same prevalence through the simulation period. Males were found to be slightly higher users at the end of the simulation period.
Figure 8. Projected e-cig prevalence by race among initial current cigarette smokers in the US.

Figure 8 presents the projected estimates of e-cig use by race among current cigarette smokers. Smokers belonging to the white race consistently showed a higher e-cig use than smokers belonging to the black and other races. Current smokers belonging to races other than black and white showed the lowest prevalence.
Figure 9 presents the projected estimates of e-cig use by education level race among current cigarette smokers. The highest e-cig use was projected in the smokers who had less than high school level education compared to smokers with either a high school education or a college degree. The prevalence was not very different between the current smokers having a high school degree or a college level education.

Figure 9. Projected e-cig prevalence by education among initial current cigarette smokers in the US.
**E-cig Prevalence in Recent Former Cigarette Smokers**

Figure 10 presents the projected e-cig use for the overall population of recent former cigarette smokers in the US. Here, the prevalence of e-cig use was found to increase steadily from around 2% in the first year to around 7.5% at the end of the simulation period. The increased in prevalence was observed to slow down near the end of the simulation period, around the 8th year.
Figure 11 presents the projected estimates of e-cig use in recent former smokers classified by different age groups. The highest prevalence at the end of the simulation period was found in smokers in the age group of 6-20 years. It was followed by smokers in the age group of 21-35 years. The prevalence in the age group 36-50 years, and 51-65 years were found to be nearly equal at the end of the simulation period. The e-cig use was found to be lowest in the age group of >65 years.
Figure 12 presents the projected estimates of e-cig use by gender among recent former cigarette smokers. Unlike the current smokers, the prevalence of e-cig use was projected to be higher in females than males. The gap between males and females however reduced as the simulation progressed.
Figure 13 presents the projected estimates of e-cig use by race among recent former cigarette smokers in the US.

Figure 13 presents the projected estimates of e-cig use by race among recent former cigarette smokers. Similar to the projection in current smokers, recent former smokers belonging to the white race consistently showed a higher e-cig use than smokers belonging to the black and other races. Recent former smokers belonging to the black race showed the lowest prevalence.
Figure 14 presents the projected estimates of e-cig use by different education level among recent former cigarette smokers. The highest e-cig use was projected in the smokers who had a less than high school education, followed closely by smokers who had a college degree, and finally in smokers who had at least a high school education.

Figure 14. Projected e-cig prevalence by education among initial recent former cigarette smokers in the US.
**E-cig Prevalence in Late Former Cigarette Smokers**

Figure 15 presents the projected e-cig use for the overall population of late former cigarette smokers in the US. Unlike the e-cig prevalence in late former smokers, the prevalence of e-cig use in late former smokers was projected to be lower in magnitude. The prevalence grew steadily from approximately 0.3% to 1% in first four years, and then showed very little increase for the rest of the simulated period. The prevalence was found to be 2.9% at the end of the simulation period.
Figure 16 presents the projected estimates of e-cig use in recent former smokers classified by different age groups. Among different age groups, the highest prevalence at the end of the simulation period was found in smokers in the age groups of 21-35 years. Following that, the age groups 36-50 years and 51-65 years showed the next highest number of e-cig users. The lowest number of e-cig users were found to be in the age groups of 6-20 years and >65 years.

Figure 16. Projected e-cig prevalence by age group among initial late former cigarette smokers in the US.
Figure 17 presents the projected estimates of e-cig use by gender among late former cigarette smokers. The projected estimates showed that the prevalence was similar in males and females through the simulation period. Initially, females had a higher number of e-cig users but at the end of the simulation period, males showed higher use than females.
Figure 18 presents the projected estimates of e-cig use by race among late former cigarette smokers. The majority of e-cig users among late former smokers belonged to the white race. Both black and other races projections showed a similar number of e-cig users at the end of the simulation period.

Figure 18. Projected e-cig prevalence by race among initial late former cigarette smokers in the US.
Figure 19 presents the projected estimates of e-cig use by different education levels among late former cigarette smokers. Among late former smokers, the highest e-cig use was projected in the smokers who had at least a college level education. Less than high school education and high school education had lower number of e-cig users.
Figure 20 presents the projected e-cig use for the overall population of never cigarette smokers in the US. Similar to the late former smokers, the e-cig prevalence in never smokers was projected to be lower in magnitude. The prevalence grew steeply from 0.12% to 1.1% in first five years, and then showed an increase to 1.8% at the end of the simulation period.
Figure 21 presents the projected estimates of e-cig use in never smokers classified by the two age groups. The prevalence at the end of the simulation period was found higher among never smokers in the age groups of 6-20 years than those in 21-35 years. Both age groups showed a steep rise in e-cig use for first 5 years and then showed a steady raise till the end of the simulation period.
Figure 22 presents the projected estimates of e-cig use by gender among never cigarette smokers. The projected estimates showed that the prevalence was almost similar in males and females at the beginning of the simulation period, and at the end of the simulation period females were found to be higher users of e-cigs.
Figure 23 presents the projected estimates of e-cig use by race among never cigarette smokers. Similar to other smoking categories, the majority of e-cig users among never smokers belonged to the white race. The projected estimates showed a consistent white majority of never smokers who became e-cig users, compared to black and other races through the simulation period. Never smokers belonging to other races showed a slightly higher number of e-cig users projections compared to black smokers.
Figure 24 presents the projected estimates of e-cig use by different education levels among never cigarette smokers. The highest number of e-cig users was projected in never smokers who had less than high school level education. It was followed by never smokers who had at least high school education. Lastly, the lowest number of e-cig users among never smokers had a college degree.
Figure 25. Projected estimate e-cig prevalence in the US population over the simulation period.

Figure 25 presents the projected e-cig use in the model population over the simulation period. It was observed that the e-cig use showed a steady growth till the 7th year (15.8%), and then showed a decline in the growth from 7th until the 15th year. The e-cig prevalence at the end of the simulation period was found to be 19.3%.
Assuming all the conventional cigarette users transitioned completely to e-cig use without any dual use period, we compared the projected e-cig use and the conventional cigarette use over the same simulation period (Figure 26). In the conventional cigarette use group, the initial population consisted of smokers in the CS, RFS and LFS groups. Each subsequent year, the total number of e-cig users at the end of each year from these three groups were subtracted from the conventional cigarette group, since we assumed that once a person switched to e-cig use, he or she could not go back to using conventional cigarette. The conventional cigarette use was found to reduce from 40% to 25% at the end of simulation period.
Figure 27 presents the projected estimates of e-cig use classified by different age groups. Among different age groups, the highest prevalence at the end of the simulation period was found in people who belonged to the age groups of <21 years and 21-35 years old. It was followed by age group 51-65 years and 36-50 years and the lowest number of e-cig users were found to be in the age groups of >65 years.

Figure 27. Projected e-cig prevalence by age groups in the US population
Figure 28 presents the projected estimates of e-cig use by gender. It was observed that in the initial stages, e-cig use was more prevalent in females compared to males. However, at the end of the simulation period the prevalence was almost similar in males and females, approximately 9.5%.
Figure 29. Projected e-cig prevalence by race in the US population

Figure 29 presents the projected estimates of e-cig use by race. It was observed that the majority of e-cig users belonged to the white race. The projected estimates showed a consistent white majority of e-cig users through the simulation period, compared to black and other races. Further, people who belonged to the black race showed a higher e-cig use than other racial groups.
Figure 30 presents the projected estimates of e-cig use by different education levels. The highest number of e-cig users belonged to people with less than high school education. It was followed by people who had at least a college degree, and then people who had at least high school level education.
Prevalence of e-cig use was found to be most sensitive to change in risk associated with policies, and time of implementation of the policies. When the risk was increased to 2% each year, the prevalence at the end of the simulation period was found to be reduced to 18.32% from 19.33%. Increasing it further to 3% and 5% resulted in the reduction of prevalence to 16.19% and 14.78%, respectively. Similarly when the time of policy application was changed from 7 years to 5 years, prevalence reduced from 19.33% to 18.68%. When it was changed to 10 years, the prevalence increased to 21.93%. When there was no policy application at all, the prevalence was increased to 23.47%. We also evaluated

<table>
<thead>
<tr>
<th>Scenarios</th>
<th>Prevalence in current smokers (end of 15 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in initiating risk due to policy</td>
<td></td>
</tr>
<tr>
<td>2%</td>
<td>18.32%</td>
</tr>
<tr>
<td>3%</td>
<td>16.19%</td>
</tr>
<tr>
<td>5%</td>
<td>14.78%</td>
</tr>
<tr>
<td>Change in timing of policy implementation</td>
<td></td>
</tr>
<tr>
<td>5 years</td>
<td>18.68%</td>
</tr>
<tr>
<td>10 years</td>
<td>21.93%</td>
</tr>
<tr>
<td>No Policy</td>
<td>23.47%</td>
</tr>
<tr>
<td>Proportion of people making a quit attempt within a year (±15%)</td>
<td></td>
</tr>
<tr>
<td>33%</td>
<td>18.14%</td>
</tr>
<tr>
<td>63%</td>
<td>20.28%</td>
</tr>
<tr>
<td>Proportion of people staying quitter for that year (±15%)</td>
<td></td>
</tr>
<tr>
<td>14%</td>
<td>18.91%</td>
</tr>
<tr>
<td>4%</td>
<td>19.95%</td>
</tr>
</tbody>
</table>

Table 10. Prevalence estimates at the end of 15 years for different scenarios in sensitivity analyses in current smokers
the impact of changing the proportion of people making a quit attempt, and making a relapse within the same year. The results of this scenarios did not show a huge impact on the prevalence of e-cig use the end of the simulation period. On decreasing and increasing the proportion of people making a quit attempt within a year by 15% resulted in a final prevalence of 18.14% and 20.28%, respectively. On decreasing and increasing the proportion of people staying a quitter for that year after making a quit attempt by 15%, resulted in a final prevalence of 18.91% and 19.95%, respectively.
Chapter 4

Discussion
The primary objective of this study was to develop a validated DES model to allow for the assessment of e-cig use behavior and prevalence of e-cig in different population groups, using data from literature review of several cross-sectional survey and longitudinal e-cig studies done on the US population. The simulation replicated the initiating patterns, quit attempts and relapses associated with the e-cig use in current, former and never cigarette smokers. The model also allowed the change of smoking status between the three smoking groups, through the simulation period. We were also able to apply the effect of history by including information on prior simulated quit attempts, in addition to individuals’ characteristics at the time of each subsequent quit attempt, to make predictions. Further, the model gave us an opportunity to investigate the impact of e-cig related policies on the prevalence patterns into the future and examining possible real-life patterns of e-cig use.

Our study results showed that e-cig use was projected to be the highest in current cigarette smoking population, followed by recent former smokers, late former smokers and lowest in never smokers. The projected estimate after the first year of simulation in current smokers was found to be around 2.1%. This finding was found to be consistent with the results of a survey conducted by CDC which reported the prevalence of regular e-cig use to be around 1.9% (King et al., 2013). It provides initial evidence to support the model validity and its potential to obtain accurate estimates with adequate data availability. The overall projected e-cig use for the population of current cigarette smokers in the US was found to increase to 6.7% in eight years, and then to 7.9% at the end of the simulation period. The slow growth rate after 8 years could be attributed to the launch of the e-cig control policy,
which was implemented at the 7th year, and which resulted in lowering risk of initiation of e-cig each subsequent year. Next, the prevalence of e-cig use in recent former smokers was found to be less than current smokers, but still considerably higher than late former and never smokers. The e-cig use pattern followed the same trajectory as in current smokers, indicating the behavior of recent former and current smokers towards the use of e-cig is not very different. In late former smokers and never smokers, the e-cig use was projected to be lower than current and recent former smokers. This was consistent in current trend in the use of e-cig, where the only never smokers who become regular e-cig users are relatively young adults and teenagers, resulting in a low overall population prevalence (Camenga et al., 2014).

Differences in the use of e-cigarettes were observed across subpopulations. Specifically, younger age groups, whites, females and smokers having less than high school education were found to be highest users of the e-cig among current, recent former, and never smokers. Higher use among younger adults may be related to the fact that e-cigarettes are traditionally marketed through electronic and social media (Noel, Rees, & Connolly, 2011; Yamin, Bitton, & Bates, 2010). Also, the higher prevalence of use among current smokers could be related to the marketing of e-cigarettes as smoking cessation aids (Adkison et al., 2013; Etter & Bullen, 2014).

Our research provides context to identify future population-based changes related to e-cig use and guide the design of a more informative longitudinal research. National data on e-cig use by middle and high school students gathered via the National Youth Tobacco Survey
in 2011 and 2012 reported that among middle and high school students, ever-use of e-cigarettes (tried at least once) increased from 3.3% to 6.8%, whereas current use (within the last 30 days) increased from 1.1% to 2.1% (Agaku et al., 2014). That data was correctly estimated by our model as observed by the results of the 1st year simulation. Another analysis of National Youth Tobacco Survey data from the same time period confirmed that current e-cigarette users were much more likely to be current cigarette smokers, which was consistent with our findings (Bunnell et al., 2015).

Our study is also a first in modeling the impact of future policies regulating e-cigs at different times. Because e-cig is a new product, lack of scientific evidence has been a key factor for the absence of federal regulations. Our study provides an opportunity to examine the potential impact of future policies on e-cigs use by modeling risk reduction each subsequent year after implementation of a policy. Another advantage of our study was that we were able to show the impact of varying the policy effect, specifically the magnitude of risk and the time at which the policy will be implemented, in our sensitivity analyses.

Our model also enables meaningful analyses of outcomes in population subgroups. For instance, the prevalence of e-cig use among younger age group and white people could be more comprehensively captured. By accounting for subject characteristics when predicting e-cig use, relapse, and quit attempts, this model provides a powerful tool to evaluate the usefulness of e-cigs for improving quit rates, and reducing the risk of relapse among different subgroups of the population.
With the current ongoing research on the health effects related to the use of e-cigs, this model could be used to predict vaping-related disease and health utilities once the data becomes available. Although the exact information on diseases attributed to e-cig use is not expected to come out in the near future, but the effects on proxy measures, such as physiological biomarkers, will be able to provide some insight in the risks related to the use of e-cigs.

We have to be mindful of the fact that a large proportion of current e-cig users are concurrently using conventional cigarettes (Brandon et al., 2015). Since we did not have access to longitudinal individual level data, we were not able to model the time dependent aspects of e-cig behavior such as time to first quit attempt, time to relapse, time spent by a smoker in transitioning from cigarette to e-cig. This information when available, could be used by the investigators to predict the time-dependent aspects listed above to estimate important outcomes such as duration of time where the current cigarette smoker is using both product (dual use), or time taken to completely switch to e-cig.

The main strength of this model is that it was able to incorporate significant predictors of e-cig initiation obtained from the literature and show their cumulative effect in making the individuals use or not use an e-cig. Thus, this model structure could provide a solid foundation from which a flexible, lifetime e-cig use behavior model can be developed that can accommodate multiple quit attempts, relapse, transitioning between current, former and never users over time in diverse populations.
The main impediment to developing a lifetime DES is the difficulty in obtaining accurate and reliable data on long term patterns of quit attempts. Data that would allow for accurate individualized predictions on sequences of smoking behavior, intervals between quit attempts and long-term relapse rates, are required to fully harness the potential of the modelling technique. Nevertheless, even in the absence of these data, a lifetime DES built on the current model would allow for informative exploratory analyses that are grounded in reliable individualized predictions and patterns. Based on our literature review, we believe that the data is currently being collected and will be released sometime in near future. Once the data is available, capturing the time-dependent relationships will add tremendous value to a lifetime model.

We believe that the data related to e-cig attributed mortality will not become available in near future. Hence, it will not be possible to model the mortality rates related to e-cig use. However, it is certainly possible to use the rates of smoking-related disease attributed to e-cig use, compare them with disease rates attributed to conventional cigarette smoking and other tobacco products, and predict mortality after applying appropriate assumptions.

In future, additional validation of the model predictions would also increase confidence in the reliability of the current predictive equations. The structural validation and the comparison of the results against the data sources indicated that the simulation predicted the short term prevalence estimates close to the real values, and performed well when
implemented in key population subgroups. However, validation exercises performed against sources different than those used in developing the core equations would be valuable.

Data on e-cig use by youth and adults have been gathered primarily from Web-based surveys and convenience sampling, including regional samples, and from participants in online e-cigarette forums. Interpreting such data is difficult, and it is necessary that data collected at the individual level is released publicly, to foster research on different areas of interests related to e-cigs. Furthermore, most of the cross sectional or survey research published till date use has evaluated just the short term use of e-cig use, mostly for 1 or 2 years. Similarly, the clinical trials studies conducted on e-cig use have also followed the e-cig users for the duration of 6 months or 12 months. Our model used that information, incorporated into our model, followed the e-cig users for 15 years, and tried to project the behavior pattern and the use trajectory of e-cigs.

Some studies observed that e-cigs may contribute to prevent relapse in former smokers and to promote smoking cessation in current smokers, which essentially means getting them off from conventional cigarettes (Biener & Hargraves, 2015; McMillen et al., 2014). It would have been a significant outcome to look at in our model as well however, the evidence is still scarce according to our review of the published literature.
We made a strong assumption in our study that all e-cigs contained nicotine. The recent policy statement on e-cigs from the American Association for Cancer Research reported that currently there are around 7000 unique flavored e-cigs on the market (Brandon et al., 2015). The report suggested that flavored tobacco is particularly appealing to youth, and some flavored combustible products potentiate continued use and addiction. There is a concern that flavored e-cigs may have a similar effect on the youth, however there is no available studies which have accessed flavors in general (Brandon et al., 2015). In future, our model can be used when the data on flavors becomes available, to estimate the impact of different flavors on the pattern of e-cig use among the young users.

The use of e-cigs by never smokers would present a public health concern, but this is a particular concern with respect to youth, especially if e-cigs serve as a pathway to other tobacco products, including combustible cigarettes (Grana, 2013). In our study, we were limited by the data availability and could only estimate the transition of never smokers to e-cigs but could not model their transition to the use of regular tobacco products. However in near future, with the availability of adequate data, we could show transition of never smokers from e-cigs to other tobacco products can be a significant application of this model.

Population benefit or harm depends largely on public’s perception of the products and their patterns of use. The risk may increase if dual use with other tobacco products is prevalent, or cessation is deterred by persons using e-cigs to circumvent smoke-free laws.
Studies conducted with e-cigarette users, demonstrated that they perceive the products to be less toxic than conventional cigarettes and have used them as a smoking cessation device or to avoid exposing others to tobacco smoke (Brown et al., 2014; Pearson et al., 2012). However, the research on their efficacy for smoking cessation is still ongoing and most of the published studies reported a small sample size making their studies underpowered. Further research on the rates and health effects of dual use is critical for assessing and considering total public health impact of e-cigs. Future studies should try to assess the dose-response relationship for certain biomarkers of cardiovascular effects or lung cancer effects with the use of e-cigs.

The evidence regarding the risks and benefits of e-cigs in different segments of the population such as current smokers and never smokers is difficult to interpret, because the market place of e-cigs products is evolving rapidly. Research in this field is complicated by the ever-changing and wide variability among and within different e-cig products, a lack of standardized definitions of e-cigs, variable user terminology, and a lack of established protocols for conducting e-cig research, including clinical trials (Brandon et al., 2015). However, despite these challenges, research on e-cigs is on the right track and progressing rapidly. The NIH and the FDA are providing recommendations for studying these products, including different population sub groups such as healthy volunteers as well as vulnerable populations, such as people suffering from cancer and those with other acute or chronic medical conditions. More research is needed to understand how different design features relate to dependence and toxicity, including if the compounds in e-cigs react chemically and if these compounds are absorbed into the bloodstream. Research is also needed to
understand the effect e-cig use, including second- and third hand exposure to population as well. Studies should also examine the efficacy and safety of e-cigs in patients with cancer treated with surgery, chemotherapy, and radiotherapy and potential interactions with these therapies. Among smokers, long term controlled clinical trials are needed to determine whether e-cigs facilitate or hinder short- and long-term smoking cessation as well as whether it increases nicotine dependence. Studies should consider also outcomes related to health conditions such as cardiovascular diseases, COPD, lung cancer and stroke. These conditions have an established history with conventional cigarette smoking.
Limitations

The biggest limitation of this study was the use of self-reported values of e-cig use based on age, gender, race and education status. Due to the absence of standardized recorded individual level data, we were unable to obtain the mutually exclusive prediction probabilities. However, we used appropriate mathematical rules to get a correct estimate of the probabilities associated with the e-cig use. The model also relied on a number of data sources, including surveys and longitudinal e-cig studies done on the different populations, which may be responsible for variation in the results across different groups. Another limitation was not able to differentiate people who make a quit attempt and relapse, and those who do not relapse. We did allow a definite proportion of people to pass through, but that proportion was directly utilized from a survey without the knowledge of individual characteristics of people making or not making the quit attempt or relapse (Kasza et al., 2014). Next important limitation was that we could not validate our model projections against real world data. Because e-cig is a relatively new product, long term longitudinal studies will be required to compare and validate the results of our model. Additionally, time to quit attempt, time to relapse, and time to transition from regular cigarette to e-cig was not modelled because of lack of time dependent data. Because the smokers were generated and assigned attributes based on the NHIS data, simulated patients may not accurately represent real-world patients, which could limit generalizability to real-world settings. In addition, we assumed everyone to be undergoing the changes and going through different states as defined by the path of the model. This does not happen in the real world, where the movement of people is more dynamic and random.
Chapter 5

Conclusion
The benefits and harms of e-cig use must be evaluated with respect to the population as a whole and take into account the effect on youth, adults, never smokers, former smokers and current smokers. There are currently too few data on the behavior pattern of e-cigs and their efficacy as cessation products to recommend their use for the general population. Our study evaluates the long term use pattern of e-cigs in the US population. We mainly estimated the prevalence of e-cigs in current, former and never smokers for the period of 15 years, using the current data. Our population model will help predict changes in individual behaviors and patterns associated with the use of e-cigs. It will also help to address the problem of scarce data resources related to e-cig use and provide guidance for conducting more research on generating real world evidence to look into more relevant outcomes. It will also encourage policymakers to review the rapidly changing pattern of e-cig use and make public health decisions by using our future projection of e-cig use.
References


*FDCA. (2013). (Pandemic and All Hazards Preparedness Reauthorization Act of 2013 No. 113-5).* Food, Drug, and Cosmetic Act: FDA.


Herzog, B. (2013). *E-cigs revolutionizing the tobacco industry, wells fargo securities - equity research*. ()


**Adolescent Health : Official Publication of the Society for Adolescent Medicine, 52(2), 144-150.**

doi:10.1161/CIR.0b013e3181f432c3 [doi]


TVECA. (2013). *The tobacco vapor electronic cigarette association*.


Appendix
Table 11. Model Population descriptive results:

<table>
<thead>
<tr>
<th>Age (%)</th>
<th>Current smokers (N= 12665)</th>
<th>Former smokers (N= 15226)</th>
<th>Never smokers (N=40801)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;21 years</td>
<td>1.825</td>
<td>0.511</td>
<td>2.771</td>
</tr>
<tr>
<td>21-35 years</td>
<td>34.701</td>
<td>13.602</td>
<td>29.484</td>
</tr>
<tr>
<td>36-50 years</td>
<td>33.901</td>
<td>18.954</td>
<td>30.732</td>
</tr>
<tr>
<td>51-65 years</td>
<td>23.760</td>
<td>31.671</td>
<td>22.859</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>5.811</td>
<td>35.272</td>
<td>14.151</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>55.554</td>
<td>52.453</td>
<td>42.115</td>
</tr>
<tr>
<td>Female</td>
<td>44.445</td>
<td>47.556</td>
<td>57.884</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>68.279</td>
<td>80.394</td>
<td>66.37</td>
</tr>
<tr>
<td>Black</td>
<td>13.949</td>
<td>8.061</td>
<td>12.228</td>
</tr>
<tr>
<td>Other</td>
<td>17.771</td>
<td>11.552</td>
<td>24.534</td>
</tr>
<tr>
<td>Education status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>9.615</td>
<td>11.598</td>
<td>63.237</td>
</tr>
<tr>
<td>High school diploma</td>
<td>43.781</td>
<td>37.813</td>
<td>12.228</td>
</tr>
<tr>
<td>Any college</td>
<td>46.603</td>
<td>50.589</td>
<td>24.534</td>
</tr>
<tr>
<td>CPD (Means, SD)</td>
<td>11.87, 8.80</td>
<td>--------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Years of regular smoking (Means, SD)</td>
<td>27.02, 15.69</td>
<td></td>
<td></td>
</tr>
<tr>
<td>At least 1 quit attempt in past 12 months</td>
<td>46.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years</td>
<td>Initial N=</td>
<td>+ Birth rate</td>
<td>-Death rate</td>
</tr>
<tr>
<td>------</td>
<td>-----------</td>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>1</td>
<td>100000.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>2</td>
<td>100000.00</td>
<td>101330.00</td>
<td>100478.83</td>
</tr>
<tr>
<td>3</td>
<td>100478.83</td>
<td>101815.20</td>
<td>100959.95</td>
</tr>
<tr>
<td>4</td>
<td>100959.95</td>
<td>102302.72</td>
<td>101443.37</td>
</tr>
<tr>
<td>5</td>
<td>101443.37</td>
<td>102792.57</td>
<td>101929.11</td>
</tr>
<tr>
<td>6</td>
<td>101929.11</td>
<td>103284.77</td>
<td>102417.18</td>
</tr>
<tr>
<td>7</td>
<td>102417.18</td>
<td>103779.33</td>
<td>102907.58</td>
</tr>
<tr>
<td>8</td>
<td>102907.58</td>
<td>104276.25</td>
<td>103400.33</td>
</tr>
<tr>
<td>9</td>
<td>103400.33</td>
<td>104775.55</td>
<td>103895.44</td>
</tr>
<tr>
<td>10</td>
<td>103895.44</td>
<td>105277.25</td>
<td>104392.92</td>
</tr>
<tr>
<td>11</td>
<td>104392.92</td>
<td>105781.35</td>
<td>104892.78</td>
</tr>
<tr>
<td>12</td>
<td>104892.78</td>
<td>106287.86</td>
<td>105395.04</td>
</tr>
<tr>
<td>13</td>
<td>105395.04</td>
<td>106796.79</td>
<td>105899.70</td>
</tr>
<tr>
<td>14</td>
<td>105899.70</td>
<td>107308.17</td>
<td>106406.78</td>
</tr>
<tr>
<td>15</td>
<td>106406.78</td>
<td>107821.99</td>
<td>106916.28</td>
</tr>
</tbody>
</table>

Table 12. Simulated population for each year after applying the birth and death rates
## Prevalence estimates for each year

<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard errors</td>
<td>0.852</td>
<td>0.767</td>
<td>0.813</td>
<td>0.675</td>
<td>0.684</td>
<td>0.774</td>
<td>0.868</td>
<td>0.796</td>
<td>0.873</td>
<td>0.782</td>
<td>0.654</td>
<td>0.861</td>
<td>0.882</td>
<td>0.768</td>
<td>0.685</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-20 years</td>
<td>0.5826</td>
<td>0.9695</td>
<td>1.2824</td>
<td>1.4517</td>
<td>1.6182</td>
<td>1.8133</td>
<td>2.0445</td>
<td>2.0865</td>
<td>2.1158</td>
<td>2.2344</td>
<td>2.2705</td>
<td>2.2953</td>
<td>2.3284</td>
<td>2.3164</td>
<td>2.3941</td>
</tr>
<tr>
<td>21-35 years</td>
<td>0.5381</td>
<td>0.7115</td>
<td>0.9218</td>
<td>1.2703</td>
<td>1.4681</td>
<td>1.5212</td>
<td>1.6367</td>
<td>1.7366</td>
<td>1.9511</td>
<td>2.0468</td>
<td>2.1718</td>
<td>2.2674</td>
<td>2.2931</td>
<td>2.3075</td>
<td>2.3413</td>
</tr>
<tr>
<td>36-50 years</td>
<td>0.1794</td>
<td>0.2285</td>
<td>0.4001</td>
<td>0.6269</td>
<td>0.8405</td>
<td>0.9502</td>
<td>1.0414</td>
<td>1.0508</td>
<td>1.0843</td>
<td>1.0229</td>
<td>1.0643</td>
<td>1.0834</td>
<td>1.1648</td>
<td>1.1592</td>
<td>1.1692</td>
</tr>
<tr>
<td>51-65 years</td>
<td>0.5939</td>
<td>0.6424</td>
<td>0.9912</td>
<td>1.2189</td>
<td>1.3881</td>
<td>1.4943</td>
<td>1.5048</td>
<td>1.6676</td>
<td>1.6991</td>
<td>1.8369</td>
<td>1.7642</td>
<td>1.7149</td>
<td>1.7298</td>
<td>1.7643</td>
<td>1.7985</td>
</tr>
<tr>
<td>&gt;65 years</td>
<td>0.2012</td>
<td>0.2112</td>
<td>0.2088</td>
<td>0.1888</td>
<td>0.1315</td>
<td>0.1244</td>
<td>0.1561</td>
<td>0.1625</td>
<td>0.1225</td>
<td>0.0625</td>
<td>0.0682</td>
<td>0.0546</td>
<td>0.0513</td>
<td>0.0496</td>
<td>0.0482</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.9312</td>
<td>1.4244</td>
<td>1.8615</td>
<td>2.1164</td>
<td>2.5347</td>
<td>2.8361</td>
<td>2.9832</td>
<td>3.3398</td>
<td>3.6464</td>
<td>3.7331</td>
<td>3.7251</td>
<td>3.8563</td>
<td>3.8426</td>
<td>3.9321</td>
<td>3.9167</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>0.8543</td>
<td>1.1145</td>
<td>1.4529</td>
<td>1.7638</td>
<td>1.9286</td>
<td>2.1242</td>
<td>2.2404</td>
<td>2.4497</td>
<td>2.5234</td>
<td>2.6493</td>
<td>2.6643</td>
<td>2.7673</td>
<td>2.7965</td>
<td>2.8052</td>
<td>2.8543</td>
</tr>
<tr>
<td>Other</td>
<td>0.3424</td>
<td>0.5619</td>
<td>0.6588</td>
<td>0.8034</td>
<td>0.8408</td>
<td>1.1254</td>
<td>1.1335</td>
<td>1.3289</td>
<td>1.3856</td>
<td>1.4675</td>
<td>1.5124</td>
<td>1.5243</td>
<td>1.5671</td>
<td>1.5241</td>
<td>1.5934</td>
</tr>
<tr>
<td><strong>Education level</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>0.8367</td>
<td>1.4694</td>
<td>1.7032</td>
<td>1.9367</td>
<td>2.2411</td>
<td>2.4358</td>
<td>2.5636</td>
<td>2.7027</td>
<td>2.8613</td>
<td>2.9152</td>
<td>3.0734</td>
<td>3.1243</td>
<td>3.1906</td>
<td>3.2834</td>
<td>3.3127</td>
</tr>
<tr>
<td>Year</td>
<td>High school</td>
<td>College</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>------</td>
<td>-------------</td>
<td>---------</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.5985</td>
<td>0.66</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.8163</td>
<td>1.0174</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1.0102</td>
<td>1.2418</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1.1423</td>
<td>1.4666</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1.3365</td>
<td>1.5612</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1.5272</td>
<td>1.8809</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1.6598</td>
<td>1.9484</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>1.7668</td>
<td>2.1643</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>1.8379</td>
<td>2.2134</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1.9316</td>
<td>2.3123</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>1.8854</td>
<td>2.3965</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>1.9465</td>
<td>2.5119</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>1.8437</td>
<td>2.5974</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>1.8671</td>
<td>2.6074</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>1.8207</td>
<td>2.6846</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 13. Projected e-cig prevalence for each year in the simulation period within different demographic categories of current cigarette smokers.
## Prevalence estimates for each year

<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard errors</td>
<td>0.852</td>
<td>0.767</td>
<td>0.813</td>
<td>0.675</td>
<td>0.684</td>
<td>0.774</td>
<td>0.868</td>
<td>0.796</td>
<td>0.873</td>
<td>0.782</td>
<td>0.654</td>
<td>0.861</td>
<td>0.882</td>
<td>0.768</td>
<td>0.685</td>
</tr>
</tbody>
</table>

### Age

- **6-20 years**
  - 0.8584
  - 1.4431
  - 1.8023
  - 2.1168
  - 2.2941
  - 2.4029
  - 2.4967
  - 2.5069
  - 2.5993
  - 2.6021
  - 2.5993
  - 2.6026
  - 2.6037

- **21-35 years**
  - 0.5852
  - 0.9058
  - 1.1331
  - 1.3213
  - 1.4415
  - 1.6039
  - 1.8146
  - 2.0217
  - 2.1132
  - 2.2102
  - 2.2167
  - 2.2583
  - 2.3119

- **36-50 years**
  - 0.3803
  - 0.6961
  - 0.9849
  - 1.0673
  - 1.1589
  - 1.2704
  - 1.3198
  - 1.4625
  - 1.4951
  - 1.4803
  - 1.4545
  - 1.4237
  - 1.4068

- **51-65 years**
  - 0.117
  - 0.3275
  - 0.4829
  - 0.6125
  - 0.8047
  - 0.9754
  - 1.0975
  - 1.1189
  - 1.1136
  - 1.0239
  - 1.0228
  - 1.0193
  - 1.0346

- **>65 years**
  - 0.06963
  - 0.0718
  - 0.0926
  - 0.1006
  - 0.09872
  - 0.09312
  - 0.0857
  - 0.0755
  - 0.0729
  - 0.0615
  - 0.0601
  - 0.0583
  - 0.0549
  - 0.0486
  - 0.0431

### Gender

- **Male**
  - 0.8199
  - 1.5683
  - 2.0191
  - 2.3315
  - 2.4435
  - 2.8098
  - 3.1144
  - 3.4887
  - 3.4852
  - 3.5228
  - 3.5579
  - 3.5816
  - 3.5894
  - 3.5926
  - 3.6051

- **Female**
  - 1.2267
  - 1.9456
  - 2.4148
  - 2.9014
  - 3.2851
  - 3.3178
  - 3.5714
  - 3.6124
  - 3.7479
  - 3.7845
  - 3.7901
  - 3.8002
  - 3.8373
  - 3.8719
  - 3.9047

### Race

- **White**
  - 1.0949
  - 1.7359
  - 2.1449
  - 2.7073
  - 2.9332
  - 3.2344
  - 3.4121
  - 3.5218
  - 3.6012
  - 3.6424
  - 3.6593
  - 3.6804
  - 3.6979
  - 3.7014
  - 3.7107

- **Black**
  - 0.4163
  - 0.9577
  - 1.0825
  - 1.1312
  - 1.2802
  - 1.3151
  - 1.4754
  - 1.6535
  - 1.5981
  - 1.5972
  - 1.6043
  - 1.5941
  - 1.5538
  - 1.5406
  - 1.5912

- **Other**
  - 0.5356
  - 0.8247
  - 1.2085
  - 1.4122
  - 1.5161
  - 1.7275
  - 1.8078
  - 1.9358
  - 2.0314
  - 2.1574
  - 2.1701
  - 2.2045
  - 2.2179
  - 2.2282
  - 2.2196

### Education level

- **Less than high school**
  - 0.6832
  - 1.2108
  - 1.6356
  - 1.9082
  - 2.1088
  - 2.2772
  - 2.4736
  - 2.6997
  - 2.7104
  - 2.7829
  - 2.7902
  - 2.8007
  - 2.8517
  - 2.8861
  - 2.8942

- **High school**
  - 0.4737
  - 0.8826
  - 1.0617
  - 1.2959
  - 1.4042
  - 1.5114
  - 1.7323
  - 1.8052
  - 1.9421
  - 1.9602
  - 1.9054
  - 1.9342
  - 1.9865
  - 1.9907
  - 1.9145
| College | 0.8748 | 1.4085 | 1.7325 | 2.0284 | 2.2124 | 2.3244 | 2.4676 | 2.5215 | 2.584 | 2.6163 | 2.6304 | 2.6584 | 2.6841 | 2.689 | 2.7123 |

Table 14. Projected e-cig prevalence for each year in the simulation period within different demographic categories of recent former cigarette smokers.
<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Percent Prevalence</td>
<td>0.2968</td>
<td>0.6148</td>
<td>0.8914</td>
<td>1.1746</td>
<td>1.5313</td>
<td>1.6759</td>
<td>1.7946</td>
<td>1.9372</td>
<td>2.0112</td>
<td>2.1409</td>
<td>2.1764</td>
<td>2.2034</td>
<td>2.2374</td>
<td>2.2946</td>
<td></td>
</tr>
<tr>
<td>Standard errors</td>
<td>0.152</td>
<td>0.167</td>
<td>0.183</td>
<td>0.175</td>
<td>0.184</td>
<td>0.168</td>
<td>0.196</td>
<td>0.173</td>
<td>0.182</td>
<td>0.154</td>
<td>0.181</td>
<td>0.182</td>
<td>0.168</td>
<td>0.185</td>
<td></td>
</tr>
</tbody>
</table>

### Age

<table>
<thead>
<tr>
<th></th>
<th>6-20 years</th>
<th>21-35 years</th>
<th>36-50 years</th>
<th>51-65 years</th>
<th>&gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1433</td>
<td>0.1239</td>
<td>0.05784</td>
<td>0.0685</td>
<td>0.00317</td>
</tr>
<tr>
<td></td>
<td>0.1763</td>
<td>0.2061</td>
<td>0.1084</td>
<td>0.1258</td>
<td>0.0179</td>
</tr>
<tr>
<td></td>
<td>0.1856</td>
<td>0.2409</td>
<td>0.2691</td>
<td>0.1931</td>
<td>0.0318</td>
</tr>
<tr>
<td></td>
<td>0.1942</td>
<td>0.3909</td>
<td>0.3029</td>
<td>0.2413</td>
<td>0.0259</td>
</tr>
<tr>
<td></td>
<td>0.2243</td>
<td>0.4874</td>
<td>0.3407</td>
<td>0.3342</td>
<td>0.0357</td>
</tr>
<tr>
<td></td>
<td>0.2772</td>
<td>0.5224</td>
<td>0.3941</td>
<td>0.4022</td>
<td>0.0414</td>
</tr>
<tr>
<td></td>
<td>0.2868</td>
<td>0.5903</td>
<td>0.4172</td>
<td>0.4391</td>
<td>0.04176</td>
</tr>
<tr>
<td></td>
<td>0.3126</td>
<td>0.6493</td>
<td>0.438</td>
<td>0.4482</td>
<td>0.04123</td>
</tr>
<tr>
<td></td>
<td>0.3243</td>
<td>0.7824</td>
<td>0.4672</td>
<td>0.4691</td>
<td>0.0409</td>
</tr>
<tr>
<td></td>
<td>0.3346</td>
<td>0.8106</td>
<td>0.4827</td>
<td>0.4782</td>
<td>0.04124</td>
</tr>
<tr>
<td></td>
<td>0.3371</td>
<td>0.8476</td>
<td>0.5042</td>
<td>0.4939</td>
<td>0.0407</td>
</tr>
<tr>
<td></td>
<td>0.3458</td>
<td>0.8643</td>
<td>0.5247</td>
<td>0.5092</td>
<td>0.04084</td>
</tr>
<tr>
<td></td>
<td>0.3549</td>
<td>0.8943</td>
<td>0.5382</td>
<td>0.5247</td>
<td>0.0416</td>
</tr>
<tr>
<td></td>
<td>0.3824</td>
<td>0.8973</td>
<td></td>
<td>0.5247</td>
<td>0.04219</td>
</tr>
<tr>
<td></td>
<td>0.3945</td>
<td></td>
<td></td>
<td></td>
<td>0.04278</td>
</tr>
</tbody>
</table>

### Gender

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1415</td>
<td>0.1541</td>
</tr>
<tr>
<td></td>
<td>0.2853</td>
<td>0.2951</td>
</tr>
<tr>
<td></td>
<td>0.4312</td>
<td>0.4673</td>
</tr>
<tr>
<td></td>
<td>0.5291</td>
<td>0.6413</td>
</tr>
<tr>
<td></td>
<td>0.6407</td>
<td>0.6683</td>
</tr>
<tr>
<td></td>
<td>0.7734</td>
<td>0.7667</td>
</tr>
<tr>
<td></td>
<td>0.8125</td>
<td>0.8534</td>
</tr>
<tr>
<td></td>
<td>0.9042</td>
<td>0.8946</td>
</tr>
<tr>
<td></td>
<td>0.9313</td>
<td>0.9067</td>
</tr>
<tr>
<td></td>
<td>1.0942</td>
<td>0.9184</td>
</tr>
<tr>
<td></td>
<td>1.258</td>
<td>0.9361</td>
</tr>
<tr>
<td></td>
<td>1.21</td>
<td>0.9643</td>
</tr>
<tr>
<td></td>
<td>1.218</td>
<td>0.9833</td>
</tr>
<tr>
<td></td>
<td>1.241</td>
<td>0.9892</td>
</tr>
<tr>
<td></td>
<td>1.2954</td>
<td>1.0028</td>
</tr>
</tbody>
</table>

### Race

<table>
<thead>
<tr>
<th></th>
<th>White</th>
<th>Black</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1953</td>
<td>0.0215</td>
<td>0.0795</td>
</tr>
<tr>
<td></td>
<td>0.2774</td>
<td>0.2326</td>
<td>0.2085</td>
</tr>
<tr>
<td></td>
<td>0.3986</td>
<td>0.3201</td>
<td>0.2774</td>
</tr>
<tr>
<td></td>
<td>0.4928</td>
<td>0.3731</td>
<td>0.3695</td>
</tr>
<tr>
<td></td>
<td>0.6147</td>
<td>0.4091</td>
<td>0.4313</td>
</tr>
<tr>
<td></td>
<td>0.6913</td>
<td>0.4127</td>
<td>0.4839</td>
</tr>
<tr>
<td></td>
<td>0.7105</td>
<td>0.4977</td>
<td>0.5084</td>
</tr>
<tr>
<td></td>
<td>0.7831</td>
<td>0.5413</td>
<td>0.5225</td>
</tr>
<tr>
<td></td>
<td>0.8182</td>
<td>0.5543</td>
<td>0.5876</td>
</tr>
<tr>
<td></td>
<td>0.9395</td>
<td>0.5691</td>
<td>0.6187</td>
</tr>
<tr>
<td></td>
<td>1.0523</td>
<td>0.5724</td>
<td>0.6431</td>
</tr>
<tr>
<td></td>
<td>1.0612</td>
<td>0.5746</td>
<td>0.6582</td>
</tr>
<tr>
<td></td>
<td>1.1085</td>
<td>0.5852</td>
<td>0.6307</td>
</tr>
<tr>
<td></td>
<td>1.1191</td>
<td>0.6479</td>
<td>0.6497</td>
</tr>
<tr>
<td></td>
<td>1.1574</td>
<td>0.6852</td>
<td>0.6824</td>
</tr>
</tbody>
</table>

### Education level

<table>
<thead>
<tr>
<th></th>
<th>Less than high school</th>
<th>High school</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.1292</td>
<td>0.0773</td>
</tr>
<tr>
<td></td>
<td>0.1249</td>
<td>0.1701</td>
</tr>
<tr>
<td></td>
<td>0.2076</td>
<td>0.2331</td>
</tr>
<tr>
<td></td>
<td>0.2774</td>
<td>0.3254</td>
</tr>
<tr>
<td></td>
<td>0.2905</td>
<td>0.3803</td>
</tr>
<tr>
<td></td>
<td>0.3141</td>
<td>0.4062</td>
</tr>
<tr>
<td></td>
<td>0.3571</td>
<td>0.4851</td>
</tr>
<tr>
<td></td>
<td>0.4085</td>
<td>0.5014</td>
</tr>
<tr>
<td></td>
<td>0.4162</td>
<td>0.5273</td>
</tr>
<tr>
<td></td>
<td>0.4471</td>
<td>0.5523</td>
</tr>
<tr>
<td></td>
<td>0.4682</td>
<td>0.5973</td>
</tr>
<tr>
<td></td>
<td>0.4709</td>
<td>0.6073</td>
</tr>
<tr>
<td></td>
<td>0.4829</td>
<td>0.6243</td>
</tr>
<tr>
<td></td>
<td>0.4936</td>
<td>0.6429</td>
</tr>
<tr>
<td></td>
<td>0.5014</td>
<td>0.6824</td>
</tr>
<tr>
<td>College</td>
<td>0.0903</td>
<td>0.2049</td>
</tr>
</tbody>
</table>

Table 15. Projected e-cig prevalence for each year in the simulation period within different demographic categories of late former cigarette smokers.
<table>
<thead>
<tr>
<th>Years</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall Percent Prevalence</td>
<td>0.1239</td>
<td>0.5103</td>
<td>0.6944</td>
<td>1.0115</td>
<td>1.3058</td>
<td>1.3778</td>
<td>1.4019</td>
<td>1.4835</td>
<td>1.5086</td>
<td>1.5619</td>
<td>1.6731</td>
<td>1.7116</td>
<td>1.7513</td>
<td>1.8092</td>
<td></td>
</tr>
<tr>
<td>Standard errors</td>
<td>0.152</td>
<td>0.167</td>
<td>0.183</td>
<td>0.175</td>
<td>0.184</td>
<td>0.174</td>
<td>0.168</td>
<td>0.196</td>
<td>0.173</td>
<td>0.182</td>
<td>0.154</td>
<td>0.181</td>
<td>0.182</td>
<td>0.168</td>
<td>0.185</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6-20 years</td>
<td>0.0749</td>
<td>0.3329</td>
<td>0.4286</td>
<td>0.6572</td>
<td>0.7224</td>
<td>0.7975</td>
<td>0.8089</td>
<td>0.8241</td>
<td>0.8537</td>
<td>0.8729</td>
<td>0.8763</td>
<td>0.914</td>
<td>0.9557</td>
<td>0.9605</td>
<td>0.9856</td>
</tr>
<tr>
<td>21-35 years</td>
<td>0.049</td>
<td>0.1774</td>
<td>0.2658</td>
<td>0.3543</td>
<td>0.4654</td>
<td>0.5142</td>
<td>0.5772</td>
<td>0.5878</td>
<td>0.6347</td>
<td>0.6392</td>
<td>0.6842</td>
<td>0.7598</td>
<td>0.7545</td>
<td>0.7981</td>
<td>0.8152</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.0453</td>
<td>0.2216</td>
<td>0.3227</td>
<td>0.4398</td>
<td>0.5021</td>
<td>0.6297</td>
<td>0.6765</td>
<td>0.6816</td>
<td>0.7181</td>
<td>0.7278</td>
<td>0.7515</td>
<td>0.7841</td>
<td>0.8071</td>
<td>0.8234</td>
<td>0.8372</td>
</tr>
<tr>
<td>Female</td>
<td>0.0717</td>
<td>0.2974</td>
<td>0.3717</td>
<td>0.5728</td>
<td>0.6263</td>
<td>0.6736</td>
<td>0.7008</td>
<td>0.7203</td>
<td>0.7695</td>
<td>0.7813</td>
<td>0.8173</td>
<td>0.8864</td>
<td>0.9054</td>
<td>0.9276</td>
<td>0.9634</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>0.0616</td>
<td>0.2274</td>
<td>0.2894</td>
<td>0.3991</td>
<td>0.4372</td>
<td>0.5106</td>
<td>0.5617</td>
<td>0.5832</td>
<td>0.5993</td>
<td>0.6076</td>
<td>0.6143</td>
<td>0.6928</td>
<td>0.7014</td>
<td>0.7153</td>
<td>0.7386</td>
</tr>
<tr>
<td>Black</td>
<td>0.0175</td>
<td>0.1104</td>
<td>0.1912</td>
<td>0.2857</td>
<td>0.3111</td>
<td>0.3735</td>
<td>0.3733</td>
<td>0.3717</td>
<td>0.4169</td>
<td>0.4247</td>
<td>0.4562</td>
<td>0.4734</td>
<td>0.4871</td>
<td>0.4985</td>
<td>0.5221</td>
</tr>
<tr>
<td>Other</td>
<td>0.0379</td>
<td>0.1635</td>
<td>0.2238</td>
<td>0.3467</td>
<td>0.3756</td>
<td>0.4212</td>
<td>0.4428</td>
<td>0.4561</td>
<td>0.4873</td>
<td>0.4862</td>
<td>0.4913</td>
<td>0.5138</td>
<td>0.5243</td>
<td>0.5382</td>
<td>0.5472</td>
</tr>
<tr>
<td>Education level</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school</td>
<td>0.0667</td>
<td>0.2259</td>
<td>0.3171</td>
<td>0.4511</td>
<td>0.5161</td>
<td>0.6135</td>
<td>0.6449</td>
<td>0.6571</td>
<td>0.6738</td>
<td>0.6917</td>
<td>0.7114</td>
<td>0.7643</td>
<td>0.7841</td>
<td>0.7937</td>
<td>0.7925</td>
</tr>
<tr>
<td>High school</td>
<td>0.0416</td>
<td>0.1845</td>
<td>0.2267</td>
<td>0.3252</td>
<td>0.3583</td>
<td>0.3835</td>
<td>0.4051</td>
<td>0.4224</td>
<td>0.4307</td>
<td>0.4415</td>
<td>0.4521</td>
<td>0.4721</td>
<td>0.4876</td>
<td>0.4908</td>
<td>0.4921</td>
</tr>
<tr>
<td>College</td>
<td>0.0087</td>
<td>0.1175</td>
<td>0.1606</td>
<td>0.2452</td>
<td>0.2638</td>
<td>0.3148</td>
<td>0.3236</td>
<td>0.3251</td>
<td>0.3801</td>
<td>0.3748</td>
<td>0.4072</td>
<td>0.4362</td>
<td>0.4472</td>
<td>0.4421</td>
<td>0.4529</td>
</tr>
</tbody>
</table>

Table 16. Projected e-cig prevalence for each year in the simulation period within different demographic categories of never cigarette smokers.
Using Arena

The Arena modeling environment can be started from the Start menu and navigated to Programs > Rockwell Software > Arena. The Arena modeling environment will open with a new model window.
To model the process in Arena, we work in three main regions of the application window. The Project Bar hosts panels with the primary types of objects that we work with: The basic Process panel contains the modeling shapes, called modules that are used to define the process. Reports panel contained the reports that are available for displaying results of simulation runs. Navigate panel allows to display different views of the model, including navigating through hierarchical sub-models and displaying a model thumbnail.
Building the model in Arena

1) Creating the smokers

First part consisted of generating 100,000 smokers and assigning an exponential distribution to their time of arrival.

![Create Smokers dialog box image]

- Name: Create Smokers
- Entity Type: Smoker
- Time Between Arrivals:
  - Type: Random (Expo)
  - Value: 1
  - Units: Minutes
- Entities per Arrival: 100000
- Max Arrivals: 1
- First Creation: 0.0

[Image of Create Smokers dialog box]
2) Sending the smokers into one of the four smoking groups

Next, based on the NHIS distribution of CS, RFS, LFS and NS, the generated smokers were sent into one of the 4 branches.

3) Assigning the baseline characteristics

Next step was to assign the baseline characteristics to the smokers based on the NHIS estimates, and assigning corresponding probability distributions. Following figure shows the assignment of baseline characteristics and smoking related characteristics to CS. Similar assignments were done to RFS, LFS and NS.
4) Assigning history

Next step in CS was to assign history of quit attempts to the generated population of current smokers. The quit attempts history were assigned in a way that any new attempt made inside the simulation model will be added on to the previous quite attempts incorporated in the history.
5) Risk assignment

The following figure shows how to assign the risk/mutually unexclusive probabilities based on the baseline and smoking related attributes.

<table>
<thead>
<tr>
<th>Variable - Basic Process</th>
<th>Name</th>
<th>Rows</th>
<th>Columns</th>
<th>Data Type</th>
<th>Clear Option</th>
<th>File Name</th>
<th>Initial Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 iRiskCSGender</td>
<td>2</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>2 rows</td>
</tr>
<tr>
<td>2 iRiskCSAge</td>
<td>5</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>5 rows</td>
</tr>
<tr>
<td>3 iRiskCSRace</td>
<td>3</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>3 rows</td>
</tr>
<tr>
<td>4 iRiskCSEducation</td>
<td>3</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>3 rows</td>
</tr>
<tr>
<td>5 iRiskCSQuitAttempts</td>
<td>2</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>2 rows</td>
</tr>
<tr>
<td>6 iRiskCNSnicDep</td>
<td>3</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>3 rows</td>
</tr>
<tr>
<td>7 iRiskFSGender</td>
<td>2</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>2 rows</td>
</tr>
<tr>
<td>8 iRiskFSAge</td>
<td>5</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>5 rows</td>
</tr>
<tr>
<td>9 iRiskFSRace</td>
<td>3</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>3 rows</td>
</tr>
<tr>
<td>10 iRiskFSEducation</td>
<td>3</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>3 rows</td>
</tr>
<tr>
<td>11 iRiskNSAge</td>
<td>5</td>
<td>Real</td>
<td>System</td>
<td></td>
<td></td>
<td></td>
<td>5 rows</td>
</tr>
</tbody>
</table>

The following figure shows the assignment of risks related to different levels of age groups, by indexing the risks in 5 different rows corresponding to 5 different age groups.
6) Decide the initiation of e-cig

This was decided by applying the probability equations discussed in the methods section. The equation was inserted to percent true module as shown in the figure below.
7) Quit attempt and relapse within one year

This was done by allowing 48% of smokers to pass through the true branch and rest 52% to pass through the false branch. Within those 48%, 9% were allowed to pass through without making a relapse. Rest of them made a relapse and went into the loop again.
8) *Increase in risk of initiation with every relapse*

The risk of initiating an e-cig in the next year increased with every quit attempt made in the simulation. This was assigned as shown below.

9) *Recording prevalence*
People who made a relapse and who were continuing to use e-cig were recorded as e-cig users, and were recorded as regular e-cig user.

10) Waiting for another year

After the end of 1 year, smokers were allowed to wait for one year and assigned a new age.
11) Modeling the effect of policy

The policy effect was modelled by assigning an overall risk which reduced by 1% each year, a person decided to wait to initiate the e-cig.
12) Setting up the simulation
Finally, the run is set up by filling up the details in the run setup window. The model was made to run 100 replications for each group for each cycle. The values can be changed by the users as per the objectives. The model clock and initial date could be assigned as shown below.