D15154: Evaluation of Appeal and Impact of E-Cigarettes Among Chronic Smokers with Smoking-related Cancers

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ABBREVIATIONS

1-HOP	1-hydroxy napthaline
AJCC	American Joint Committee on Cancer
BMI	body mass index
CI	confidence interval
CO	carbon monoxide
CPSR	Clinical Pharmacology Shared Resource of NCCC
CTP	Center for Tobacco Products at FDA
DHMC	Dartmouth-Hitchcock Medical Center
DNA	deoxyribonucleic acid
DSMAC	Data Safety Monitoring and Accrual Committee of NCCC
ENDD	electronic nicotine delivery device
FDA	Food and Drug Administration (U.S.)
FEV1	Forced Expiratory Volume in the first second
FVC	forced vital capacity
g	gram
HPLC	high performance liquid chromatography
mg	milligram
mL	milliliter
NCCC	Norris Cotton Cancer Center
NF-kB	nuclear factor-kappa B
Ng	nanogram
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNK	nicotine-derived nitrosamine ketone
NNN	N′-nitrosonornicotine
pmol	picomoles
ppm	parts per million
SPLC	second primary lung cancer
TLFB	Timeline Follow-Back Questionnaire
TSNA	tobacco-specific nitrosamine
US	United States

ABSTRACT

Smoking causes many cancers but also affects survival and quality of life. Currently, the only option available to smokers who present with cancer is to quit, a notoriously difficult undertaking. E-cigarettes represent a modified-risk tobacco product that could reduce toxicity and improve medical outcomes. We test the appeal of e-cigarettes in cancer patients that smoke, and the impact of their use on excretion of smoke-related toxic metabolites. This pilot study tests the feasibility of a larger randomized trial to examine the effect of e-cigarette use, on measures of smoke-related toxicity and medical outcomes.

We will test feasibility in 40 smokers with aerodigestive tract cancers or bladder cancer, recruited over the course of nine months. In this 12 week single-arm study, smokers will be recruited from oncology and surgical clinics that treat these cancers, supplied with a current generation e- cigarette product and will return to clinic every 3 weeks for assessments on their e-cigarette and cigarette use along with markers for toxicity from tobacco smoke inhalation.

The overarching aim of the study is to determine the appeal of e-cigarettes as measured by the degree to which smokers with cancer adopt their use over the 9 weeks they are supplied with product. We will measure past use of e-cigarettes and cigarettes at baseline, 3, 6, 9, and 12 weeks. We will also assess the effect of e-cigarette substitution on toxicity by measuring expired carbon monoxide and urine NNAL, a carcinogenic metabolite of cigarette smoke. This translational research involves a multi-disciplinary team of prevention scientists, tobacco-use experts, statisticians, cancer clinicians, and psychiatrists and uses NCCC and White River Junction VAMC statistical and clinical trials resources.

SPECIFIC AIMS AND HYPOTHESES

<u>**Aim 1:**</u> To evaluate the behavioral and psychological appeal of e-cigarettes among 40 chronic smokers with smoking-related cancers.

Hypothesis 1 (H1): Greater than 50% of study participants will report daily e-cigarette use at each assessment during the 9 weeks that e-cigs are provided, and mean satisfaction with e- cigarettes will be >4 on a 5-point scale. In a parallel process growth model for e-cigarette and cigarette use, there will be a significant negative correlation of growth slopes.

<u>**Aim 2:**</u> To evaluate the effect of e-cigarettes on biological markers of combusted tobacco toxicity.

Hypothesis 2 (H2): After 9 weeks, mean expired breath CO_2 and urine NNAL will be reduced.

Primary outcomes:

<u>Appeal</u> (H1)—E-cigarette use and amount of e-cigarette product used per week, proportion of participants that report e-cigarette use at each assessment, satisfaction scores for e-cigarettes, and whether they continue e-cigarette use at 12 weeks (3w after end of trial). Correlation between change in e-cigarette use and change in cigarette use.

Combustible Tobacco Toxicity (H2)—Exhaled CO, urine NNAL and 1-hydroxy napthaline (1- HOP). Because smokers are good at regulating nicotine intake, we expect no change in urine cotinine over time.

STUDY OVERVIEW

This pilot study will test the appeal and toxicity of e-cigarettes as a substitute for cigarettes among smokers with aerodigestive tract cancers or bladder cancer. Participants will receive e- cigarettes for 9 weeks and be asked to substitute the e-cigarette product for their usual combustible product. Primary outcomes include e-cigarette appeal, e-cigarette use/satisfaction and combustible tobacco toxicity.

STUDY DESIGN CONSIDERATIONS

INTRODUCTION

Smoking is responsible for $130 billion in direct healthcare expenditures and half a million deaths every year in the United States, primarily from cancers, cardiovascular disease and chronic lung disease. The most recent Surgeon General report added new causal associations between active smoking and age-related macular degeneration, diabetes, colorectal cancer, liver cancer, adverse health outcomes in cancer patients and survivors, tuberculosis, erectile dysfunction, orofacial clefts in infants, ectopic pregnancy, rheumatoid arthritis, inflammation, and impaired immune function.[4] Of all the preventable causes of disease, smoking ranks by far as the most important single modifiable risk factor because it remains a prevalent behavior (affecting about 20% of the population), because of its strong relation to many disease outcomes, and because of its lack of specificity: Smoking is linked with almost every important chronic disease.


SMOKING AS A CAUSE OF CANCER

Among all modifiable risk factors for cancer, cigarette smoking exerts the greatest single effect, being responsible for about one-third of cancer deaths.[5] With respect to cancer, cigarettes deliver dozens of toxins to the lung in the tar component of smoke, where they are absorbed into the surrounding tissues and transmitted to other tissues through the blood stream. Figure 1 illustrates the known mechanisms that relate continued exposure to these toxins and the onset and development of cancers. Tobacco smoke contains more than 7,000 chemicals, and at least 69 of these can cause cancer.[6] These carcinogenic compounds deposit in the lung tissues and act locally, and are transmitted through the circulatory system to tissues remote from the lung.

For example, N-nitrosodimethylamine, and 4-aminobiphenyl are liver metabolites implicated in the association between smoking and cancer of the liver.[4] Other metabolites, e.g. urinary 4- (methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), N′-nitrosonornicotine (NNN), and their glucuronide metabolites of the tobacco-specific nitrosamine (TSNA), nicotine-derived nitrosamine ketone (NNK), are subsequently concentrated in the kidney, leading to high organ exposure in those tissues and the bladder.

Some constituents (or metabolites) of tobacco smoke bind to cellular receptors and

activate protein kinases and growth receptors, which can induce inflammation,[7] resulting in enhanced pneumocyte proliferation, activation of nuclear factor-kappa B (NF-kB), and tumor promotion.[8] These same mechanisms could affect tumor growth rates after diagnosis and risk of secondary recurrence after successful treatment of the primary tumor.

Figure 1   Pathway for causation of cancer by carcinogens in tobacco smoke
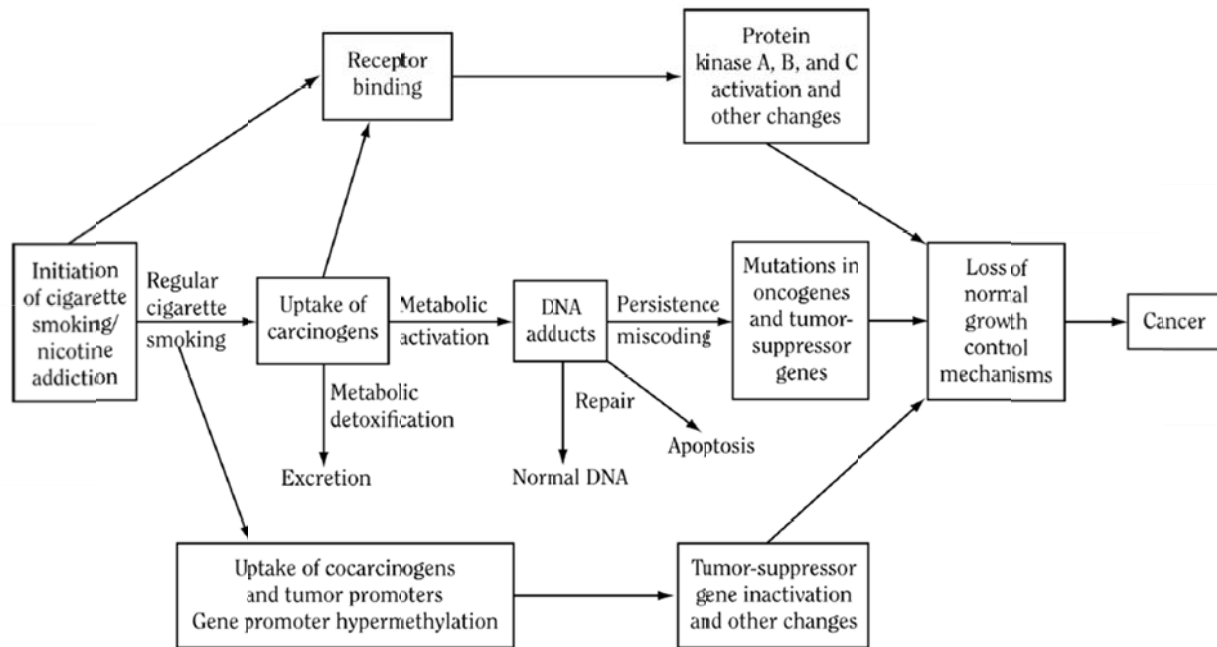
The main addictive component in tobacco, nicotine, has little toxicity in cigarette doses, especially to smokers, who are tolerant to its effects on the brain and other systems. Nicotine is also available from various nicotine replacement products that have been found to reduce cigarette consumption when given to active smokers.[9]

Reviews of studies have found that this approach does not reduce the chances that a smoker will quit smoking.[10] Moreover, smoker titrate their nicotine intake when given multiple nicotine products, such that urine cotinine levels remain the same when smokers are given a nicotine replacement product.[11] More recent unpublished data show that introduction of e-cigarettes in smokers does not result in rises in saliva cotinine, but is associated with changes in cigarette consumption.[12]

SMOKING AMONG CANCER PATIENTS

Given the prominent role smoking plays in carcinogenesis, it is not surprising that smoking is more common in cancer patients than in the general population. In a cohort of 5185 recently diagnosed cancer patients at Roswell Park Cancer Center,[1] 62% of all patients had some involvement with tobacco during their lives: current smokers (18%), recent quitters (10%), or former smokers (35%). Cancers with the highest rates of current

smoking included head & neck (29%), bladder (27%) and lung (24%).[13] Another study summarized cross-sectional and longitudinal studies of smoking <u>after</u> cancer diagnosis among lung and head & neck cancer patients, and found an overall rate of 33%.[14] Summary of the longitudinal studies in this review found little evidence to support the notion that cancer patients who smoke tend to quit over time. There were few studies of level of addiction among cancer patients that some, but given their life circumstances and the lack of evidence for quitting, it would be reasonable to conclude that these individuals are heavily addicted smokers that would be expected to be relatively refractory to treatment and for whom alternatives to cessation should be considered.

OUTCOMES FOR SMOKING-RELATED CANCERS IN SMOKERS VS. FORMER SMOKERS

EFFECT ON MORTALITY

In the Roswell Park study investigators assessed smoking status for 5185 cancer patients enrolled into treatment programs between 1982 and 1998.[1] Survival curves like the one in Figure 2 compared survival by disease site for current vs former smokers/recent quitters. Not all the curves are as striking as this one, which shows overall survival for head & neck cancer, but continued smoking was an important risk factor for many cancers and overall, with adjusted hazard ratio for time to mortality being 1.29 (95% CI 1.17, 1.42) for current vs. former smokers and 1.18 (1.04, 1.33) for current vs. recent quitters after adjusting for grade and stage, age, BMI, and several other risk factors. Given that many of the recent quitters would have relapsed (see below), the increased survival in recent quitters represents a possible harm reduction influence conferred by decreased daily cigarette consumption. Furthermore, a systematic review of observational studies examining the influence of smoking cessation after diagnosis of early stage lung cancer suggested that the mortality benefit seen with smoking cessation was due more to reduced cancer progression rather than fewer cardiorespiratory deaths.[15]

Figure 2. Overall survival: head & neck cancer, men, adjusted for age and stage
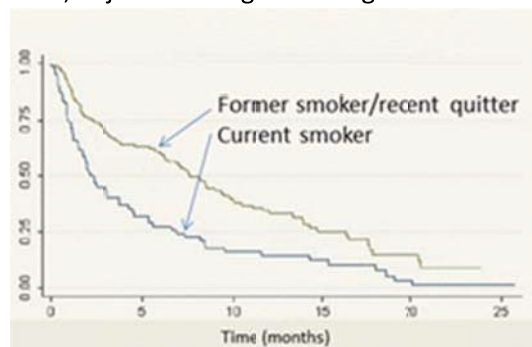
From Warren, et al. [1]

EFFECT ON RISK FOR SECOND PRIMARY CANCER

Other studies have looked specifically at how smoking status relates to the probability of developing a second primary. A study of over 1484 patients with a primary non-small cell lung carcinoma (median follow-up 26 months) found that 66 developed a second primary lung cancer (SPLC).[16] Among smokers the only variable associated with SPLC development was smoking pack-years (entered as a continuous variable), with hazard ratios indicating an 8% increase in risk for SPLC development for each additional 10 pack-years. A much larger prospective study[17] pooled data from five prospective cohorts, examining hazard of developing second primary cancers and compared never-smokers with former smokers <20 cigarettes per day, former smoker > 20 cigarettes per day, current smoker < 20 cigarettes per day, and current smoker ≥ 20 cigarettes per day. Table 1, adapted from the study, shows hazard ratios for second cancer development for lung, bladder, kidney, and head/neck cancers. Compared to never smokers, higher levels of former and current smoking showed substantially greater hazard of second primary cancers in all categories, with current smokers having higher risk compared to former smokers. Note the finding of a dose-response among smokers, showing consistently higher hazard ratios for those who smoked ≥ 20 cigarettes per day vs. those who smoked less. This adds justification to the idea that e-cigarette substitution could improve cancer outcomes even if the smoker was not able to achieve complete substitution of the e-cigarette product.

Table 1. Association between smoking status and cigarettes smoked per day and risk of a second primary smoking-associated cancer among survivors of lung, bladder, and head & neck cancers. Adapted from Shiels, et al.[17]

Smoking Status	Stage I Lung Cancer				Bladder Cancer				Head/Neck Cancer			
	Second Cancer				Second Cancer				Second Cancer			
	No	Yes	HR	95% CI	No	Yes	HR	95% CI	No	Yes	HR	95% CI
Never	186	3	1.0	Referent	1,080	28	1.0	Referent	542	18	1.0	Referent
Former												
< 20 cig/d	419	6	0.90	0.22 to 3.68	1,523	78	1.84	1.19 to 2.85	511	32	1.60	0.87 to 2.8
≥ 20 cig/d*	674	19	1.69	0.48 to 5.94	1,793	106	2.12	1.38 to 3.26	567	66	2.97	1.74 to 5.0
Current												
< 20 cig/d	482	18	2.58	0.74 to 8.98	623	49	2.81	1.76 to 4.50	408	42	2.89	1.64 to 5.0
≥ 20 cig/d*	389	17	3.26	0.92 to 11.6	448	41	3.67	2.25 to 5.99	345	51	4.45	2.56 to 7.7
P trend†			.002				< .001				< .001	

Adjusted for age, sex, race, education, BMI, cohort, time from baseline to first cancer, and follow-up time.

ONLY A SMALL PROPORTION OF CANCER PATIENTS SUCCEED AT QUITTING SMOKING

The information from the Roswell Park study would suggest that approximately 30-40% of smokers attempt to quit at or around the time of their cancer diagnosis. A recent publication from a large, well-funded cessation service at Sloan-Kettering[18] offering intensive cessation support, found that of over 4500 tobacco user referrals, 3430 (75%) were unreachable or refused cessation assistance. Of the over 1000 enrolled in the service, about 25% did not complete the protocol, 25% either died or were lost to follow-

up, and 43% reported no tobacco use at 6 months. In summary, the data from a large cessation service at a major cancer center suggest that these state-of-the art programs benefit only about 10% of smokers with cancer. This is, again, consistent with the findings above that suggest these individuals are heavily addicted and relatively refractory to cessation treatment, leaving about 90 percent who continue to expose themselves to smoke-derived carcinogens during the course of their therapy.

The Sloan-Kettering program assessed e-cigarette use among patients trying to quit smoking and found that as many as half of these patients were experimenting with e-cigarettes during 2013, but that e-cigarette use did not affect successful quit rates. This is becoming a common finding in population studies of e-cigarettes, in part because people receive mixed messages from the public health community regarding whether these products represent an appropriate substitute for smoking. In the present study, we will test the appeal and toxicity of e-cigarettes in smokers with cancer.

E-CIGARETTES

WHAT ARE THEY AND HOW DO THEY WORK

Electronic cigarettes, also known as e-cigarettes, create an inhalable nicotine aerosol by heating a liquid nicotine solution. Unregulated in the US, e-cigarette sales have seen a rapid rise unparalleled by any other non-combustible nicotine delivery system.[19] The main components of the e-cigarette include a battery, a cartridge with nicotine dissolved in propylene glycol or vegetable glycerol, and a heater that aerosolizes the nicotine—propylene glycol solution. When the user puffs on the end of the device and creates a vacuum, the battery powers the heater and creates aerosol, which is drawn into the mouth piece and inhaled (Figure 3). E-cigarettes come in many styles and are rapidly evolving. This was true for first gen e-cigs. Later models have a button to push on the battery, which creates a bolus of vapor ready for immediate inhalation when the e-cig reaches the mouth.

Figure 3. Schematic for key components of the e-cigarette (image taken from the internet).
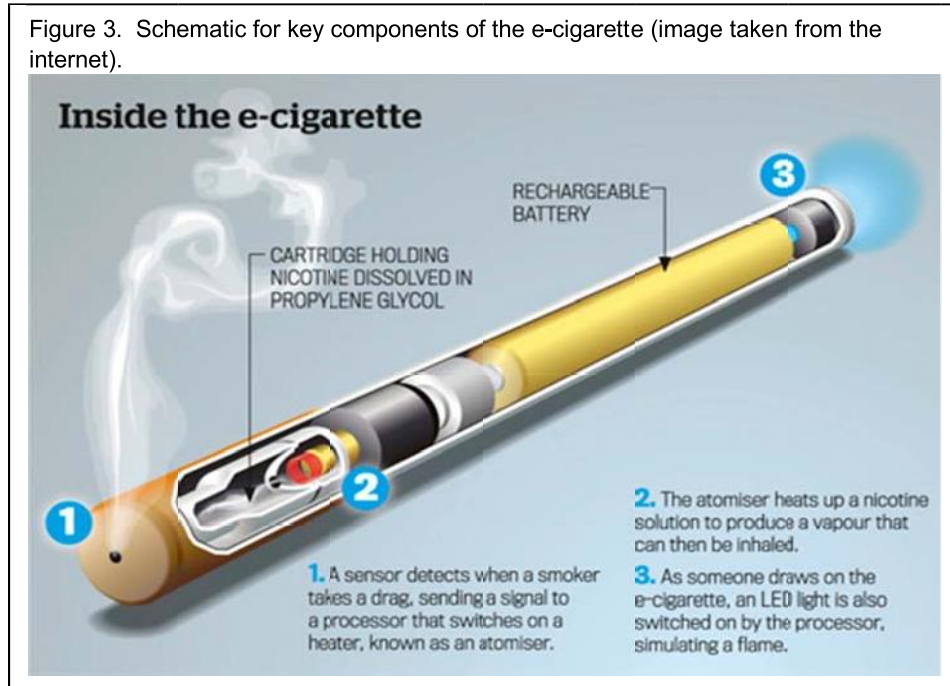
THEORETICAL CASE FOR E-CIGARETTE HARM REDUCTION IN SMOKERS WITH CANCER

TOXICOLOGY

E-cigarettes are not currently regulated, and the Food and Drug Administration has required no information from manufacturers on their ability to deliver nicotine and potential toxicity.

However, compared to cigarettes, they should deliver comparatively fewer toxic chemicals to the lung; available evidence strongly suggests this is true. Compared to tobacco smoke, studies have found e-cigarette smoke to be substantially lower in toxic content, cytotoxicity, and adverse side effects.[20]   One laboratory study comparing the toxicity profile of e-cigarette aerosols and tobacco smoke found that known tobacco toxins in e-cigarette aerosols were 100 to 1000 times lower than those found in tobacco smoke.[21] Another FDA study found that carcinogenic tobacco specific nitrosamines in e-cigarette vapor was 8.2 ng/g, similar to the level in nicotine patch users (8.0 ng/g) and much less than the level in Marlboro cigarette smoke (6260ng/g).[22] Another study found that toxic metabolites of cigarette smoke were greatly reduced in the urine of e-cigarette users compared to smokers.[23]

Studies have also reported that e-cigarette use had no inflammatory effect on complete blood count indices,[24] nor did it cause significant reduction in lung function (3% reduction FEV1/FVC) compared to cigarette smoke (7% reduction FEV1/FVC),[25] and that e-cigarette use had no negative effects on myocardial function.[26] Based on these and other studies, Public Health England has published a public statement that e-cigarettes are 95% safer than smoking.[27]
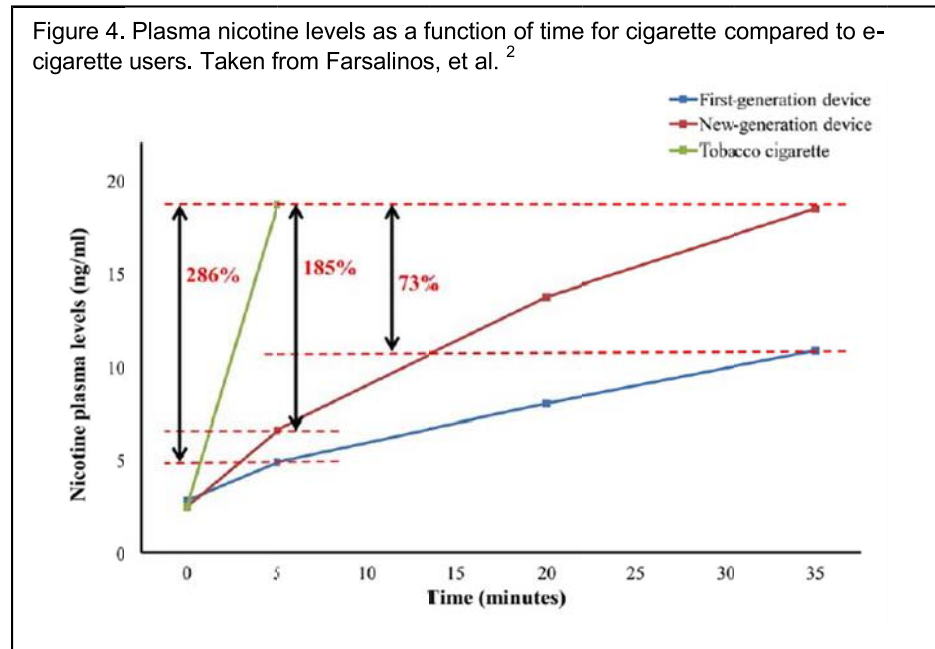
Although e-cigarettes appear to have much lower toxic potential compared to cigarettes,

and are being embraced by some public health programs, they are not free from toxicity. Because of the lack of regulation of these products, we are now faced with an array of products, and no standardization of nicotine concentration, flavoring, and contaminant allowance.[28] Lipoid pneumonia has been reported in one e-cigarette user, probably as a result of flavoring oils or oil contaminated glycerol.[29] Use of high voltage batteries in refillable tank devices converts propylene glycol at very high temperatures to formaldehyde, but not to the levels found in tobacco smoke.[30]   Data are starting to appear that suggest that some of the flavor components of e-cigarettes may affect lung epithelial cells and inflammation,[31] and even nonflavored vapor affected macrophage-moderated inflammation in mice exposed to the vapor.[32] Thus, the sum of the limited data available so far suggests that, compared to cigarette smoke, e-cigarette vapor exposes users to much lower levels of toxins. While it remains unknown what the impact on health or oncological outcomes of e-cigarettes may be, the factors outlined above suggest a clear theoretical safety advantage over continued use of combustible tobacco products for patients with cancer. Given almost universal access to these products and the fact that cancer patients are using them, we have an obligation to determine how they affect consumption of combustible tobacco and whether their use affects intermediate medical outcomes. That is the overarching purpose of the present research.

NICOTINE DELIVERY

Much of the nicotine from cigarettes is delivered to the brain by arterial circulation within seconds of puffing on the cigarette.[33] This is one of the reasons for high abuse liability for cigarettes. Nicotine delivered from the oropharynx (e.g., when smokeless or nicotine gum is used) enters the venous blood and passes through the liver before going to the brain. This not only delays its delivery to the brain, but it lowers the dose because some of the nicotine is changed to cotinine in the liver. For e-cigarette aerosols, about half the nicotine absorbed is delivered through the alveoli, with the other half being delivered to the venous circulation through absorption from the oropharynx and bronchial tree.[34] Delivery of nicotine is improving as e-cigarette manufacturers improve design. First generation e-cigarette devices, released between 2008 and 2010, delivered nicotine primarily to the mouth and oropharynx and could not product plasma nicotine concentrations equivalent to cigarettes (blue line in Figure 4 below).

Nicotine absorption from new generation devices (produced after 2010, red line in Figure 4) are able to equivalent levels of plasma nicotine, but only after 20-30 minutes of puffing.[2] However, nicotine delivery from e-cigarettes has been shown to improve with practice,[35] and more recent studies find that experienced users of some products can quickly deliver cigarette-like nicotine doses.[36]

Figure 4. Plasma nicotine levels as a function of time for cigarette compared to e-cigarette users. Taken from Farsalinos, et al. [2]

BEHAVIORAL ADVANTAGES

Despite some disadvantages of nicotine delivery compared to cigarettes, e-cigarettes represent an improvement in nicotine delivery compared to available nicotine replacement products, such as nicotine gum or patch, products that were intentionally meant to be slowly absorbed.[35] Part of the appeal of the e-cigarette is in how it mimics the behavioral process of smoking. The importance of the behavior in maintaining the smoking habit was recognized over 30 years ago by chief Philip Morris scientist William Dunn, who stated, "The smoking act has many dimensions. The motor aspects, drawing the smoke into the mouth, inhaling the smoke into the lungs … taste and olfactory sensations are elicited, sensations are elicited when the smoke is drawn down into the lungs, psychosocial symbolism is imparted to the person, and a large number of chemical compounds pass rapidly into the bloodstream."[37] Nicotine replacement therapy emphasizes the effects of one of those compounds and largely ignores the important behavioral aspects of the habit. The effect of the behavioral components of the e-cigarette are apparent in a study of e-cigarette use and cigarette craving.[3] As illustrated in Figure 5 below, e-cigarette use was associated with substantial reductions in cigarette craving, and these immediate reductions were independent of whether the device contained nicotine.

Figure 5. Craving to smoke a cigarette as a function of time and whether the smoker was inhaling a cigarette or an electronic nicotine delivery device (ENDD) with and without nicotine or a nicotine inhaler (one form of nicotine replacement therapy). Taken from Bullen, et al. 3
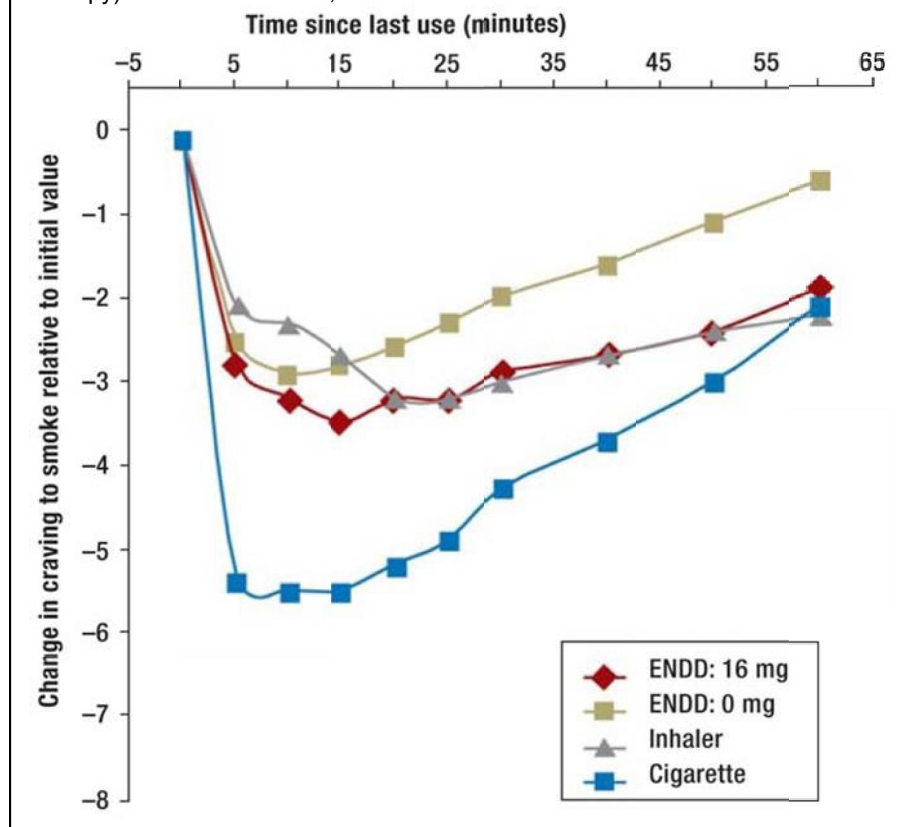
E-CIGARETTE REGULATION: IMPLICATIONS ON STUDY DESIGN

As detailed below, the specific aims of this project are to determine the appeal and toxicity of e-cigarettes in current smokers with a smoking-related cancer. This is NOT a smoking cessation study; instead, it examines changes in intake for two tobacco products when administered together. There is a regulatory basis for the decision to focus on appeal and toxicity, and not smoking cessation. When e-cigarette devices first attempted to enter the US market, the Food and Drug Administration (FDA) blocked shipments on the basis that e-cigarettes were unapproved drug delivery devices and must first pass through FDA's New Drug Application process before they could be legally sold. E-cigarette manufacturers sued, arguing that e-cigarettes contained nicotine derived from tobacco and were therefore a tobacco product; the US Court of Appeals (Washington DC) ruled in their favor; and the FDA decided not to seek further review. The FDA then determined that they would "deem" e-cigarettes to be covered under the *Family Smoking Prevention and Tobacco Control Act* (deeming is in process at this date). In the meantime, the FDA has determined that any evaluation of the e-cigarette product for a therapeutic endpoint (such as treating nicotine addiction) requires an Investigational New Drug Application (involving animal pharmacology and toxicity studies, manufacturing information on the product, etc.). This regulation does not allow scientists not closely affiliated with an

e-cigarette company to study these products as therapeutic devices. Moreover, e-cigarette companies have made it clear in US courts that they do not seek approval as a drug delivery device.

The Center for Tobacco Products (CTP) at FDA is charged with regulating the tobacco market under the *Family Smoking Prevention and Tobacco Control Act,* which charges the FDA, among other things, "to promote cessation to reduce disease risk and the social costs associated with tobacco-related diseases." CTP funds investigators to help the agency compare tobacco products with respect to three issues of interest—their relative appeal, toxicity, and effect on health. This leaves scientists the option of studying the e-cigarette as a modified risk tobacco product in smokers with respect to those three types of outcomes. The ultimate goal is to reduce the harm caused by cigarettes and other combustible tobacco products by substituting less toxic delivery devices for the primary drug, nicotine. This pilot project begins this line of investigation with a short-term study of e-cigarette appeal and toxicity among cancer patients that smoke.

TRIAL PROTOCOL

      STUDY DESIGN

We will enroll 40 chronic smokers from the Norris Cotton Cancer Center and the White River Junction VAMC, approximately 15 of which will be accrued from the White River Junction VAMC. Participants will be given access to e-cigarettes for a 9-week period. Consecutive patients with stage I-IV aerodigestive tract cancers or bladder cancer who are current daily smokers will be identified two ways:

1) Clinic Recruitment - Potential participants will be identified by the treating physician during routine clinic visits. Patients will be advised to quit smoking as per the standard of care. Any patient wishing to quit smoking will be referred for smoking cessation counselling through the DHMC program, the White River Junction VAMC program, or their state help-line. Once eligibility is confirmed and informed consent is obtained and signed, patients will be enrolled in the study.

2) EMR Recruitment: In a recruitment strategy that parallels clinic recruitment, we will use the EMR to identify all potentially eligible smokers (with the diagnosis of aerodigestive tract cancers or bladder cancer) that have been seen in the NCCC in the past 3 years. EMR records will be searched by the D-HRDS Analytics Institute who will then forward a list of potential subjects to the project coordinator with their diagnoses and contact information, consistent with our partial HIPAA waiver. The project coordinator will then send this list of potential subjects to their providers to be approved to be contacted about the study. Approved potential subjects will then be contacted by mail through a letter from their NCCC oncology group. The subjects will have an opportunity to opt out of receiving a phone call through a prepaid return mailer or by calling a telephone number. If we do not hear from them in 2 weeks, we will then attempt to call them. We will attempt to call one time a week for 3 weeks. If there is no answer we will leave a brief, generic message. The call will assess their smoking status, and their willingness to quit. Nonsmokers are not eligible. If they smoke and are interested in quitting, they will be referred to their state quit line. If they are not interested in quitting at this time, they will be

offered participation in the study, and we will confirm eligibility.   The mailing will include: A letter from their oncology group at NCCC, the brochure for their state quit line, a handout about the study, and a paper to return to us in a postage-paid envelope. If they return the paper to us requesting a referral to the quit line we will notify the D-H smoking cessation specialist. He/She will then process the referral to the quit line in EDH. The patient will then be contacted directly by the quit line. We will also provide them with their state smoking cessation help-line numbers. If they return the paper to us indicating they do not wish to quit and would like more information regarding the study, a coordinator will contact them.

Once enrolled, participants will receive the e-cigarette product described below, will be instructed on use of the e-cigarette, and given a supply that is approximately equivalent to their current nicotine intake. They will be told that e-cigarettes are theoretically safer than cigarettes, and that this trial aims to test how appealing the product is for smokers not willing to quit consuming nicotine.

We have opted to use e-cigarette products produced by Halo, a US manufacturing company that emphasizes the purity of its products and its approach to quality control in the manufacturing process. Patients will be given Halo Triton, which uses a leak-proof refillable tank system that has had a recent technological update. The patient will be shown how to fill the tank and will be observed filling it. Those not able to manage the tank refill will be given Halo G6 leak proof prefilled cartomizers (the part of the e-cigarette that contains the nicotine solution and the heating filament); these can be substituted for the tank on the Triton battery. The starter kit that will be distributed to patients is illustrated in Figure 6.

HALO manufactures its e-cigarette and the nicotine solutions in the United States. The HALO solution e-cigarettes contain 0, 12, 18, 24, or 36 mg/ml nicotine. We have been advised to begin our participants with 18mg/ml and move up or down based on patient preference. E-cigarette liquid also comes in many flavors, and we have decided to allow participants to choose from four options. Halo has agreed to provide us with the names of their 4 highest selling liquids. They have shared an ingredients list with the Drs. Sargent and Lewis for the purposes of adverse event monitoring and in the event that our IRB members request information about the ingredients.

Figure 6. Starter kit for the Halo Triton tank.

Coordinators will assess participants at baseline and weeks 3, 6, 9, and 12. Although most of our patients are expected to have completed their therapy, the schedule is designed to integrate with return schedules for many chemotherapeutic regimens, if possible. We have considered the concern that chemotherapy could affect cigarette consumption or excretion of nicotine metabolites. According to our clinicians, the current chemotherapy regimens for these cancers are not associated with severe symptoms, such that patients rarely decrease their smoking during treatment. Nevertheless, we will assess the severity of 6 common chemotherapy side effects at each visit so that may be entered as a covariate in our analytic models. Regarding metabolites, for nicotine, the major metabolite cotinine is formed via CYP2A6 and CYP2B6 metabolism, and the traditional cytotoxic chemotherapeutic agents used in the cancer treatment are not known to affect the activity of these CYP450 /UGT enzymes significantly. Additionally, cyclical cytotoxic chemotherapy is not given every day throughout a cycle. The most well characterized carcinogens of smoking so far are NNK (4-(methylnitrosamino)1(3-pyridyl)-1-butanone) and NNAL (4-(methylnitrosamino)1(3-pyridyl)-1-butanol). These carcinogens are also metabolized by some of the same enzymes that metabolize nicotine including CYP2A6, UGT2B10, UGT1A4 and CYP2A13, so these should not be affected by most chemotherapeutic regimens.

Coordinators will assess eligibility, collect specimens, administer CO_2 measurements and administer the surveys during the baseline and follow up visits.

PARTICIPANTS

Inclusion Criteria:

1) Histological or cytological diagnosis of aerodigestive tract cancers or bladder cancer within the past 5 years (more than one tobacco-related malignancy is allowed)

2) AJCC stages I-IV

3) Daily smoking (at least 10 cigarettes per day for 10 years) and breath CO_2 ≥8 ppm

4) Does not wish to quit smoking now (anyone wishing to quit smoking will be referred for smoking cessation counselling through the WRJ VAMC or DHMC program)

5) May be receiving anti-cancer agents

6) Age 18 or older

7) Fluent in English

8) Patient must be capable and willing to provide informed written consent for study participation

9) Able to participate in study visits

Exclusion Criteria:

1) Cancer surgery planned in the next 9 weeks

2) Treatment with radiation planned for the next 9 weeks

3) Actively trying to quit smoking, or planning to in the next 30 days. (If a subject reports that they plan to quit smoking in the next 30 days, we will call them after the 30 days to see if they are still trying to quit.)

4) Any use of e-cigarettes in the past 30 days

5) Pregnant or trying to get pregnant

RECRUITMENT

Potentially eligible patients will be identified by clinician-researcher collaborators and through clinical trials nurses or clinical research coordinators, who monitor the cancer patient population for recruitment into clinical studies. Patients may be identified in multiple clinical settings, including outpatient clinics and the infusion suite. Once a potentially eligible patient is identified, a referral will be made to the site coordinator, who will meet with the patient, confirm eligibility, and obtain consent for the patient to participate in the study, and register the patient in the Velos e-Research database. (If a site coordinator is unable to utilize Velos, that coordinator will submit participant data to another coordinator with access and it will be entered into the Velos e-Research database.) The coordinator will conduct baseline web assessments, provide e-cigarettes and instruction on how to use the product, and conduct all follow up assessments.

STUDY TIMELINE AND FOLLOW-UP

The trial is designed to allow for patient visits every 3 weeks for 12 weeks. The coordinators will work with the participant and the participants' medical care teams to schedule and conduct the visits. We will contact enrolled subjects for follow-up at 6 and 12 months after enrollment. Each time, we will attempt to contact the subjects 3 times by phone over a period of 3 weeks. During the call the subject will be asked if they are still using an e-cigarette, what brand they are using, what concentration of nicotine they use, how many times a day they use it, and how often they currently smoking any combustible tobacco products.

Participants will receive free e-cigarette products for the first 9 weeks of the trial and $20 for each visit ($100 total). Participants that travel more than 20 miles one-way for a study-only visit (no other appointments scheduled on the day of their study visit) will be given a $10 gas card.

Table 2. Timeline for study activities and compensation					
Time	Baseline	3 weeks	6 weeks	9 weeks	12 weeks
Activity	Consent; survey; ecig instruction; urine; CO	Survey; ecig refill; urine; CO	Survey; ecig refill; CO	Survey; qualitative interview; urine; CO	Survey; CO
Compensation	$20	$20	$20	$20	$20

OUTCOMES ASSESSMENT

Each visit will include a checklist that assesses how the participant is using the e-cigarettes and what problems he/she may be encountering with the use of the e-cigarette device. Adverse events will be assessed with a checklist for commonly occurring side effects from e-cigarettes and nicotine products. The coordinators will conduct and audio-record a 10-15 minute qualitative interview at 9 weeks soliciting perceptions about e-cigarettes to be transcribed and analyzed for common themes that could be useful in developing the larger intervention.

Behavioral assessments: We will use a Timeline Follow-Back Questionnaire (TLFB)[38,39] to document use of cigarettes at baseline and cigarettes/e-cigarettes at baseline, 3, 6, 9, and 12 weeks. At follow up visits participants will be instructed to bring in all used and unused e- cigarettes, in order to verify reports of e-cigarette use. We will evaluate appeal with attitudinal ratings, on a 5-point Likert-type scale, e-cigarette ease of use, satisfaction, and enjoyment, and willingness to continue to purchase e-cigarettes in the future. All questionnaires are being programmed using a secure web-based system set up and maintained by the Dartmouth Bioinformatics group led by Kristen Anton.

Biomarkers of behavior: Cigarette smoking will also be measured with exhaled carbon dioxide. We will assess expired breath CO_2 using Micro Smokerlyzer meters (Bedfont Scientific), which have already been purchased for a previous study. The protocol will follow operating instructions that come with the devices, and the devices will be calibrated weekly with 40PPM CO_2/air mixture. E-cigarette smoking will be measured with urine propylene glycol, the main constituent of e-cigarette aerosol. Some 40% of ingested

propylene glycol is excreted unchanged in the urine.

The NCCC Clinical Pharmacology Shared Resource (CPSR) will conduct assays of urine for smoke-related carcinogens. Urine samples (at least 20 mL) will be collected at the study defined time points from study participants in standard urine containers. These will be delivered to the NCCC CPSR, divided into 5 mL aliquots and stored at -20°C or below until analysis. Urine aliquots will be assayed in batches based on the published assays for urine nicotine, cotinine, 4- (methylnitrosamino)-1-(-3pyridyl)-1butanol (NNAL)[40] and 1-hydroxy naphthalene (1-HOP)[41] concentrations. These assays can and will be established and validated in the NCCC CPSR using the LC-MS/MS and HPLC-Fluorescence services available in the CPSR.
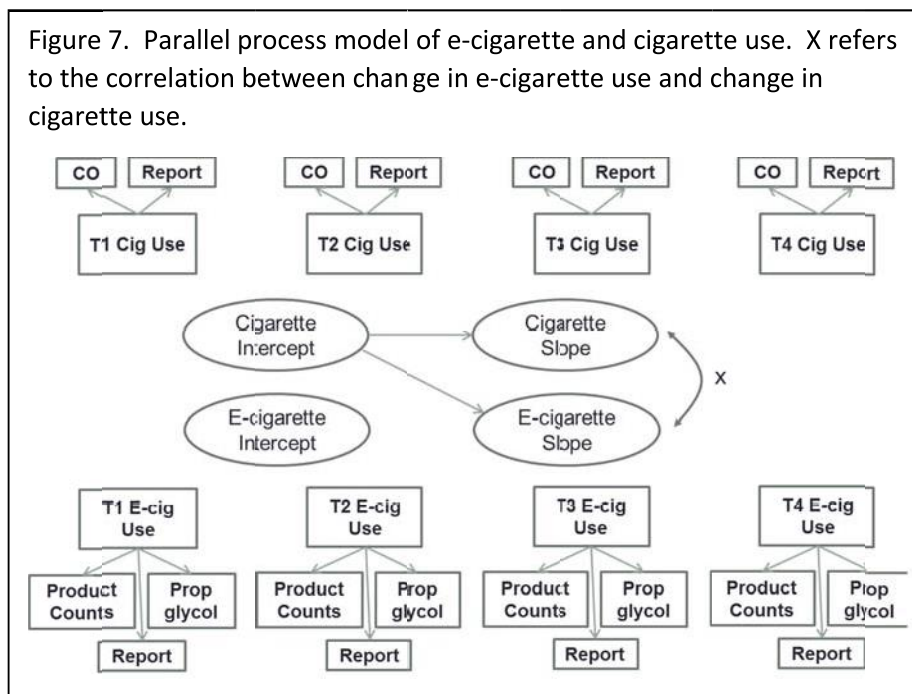

STATISTICAL ANALYSIS AND POWER CONSIDERATIONS

<u>Qualitative Analysis</u>

A follow up interview will be conducted at week 9. The interview will be transcribed and a thematic analysis will be conducted to evaluate common issues encountered by smokers with cancer patients who use e-cigarettes. Thematic analysis consists of examination of text by identifying and grouping themes, followed by coding, classifying, and developing categories. Transcripts are uploaded into a qualitative analytic software program and analyzed using Atlas.ti, a qualitative coding program. Co-investigator Sarah Pratt has experience using similar qualitative methods to interview health professionals. She will supervise the coders, staff at the Centers for Health and Aging at Dartmouth who have been trained to perform similar analyses in other studies.

Substitution assessment: The proportion of participants who report use of e-cigarettes during each follow-up visit during treatment will also be computed (along with a 95% confidence interval). This proportion is expected to be at least 0.5. With 40 participants, width of a 95% confidence interval around this proportion will be at most 0.32. The satisfaction with e- cigarettes (averaged across 3 treatment assessments) will be summarized among participants using descriptive statistics and the amount of e-cigarette product returned at each follow-up period will be summarized across the treatment period.

To explicitly test the substitution/replacement mechanism of e-cigarettes, we will perform an exploratory parallel process growth model fit within a structural equation modeling framework.[42] In this model the trajectory over time of both frequency/quantity of cigarette use and frequency/quantity of e-cigarette use will be modeled assuming individual-level latent intercept and slope (i.e., latent growth curve model). A significant negative association between the latent slope of e-cigarettes and the latent slope of combustible cigarettes would be consistent with the replacement/substitution hypothesis. The model provides an explicit statistical test of the hypothesis that, as e-cigarette usage increases, combustible cigarette usage decreases. Power for this analysis is computed as that for an individual-level correlation coefficient assuming 40 participants. There will be at least 80% power to detect a correlation that is at least -0.4 between these two individual-level slopes. Figure 7 shows a diagram of the parallel process growth model.

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Figure 7. Parallel process model of e-cigarette and cigarette use. X refers to the correlation between change in e-cigarette use and change in cigarette use.

Toxicity Assessment: Our measures of toxicity, urine NNAL, 1-HOP and CO_2 will be compared between the baseline and 9-week assessments via paired t-test. For NNAL, assuming a standard deviation of change in this measure of 3.8 pmol/mg creatinine (as was seen in Joseph et al. 2008), with 40 participants, this test will have 80% power at the two-sided 0.05 significance level to detect a change from baseline of 1.7 pmol/mg creatinine. There is not enough information available on 1-HOP to perform a test of power, so analysis of this metabolite is considered exploratory. For expired CO, assuming a standard deviation of change in this measure of 17.0 ppm,[43] with 40 participants, a paired t-test comparing baseline to 9-week will have 80% power at the two-sided 0.05 significance level to detect a change from baseline that is 7.7 ppm. Additionally, since CO_2 will be measured several times throughout the treatment period, the trajectory of change over time in this measure will be modeled via linear mixed effects models including random intercept and slope terms to account for repeated observations within individual. With repeated measurements of CO, the power for the mixed model will be greater than that of the paired t-test of change from baseline to detect this change over time.

We will also evaluate toxicity by analyzing cotinine level to assure that the adverse effect of increased cotinine (resultant from increased e-cigarette usage without similar decrease in combustible cigarettes). To do this, we will compute the number of participants with an increase in cotinine over the course of the study and consider this an adverse event. With 40 participants, confidence intervals around this adverse event percentage will be at most 0.32 percentage points. The table below gives the probability of observing at least 1 participant with an increase in cotinine given different true percentage of participants with this adverse event. For example, if the population-wide true percentage of participants with cotinine increase is 0.5%, then the probability of observing at least 1 of the 40 study participants with an increase is 0.18.

True percentage of participants with increase cotinine	Probability of observing at least 1 adverse event (increase in cotinine)
0.5%	0.18
1%	0.33
2%	0.55
5%	0.87
10%	0.99

ON-SITE MONITORING

Clinical research monitoring for regulatory compliance and data integrity will be conducted according to the NCI-approved NCCC Data and Safety Monitoring Plan. Internal monitoring is conducted by appropriately trained staff of the NCCC Office of Clinical Research and Dartmouth-Hitchcock Medical Center Clinical Trials Office (CTO) and the White River Junction VA Medical Center who are not involved in the study. This monitoring will include periodic assessment of the regulatory compliance, data quality, and study integrity. Study records will be reviewed and directly compared to source documents and the conduct of the study will be discussed with the investigator. Monitors may request access to all regulatory documents, source documents, CRFs, and other study documentation for on-site inspection. Direct access to these documents is guaranteed by the investigator, who must provide support at all times for these activities.

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable Dartmouth research compliance and quality assurance offices. The investigator will permit study protocol related audits and inspections by the Dartmouth CPHS, government regulatory bodies, and the Dartmouth compliance and quality assurance groups of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., diagnostic laboratory).

RECORD RETENTION

Following closure of the study, the investigator will maintain all site study records in a safe and secure location. The records are maintained to allow easy and timely retrieval when needed (e.g., audit or inspection) and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and staff. Upon completion of study analysis, research information is stored in a password protected, secure research server behind the firewall at the WRJ VA indefinitely or at Dartmouth College Records Management off-site storage located at 6218 Etna Road, Hanover, NH. Documents are shredded on site after 50 years of storage.

Electronic case report forms, participant, and study information will be kept in the Velos eResearch password-protected database (or equivalent) indefinitely.

SAFETY AND DATA MONITORING

This study will be monitored by the Data Safety Monitoring and Accrual Committee (DSMAC) of the Norris Cotton Cancer Center. The Committee meets quarterly to review accrual rates and information for studies that have accrued participants. The Clinical Cancer Review Committee (CCRC) determines the frequency of DSMAC review. The DSMAC has the authority to suspend or to recommend termination to the CCRC of all research activities that fall within its jurisdiction. In the event that a study is suspended or terminated, that information will be forwarded to the CPHS (Dartmouth IRB) office.

References

1. Warren GW, Kasza KA, Reid ME, Cummings KM, Marshall JR. Smoking at diagnosis and survival in cancer patients. *International Journal of Cancer.* 2013;132(2):401-410.

2. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Scientific reports.* 2014;4.

3. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tobacco control.* 2010;19(2):98-103.

4. U.S. Department of Health and Human Services. The Health Consequences of Smoking: 50 Years of Progress. A Report of the Surgeon General. Atlanta GUSD. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014.

5. Jacobs EJ, Newton CC, Carter BD, et al. What proportion of cancer deaths in the contemporary United States is attributable to cigarette smoking? *Annals of epidemiology.* 2014.

6. (GA): U.S. Department of Health and Human Services, USDoHaHSHTSCDTBaBBfS-ADARotSGA. Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2010.

7. Shizu M, Itoh Y, Sunahara R, et al. Cigarette smoke condensate upregulates the gene and protein expression of proinflammatory cytokines in human fibroblast-like synoviocyte line. *Journal of Interferon & Cytokine Research.* 2007;28(8):509-522.

8. Takahashi H, Ogata H, Nishigaki R, Broide DH, Karin M. Tobacco smoke promotes lung tumorigenesis by triggering IKKβ-and JNK1-dependent inflammation. *Cancer cell.* 2010;17(1):89- 97.

9. Hughes JR, Carpenter MJ. The feasibility of smoking reduction: an update. *Addiction.* 2005;100(8):1074-1089.

10. Hughes JR, Carpenter MJ. Does smoking reduction increase future cessation and decrease disease risk? A qualitative review. *Nicotine & Tobacco Research.*

2006;8(6):739-749.

11. Fagerström KO, Tejding R, Westin A, Lunell E. Aiding reduction of smoking with nicotine replacement medications: hope for the recalcitrant smoker? *Tobacco Control.* 1997;6(4):311- 316.

12. Goniewicz M. Saliva cotinine and nicotine levels among tobacco cigarette smokers, electronic cigarette users, NRT users and dual users. SRNT Europe 16th Annual Conference; September 12, 2015, 2015; Maastricht, The Netherlands.

13. Morales NA, Romano MA, Cummings KM, et al. Accuracy of self-reported tobacco use in newly diagnosed cancer patients. *Cancer Causes & Control.* 2013;24(6):1223-1230.

14. Burris JL, Studts JL, DeRosa AP, Ostroff JS. Systematic Review of Tobacco Use after Lung or Head/Neck Cancer Diagnosis: Results and Recommendations for Future Research. *Cancer Epidemiology Biomarkers & Prevention.* October 1, 2015 2015;24(10):1450-1461.

15. Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. *Bmj.* 2010;340.

16. Boyle JM, Tandberg DJ, Chino JP, D'Amico TA, Ready NE, Kelsey CR. Smoking history predicts for increased risk of second primary lung cancer: a comprehensive analysis. *Cancer.* Feb 15 2015;121(4):598-604.

17. Shiels MS, Gibson T, Sampson J, et al. Cigarette smoking prior to first cancer and risk of second smoking-associated cancers among survivors of bladder, kidney, head and neck, and stage I lung cancers. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Dec 10 2014;32(35):3989-3995.

18. Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer.* Nov 15 2014;120(22):3527-3535.

19. Ayers JW, Ribisl KM, Brownstein JS. Tracking the rise in popularity of electronic nicotine delivery systems (electronic cigarettes) using search query surveillance. *American journal of preventive medicine.* Apr 2011;40(4):448-453.

20. Harrell PT, Simmons VN, Correa JB, Padhya TA, Brandon TH. Electronic nicotine delivery systems ("e-cigarettes"): review of safety and smoking cessation efficacy. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* Sep 2014;151(3):381-393.

21. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco control.* 2014;23(2):133-139.

22. http://www.fda.gov/downloads/drugs/scienceresearch/ucm173250.pdf., WBEoe-cFCfDEaRDoPAAo.

23. Hecht SS, Carmella SG, Kotandeniya D, et al. Evaluation of toxicant and

carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine & Tobacco Research.* 2014:ntu218.

24. Flouris AD, Poulianiti KP, Chorti MS, et al. Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food and chemical toxicology.* 2012;50(10):3600-3603.

25. Flouris AD, Chorti MS, Poulianiti KP, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation toxicology.* 2013;25(2):91-101.

26. Farsalinos KE, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voudris V. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC cardiovascular disorders.* 2014;14(1):78.

27. Public Health England. Underpinning evidence for the estimate that e-cigarette use is around 95% safer than smoking: authors' note. 2015. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/456704/McN eill-Hajek_report_authors_note_on_evidence_for_95_estimate.pdf. Accessed September 9, 2015.

28. Cheng T. Chemical evaluation of electronic cigarettes. *Tob Control.* May 2014;23 Suppl 2:ii11-17.

29. McCauley L, Markin C, Hosmer D. An unexpected consequence of electronic cigarette use. *CHEST Journal.* 2012;141(4):1110-1113.

30. Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden Formaldehyde in E-Cigarette Aerosols. *New England Journal of Medicine.* 2015;372(4):392-394.

31. Lerner CA, Sundar IK, Yao H, et al. Vapors Produced by Electronic Cigarettes and E-Juices with Flavorings Induce Toxicity, Oxidative Stress, and Inflammatory Response in Lung Epithelial Cells and in Mouse Lung. *PLoS One.* 2015;10(2).

32. Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PLoS One.* 2015;10(2):e0116861.

33. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. *Journal of consulting and clinical psychology.* 1993;61(5):743.

34. Zhang Y, Sumner W, Chen D-R. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. *Nicotine & tobacco research.* 2013;15(2):501-508.

35. Hajek P, Goniewicz ML, Phillips A, Myers Smith K, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. *Nicotine & tobacco research: official journal of the Society for Research on Nicotine and Tobacco.* Feb 2015;17(2):175-179.

36. Talih S, Balhas Z, Eissenberg T, et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. *Nicotine & tobacco research : official journal*

of the Society for Research on Nicotine and Tobacco. Feb 2015;17(2):150-157.

37. Dunn WL. *Smoker Psychology Program Review.* Philip Morris;1977.

38. Brown RA, Burgess ES, Sales SD, Whiteley JA, Evans DM, Miller IW. Reliability and validity of a smoking timeline follow-back interview. *Psychology of Addictive Behaviors.* 1998;12(2):101.

39. Sobell LC, Sobell MB. Timeline follow-back. *Measuring alcohol consumption*: Springer; 1992:41- 72.

40. Kotandeniya D, Carmella SG, Ming X, Murphy SE, Hecht SS. Combined analysis of the tobacco metabolites cotinine and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol in human urine. *Analytical chemistry.* Feb 3 2015;87(3):1514-1517.

41. Carmella SG, Le KA, Hecht SS. Improved method for determination of 1-hydroxypyrene in human urine. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology.* Jul 2004;13(7):1261-1264.

42. Cheong J, Mackinnon DP, Khoo ST. Investigation of Mediational Processes Using Parallel Process Latent Growth Curve Modeling. *Structural equation modeling : a multidisciplinary journal.* Apr 1 2003;10(2):238.

43. Joseph AM, Hecht SS, Murphy SE, et al. Smoking reduction fails to improve clinical and biological markers of cardiac disease: a randomized controlled trial. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco.* Mar 2008;10(3):471-481.