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Smoking Cessation Self-Help for Dual Users of Tobacco Cigarettes and E- Cigarettes

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SPECIFIC AIMS

Although electronic cigarettes (e-cigarettes) have been on the market for less than a decade, use has been doubling each year since 2008, and sales are projected to reach $2.2 billion in 2014. Moreover, the traditional tobacco industry has begun to move into this market, projecting greater growth in the future. Research on e-cigarettes is still in the nascent stage, with open questions about their health consequences, addiction liability, and smoking cessation potential. E-cigarettes are not regulated—and therefore cannot be overtly marketed—as pharmacotherapy for treating tobacco dependence, yet survey research has found that the primary motivations for their use are to aid smoking cessation or smoking reduction. To date there is insufficient research to reach conclusions about the effectiveness of e-cigarettes for achieving these goals, although one hypothesis is that they might function similar to traditional FDA-approved nicotine replacement therapy (NRT). The efficacy of NRT is improved when combined with even minimal behavioral interventions. Although millions of smokers are simultaneously using e-cigarettes (dual users), often for the purpose of quitting smoking, they usually do so without receiving any behavioral assistance. Thus, the opportunity exists to assist the large population of dual users—smokers who have already demonstrated initial action toward smoking cessation by commencing use of e-cigarettes. This naturally-occurring, self-selected, and motivated group may be ideally primed to benefit from a minimal intervention that may enhance their chances of achieving and maintaining tobacco abstinence.

The first two aims of the present proposal are to adapt a validated self-help, smoking-cessation intervention to meet the needs of current dual users, and to test this new intervention in a randomized controlled trial (RCT). A third primary aim is to calculate the cost-effectiveness of the intervention. A secondary aim is to gather longitudinal data regarding the patterns of tobacco and e-cigarette use and the course of cessation of either product among dual users.

Specific Aim 1. To create a minimal smoking-cessation intervention for current dual users of tobacco cigarettes and e-cigarettes (Study I). The intervention will comprise a series of booklets modeled after the *Forever Free* booklets found to be successful at producing long-term abstinence among the general population of smokers, but adapted to the special needs, circumstances, and risk factors of dual users. Validated methodologies used for adapting the intervention mirror those used in our prior smoking cessation studies, and reflect systematic approaches across three-phases informed by focus group and learner verification methodologies. The intervention will provide assistance for smoking cessation, and also encourage users to taper and eventually terminate their e-cigarette use as per traditional NRT. The end product of Study I will be a series of booklets tentatively titled, "*If You Vape: Guide to Quitting Smoking,"* available both in printed and electronic formats.

Specific Aim 2. **To evaluate the efficacy of the intervention via a randomized, controlled clinical trial of current dual users (Study II).** We will compare the intervention developed under Specific Aim 1 with both an assessment-only condition and a generic self-help condition comprising existing smoking cessation booklets. We hypothesize that recipients of our targeted *If You Vape* booklets will show higher rates of tobacco abstinence at 6, 12, 18, and 24 months after enrollment, as compared to both comparison conditions. A secondary hypothesis is that the new intervention will produce higher rates of abstinence from e-cigarettes themselves. To identify mechanism of change, we will also test several *a priori* moderator and mediator variables, including gender, socio-economic status, motivation to quit, nicotine dependence, e-cigarette expectancies, and magnitude of e-cigarette use (frequency, dosage).

Specific Aim 3. **To calculate and compare the cost-effectiveness of the interventions.** Cost-effectiveness data are vital for evaluating the real-world feasibility of an intervention. Small improvements in treatment efficacy may not be justified if they require substantially greater cost. We will compare the interventions not only on outcome efficacy, but on cost-effectiveness with respect to cost per incremental cessation and expected life-years saved.

Secondary Aim. To assess longitudinally the dynamic process of tobacco smoking and e-cigarette use among dual users. The large sample enrolled in the RCT will also offer a unique opportunity to assess longitudinally the dual use of tobacco cigarettes and e-cigarettes in a community-based sample. As a surveillance study, we will be able to track changes in the use of both products over time and examine predictors of cessation. We will also be able to examine whether provision of the self-help intervention alters either the patterns of use or cessation predictors.

In summary, this project tests whether the high-risk behavior of dual use can be capitalized upon to facilitate smoking cessation and, ultimately, cessation of all nicotine products.

A. SIGNIFICANCE

A.1. The Public Health Toll of Tobacco Smoking

Tobacco smoking is responsible for approximately 400,000 premature deaths in the United States annually, and 5 million worldwide, with causal links to cancers at 18 different organ sites, as well as coronary heart disease, chronic obstructive pulmonary disease, cardiovascular disease, and stroke (CDC, 2008; Rostron, 2013, USDHHS, 2014). Despite the well-known health consequences of smoking, and the benefits of quitting (Jha et al., 2013), 18% of American adults continue to smoke (CDC, 2014), primarily because they have developed dependence to nicotine, the major psychoactive substance in tobacco. Smoking-related mortality is, therefore, the distal consequence of this substance dependence. Thus, the treatment of tobacco (nicotine) dependence remains a public health priority of paramount significance.

A.2. Electronic Cigarettes

A.2.1. Description and Prevalence

Electronic cigarettes ("e-cigarettes") are a type of electronic nicotine delivery system in which nicotine is delivered via inhalation of vapor. The basic components of e-cigarettes include a battery, switch, heating element, and reservoir of liquid nicotine solution. Nicotine solution also contains water, propylene glycol and/or vegetable glycerin, and flavorings. E-cigarettes may resemble a tobacco cigarette in appearance, or they may be larger, with a refillable solution reservoir. When the user puffs upon the mouthpiece or pushes a button, the heating element produces a nicotine-containing vapor that is inhaled and exhaled like tobacco cigarette smoke.

E-cigarettes were introduced to the US Market in 2006. There are over 200 manufacturers, primarily in China, and the products have been inconsistent in both quality and nicotine delivery (Cobb & Abrams, 2011). Of note, eventual consolidation of the industry is expected, which should yield more standardized products. Recently, the tobacco industry has entered the market, with most major brands now selling or test-marketing e-cigarettes. A 2011 survey found that ever-use of e-cigarettes was 6.2% among all adults, 22.2% among current smokers, and 7.4% among former smokers—all dramatic increases over the prior year (King et al., 2013). Given the doubling of e-cigarette sales each year since 2008, and expected sales to exceed $2.2 billion in 2014, it is clear that current usage surpasses the 2011 rates. Despite exponential growth of this product, research on e-cigarettes is still in its nascent stage, comprising mostly prevalence and survey studies.

A.2.2. Health Risks

The health risks of chronic e-cigarette use are largely unknown (e.g., Cobb & Abrams, 2011; Orr, 2014; Wagener et al., 2012). In contrast to smoking, there is relatively little research on the effects of frequent and chronic inhaling of vaporized nicotine, per se (Etter et al., 2011), although trace components found in analyses of nicotine solution and aerosol (e.g., propylene glycol, diethylene glycol, metal and silicate particles) have been associated with negative health consequences (Goniewicz et al., 2013; Westbenberger, 2009, Williams et al., 2013). Moreover, nicotine, while not carcinogenic itself, may promote existing cancer growth (Heeschen et al., 2001). Nevertheless, despite these unknowns, it is unlikely that the risks of e-cigarette use alone would approach those of tobacco smoking (Keller, 2010). Indeed, e-cigarettes are marketed to cigarette smokers as a harm-reduction strategy, the majority of e-cigarette users believe that the product is safer than smoking, and they report reduced harm as a leading motivation behind their use of the product (Etter & Bullen, 2011; Harrell et al., 2014). However, there is also concern about "dual use," in that e-cigarettes may facilitate continued smoking among those otherwise motivated to quit, which would not only maintain the known health risks of smoking, but add the unknown health risks of e-cigarette use.

A.2.3. E-Cigarettes and Smoking Cessation

There is little direct evidence about the efficacy of e-cigarettes for promoting smoking cessation. Although e-cigarette manufacturers cannot market their products as pharmacotherapy, it is clear from surveys that e-cigarette users are purchasing them for this reason (Adkison et al., 2013; Etter, 2010; Etter & Bullen, 2011; Goniewicz et al., 2012; Pokhrel et al., 2013). For example, Etter and Bullen (2011) found that 77% of e-cigarette users surveyed reported initiating use to quit smoking or prevent smoking relapse. In our own recent survey (see C.1.4), 84% reported that smoking cessation was a reason for initiating e-cigarette use, and 56% listed it as their primary reason. Qualitative research suggests that smokers find e-cigarettes more appealing than conventional NRT because of perceived greater biobehavioral similarity to cigarette smoking, better reduction of cravings, and fewer side effects (Barbeau et al., 2013; McQueen et al., 2011). We similarly found in our survey that in comparison to NRT, e-cigarettes were rated more useful for quitting smoking, better at reducing tobacco cravings, healthier, less addictive, more convenient, and less expensive (Harrell et al., 2014).

Population-based surveys of adults have consistently found the highest prevalence of e-cigarette use among current smokers (i.e., dual users), followed by former smokers, with little use among nonsmokers (see Grana et al., 2013). Longitudinal studies of dual users find that the vast majority (e.g., 89%; Etter & Bullen, 2014) remain dual users a year later, and the association between e-cigarette use and smoking cessation has been weak (Adkison et al., 2013; Vickerman et al., 2013). However, a recent large British retrospective study found that among those who attempted to quit smoking in the previous year, e-cigarette users were more likely to have

quit than those who used NRT or no aid (20.0%, 10.1%, 15.4%, respectively; Brown et al., 2014).

Two RCTs of e-cigarettes for cessation have been reported. Caponnetto et al. (2013) used a three-arm study to compare two e-cigarette nicotine-dosing schedules against non-nicotine e-cigarettes in a sample of 300 Italian smokers not intending to quit. Similar reductions in smoking rate and increases in abstinence were found for all three conditions. However, the lack of a no-treatment control group prevents strong conclusions about cessation efficacy. Moreover, equivalent outcomes across nicotine doses (including non-nicotine) suggests that any treatment effects may be due to non-pharmacological factors (i.e., behavioral similarity to smoking). The second RCT (Bullen et al., 2013) randomized 657 smokers in New Zealand to nicotine patch, nicotine e-cigarettes, or placebo e-cigarettes. Six-month point-prevalence abstinence rates were statistically equivalent at 15.6%, 21.1%, and 21.9%, respectively. The authors concluded that e-cigarettes were as effective as nicotine patch. As with the Caponnetto study, this study lacked a no-treatment control, and it found no difference between nicotine and non-nicotine e-cigarettes, although the study was underpowered to test this (only 75 in placebo arm). Additionally, the authors note that no behavioral support was provided.

Thus, the limited data to date suggest the following: (1) Dual users are motivated to quit smoking, as evidenced by smoking cessation being the primary reason for initiating e-cigarette use. (2) Dual use is usually maintained. (3) There is some weak evidence suggesting that e-cigarettes may aid smoking cessation. (4) Behavioral factors may contribute to the efficacy of e-cigarettes for smoking cessation. In summary, dual users are ideally primed to benefit from a behavioral intervention for smoking cessation, yet a targeted intervention for this population has not been developed or tested.

A.3. Self-Help Approaches to Smoking Cessation

Self-help refers to very minimal types of interventions, such as print and electronic media provided to smokers. The best-known examples are the American Lung Association's "Freedom from Smoking" booklets. Because few smokers seek more intensive interventions, self-help materials have the potential for high public health impact if they can reach large numbers of smokers and aid them in achieving cessation. Their ease of administration and distribution maximizes the Adoption, Implementation, and Maintenance variables within the RE-AIM model of implementation (Glasgow et al., 1999). Curry et al. (2003) summarized the appealing features of self-help manuals, including: (1) They package state-of-the-art, cognitive-behavioral intervention components in a format that can be disseminated. (2) Distribution can occur through a variety of channels at a relatively low cost. (3) Smokers can customize program recommendations to their specific needs and interests. (4) Written materials are easy to keep so that smokers can refer back to them or use them again in a future quit attempt. Unfortunately, recent meta-analyses indicate little efficacy for self-help interventions. Both the US Public Health Service's Clinical Practice Guidelines for Treating Tobacco Use and Dependence (Fiore et al., 2008) and a Cochrane Review (Lancaster & Stead, 2005) concluded that self-help materials have at best marginal efficacy, improving cessation rates by about 1% compared to no-treatment controls.

In summary, self-help interventions have potential for vast reach, but their public health impact had been limited by low efficacy. This contrasts with greater efficacy, but poorer reach, of intensive behavioral interventions (Fiore et al., 2008). A logical goal, therefore, was to develop a self-help intervention that maintains the potential for high reach and draws upon cognitive-behavioral counseling to enhance its efficacy.

A.3.1. The "Forever Free" Self-Help Interventions

Unlike previous self-help interventions (usually a single, brief pamphlet), our extended self-help interventions (currently called *Forever Free*) were designed to capture key content from empirically supported cognitive-behavioral interventions (cf. Perkins et al., 2008) and to provide it over an extended period of time so as to maintain abstinence motivation. We originally developed this approach with a focus on preventing smoking relapse (Brandon et al., 2000, 2004, 2012), and a recent meta-analysis found self-help to be the only efficacious relapse-prevention modality (Agboola et al., 2010). Moreover, the interventions are highly cost-effective (Brandon et al., 2004; Chirikos et al., 2004). We have since developed a version to assist current smokers with initial cessation (*Forever Free: Stop Smoking For Good*) as well as relapse-prevention, and this version has demonstrated efficacy in a recent RCT. Key studies are described in Section C.1.2. **In summary, extended self-help is an efficacious tool for promoting tobacco abstinence.**

A.3.2. Adapting Self-Help for Dual Users: The Current Proposal

The current proposal represents the confluence of the following empirical findings reviewed above: (1) E-cigarette use by current tobacco smokers is increasing exponentially, creating a rapidly growing population of dual users. (2) Dual users are motivated to quit smoking. (3) Although the evidence is weak at this time, e-cigarettes may aid smoking cessation, either as a form of NRT and/or because of their socio-behavioral similarities to cigarettes. (4) Behavioral support improves the efficacy of NRT (Fiore et al., 2008). (5) Extended self-help (specifically our *Forever Free* interventions) is accessible, efficacious, cost-effective, and disseminable. **Therefore, we plan to capitalize upon the motivation to quit smoking among dual users by adapting our self-help smoking cessation intervention to meet their specific needs, and to test this intervention in a RCT with comparisons to both existing, generic (i.e., non-targeted), self-help booklets**

and a no-treatment (assessment only) control.

B. INNOVATION

The fundamental rationale of this study is to take an intervention approach (extended self-help) with a demonstrated record of efficacy and apply it to a rapidly changing landscape of tobacco use marked by dramatic increases in the dual use of e-cigarettes along with conventional, combustible cigarettes. Chronic dual use maintains the multiple health risks associated with smoking (while potentially adding yet unknown risks of e-cigarettes) and is thus cause for public health concern. On the other hand, dual use also offers an opportunity to transform the dual users' e-cigarette use from a product that maintains tobacco smoking into a tool for promoting smoking cessation, with the ultimate goal of complete nicotine cessation.

Although the intervention modality (paper and internet-based media) may appear conventional at first glance, the true innovation is in transforming a validated intervention in response to a rapidly growing population (dual users). Importantly, given the reported high motivation to quit among dual users, a novel intervention opportunity has emerged to reach a primed, yet understudied population. The proposed study is innovative as it represents the first test of an intervention to facilitate smoking cessation among dual users of tobacco cigarettes and e-cigarettes, with both cessation and cost-effectiveness outcomes. Additionally, the secondary aim will provide the first long-term, prospective, longitudinal data on dual use.

C. APPROACH

Two sequential studies are proposed. The goal of Study I (Aim 1), to be conducted during Year 1, is to adapt the existing *Stop Smoking For Good* booklets, designed for the general population of smokers, into a series of booklets explicitly designed for dual users. The adaptation of the booklets will be based upon the findings from a systematic formative evaluation employing current and former dual users. After the final version of the intervention has been developed, Study II (Aim 2) will test its efficacy via an RCT.

C.1. Preliminary Studies

C.1.1. Background of the Investigative Team (see biosketches for relevant citations)

The research team is uniquely qualified for this project. The PI, Thomas Brandon, Ph.D., and co-PI, Vani Simmons, Ph.D., are longstanding collaborators on the development of self-help interventions for tobacco dependence, with special attention to the specific needs of subpopulations of smokers. As a site PI for the NIDA/FDA-funded Center for the Evaluation of Nicotine in Cigarettes (U54 DA031659), David Drobes, Ph.D., has been working in the area of harm reduction and tobacco product comparisons—areas of great relevance to the proposed study. Cathy Meade, RN, Ph.D., is a nationally recognized expert in the areas of health literacy and communications, and she has collaborated on our previous self-help interventions. *Gwen Quinn, Ph.D., has worked with our team on multiple projects and brings expertise in the use of qualitative methods and social marketing to identify determinants and psychographics related to behavior change.* Benjamin Craig, Ph.D., is a health economist and an expert in cost-effectiveness analysis, which he will conduct for the current project. Marina Unrod, Ph.D., has been co-investigator and project director for Dr. Brandon's projects over the past 8 years. Paul Harrell, Ph.D., is a current postdoctoral fellow who has led our e-cigarette research (e.g., Harrell at al., 2014, in press) and has expertise in assessment of substance-related expectancies and latent modeling. He will focus on identifying and analyzing mechanisms of action. Additionally, we have strengthened our team with co-investigator Thomas Eissenberg, Ph.D., of Virginia Commonwealth University. He is a behavioral pharmacologist with extensive experience studying alternative tobacco products, including some of the most systematic research to date on e-cigarettes. Moreover, he is PI of the new FDA/NIDA-funded Center for the Study of Tobacco Products, with e-cigarettes as its primary focus. He will provide valuable assistance regarding the recruitment of e-cigarette users, and will leverage the research and expertise of his center to apprise us of new developments in e-cigarette products and use. *Finally, one of the leading clinical researchers on e-cigarettes as cessation aids, Christopher Bullen, M.B,Ch.B., M.P.H., Ph.D., of the University of Auckland, will consult on the development of the intervention materials, recruitment, and data interpretation.*

C.1.2. Prior Research on Self-Help Smoking Interventions

Our team has conducted and published descriptive, intervention, and laboratory-based studies to investigate the nature of smoking cessation and to develop intervention strategies. Most relevant to the current proposal, three RCTs testing the efficacy of our *Forever Free* self-help interventions are described below.

C.1.2.1. Relapse Prevention I. The first of these studies (Brandon et al., 2000) involved a 2 X 2 factorial design to test the independent and combined efficacy of two types of a minimal intervention that had been identified in an earlier feasibility study (Brandon & DeMichele, 1995): (1) access to a year-long relapse prevention hotline and (2) a series of eight empirically based relapse-prevention booklets mailed to participants over the course of a year. We found that the repeated mailings of booklets significantly reduced relapse rates of recent quitters by two-thirds (12% vs. 35%, p = .001).

C.1.2.2. Relapse Prevention II. A second clinical trial (R01 CA80706; Brandon et al., 2004) parsed the effects of repeated contact and booklet content, and extended follow-up to 2 years. The main findings were that the multiple booklets continued to produce reductions in smoking relapse through 2-year follow-up

compared to a single-booklet control condition (22% vs. 32% relapsed, p = .02), and that booklet content was more important than contact. The intervention was also highly cost-effective; cost per quality-adjusted life-year (QALY) saved was estimated as low as $83 in the sample (Brandon et al., 2004; Chirikos et al., 2004). Based on the results of these two studies, the booklets have been adopted by NCI (distributed by the Cancer Information Service, available for free download at www.smokefree.gov, and identified as a Research Tested Intervention Program on cancercontrolplanet.cancer.gov) as well as by hospitals and health departments throughout the country. Moreover, an anglicized version of the booklets is currently being tested in Great Britain for possible adoption by the National Health Service.

C.1.2.3. Cessation. The most relevant study (R01 CA134347) ended data-collection in May, 2014. This study was based on preliminary data suggesting that the *Forever Free* booklets, although developed to prevent relapse, were, in fact, also efficacious for current smokers. This contrasts with the general finding that self-help is minimally effective (1% additional cessation) for smoking cessation (Lancaster & Stead, 2005)..We modified the original *Forever Free* booklets to include instruction on smoking cessation, per se, creating a new version titled, *Forever Free: Stop Smoking For Good*. We randomized 1874 current smokers to three conditions: (1) Usual Care (a standard smoking cessation booklet, *Clearing the Air,* published by NCI); (2) Standard booklets (8 *Stop Smoking For Good* booklets mailed over 12 months); or (3) Enhanced booklets (10 *Stop Smoking For Good* booklets mailed over 18 months, plus 9 brief motivational pamphlets interspersed between booklet mailings). We recently completed preliminary analyses of outcomes through 18 months.

Table 1: Percent Abstinent at 6, 12, and 18 Months in Cessation Study; Significance Levels versus Usual Care

Analysis	6 Months Follow-Up				12 Months Follow-Up				18 Months Follow-Up			
	N	UC	SB	EB	*N*	UC	SB	EB	*N*	UC	SB	EB
Responders Only	1364	12.99 (ref)	15.98 p = .20	18.37 **p = .02**	1246	15.63 (ref)	21.90 **p = .02**	29.25 **p <**	1191	21.13 (ref)	22.66 p = .60	33.3 3
Intent to Treat	1874	9.87 (ref)	11.40 p = .38	13.02 p = .08	1874	10.66 (ref)	14.66 **p = .03**	18.81 **p <**	1874	14.11 (ref)	14.17 p = .97	20.4 2

Notes: UC = Usual Care; SB = Standard Booklets; EB = Enhanced Booklets. At 18 Months, difference between EB and SB is significant for Responders Only (**p = .001**) and Intent to Treat (**p =.004**) analyses.

As seen in Table 1, both versions of the intervention were more effective in producing abstinence by 12 months than the comparison Usual Care condition, *but by 18 months, the Enhanced booklets were superior to both Usual Care and Standard booklets.* Although economic analyses have not yet been conducted, these results suggest that the intervention will continue to be far more cost-effective than most other smoking-cessation interventions (e.g., Cromwell et al., 1997; Curry et al., 1998). **This study demonstrates that a minimal, but extended, self-help intervention can significantly and cost-effectively improve smoking cessation rates, and it supports our plan to further adapt this intervention for current dual users of tobacco cigarettes and e-cigarettes.**

C.1.3. Interventions for Special Populations

Our team has substantial experience creating interventions for special populations of smokers. Using a similar formative strategy as currently proposed, we adapted the *Forever Free* intervention for pregnant women (Quinn et al., 2006). In an RCT (R01 CA94256), we compared these *Forever Free: For Baby and Me* booklets against standard, booklets (Brandon et al., 2012). We found both main effects and moderation by SES. For example, by 12 months postpartum, low-income women were particularly likely to benefit from the intervention (72% vs 51% abstinent at 12 months postpartum, p = .003).

Additionally, both the original and pregnancy-related *Forever Free* booklets have been "transcreated" (translated and culturally adapted) for Spanish-speaking smokers (Simmons, Cruz et al., 2011; Simmons, Quinn et al., 2011). Moreover, based on an analysis of predictors of posttreatment smoking among cancer patients (Simmons et al., 2013), we have adapted the *Forever Free* intervention for cancer patients by creating a supplemental informational and motivational video, *Surviving Smokefree*, and we are currently testing the combined intervention in an RCT (R01 CA154596). Also, in an ongoing study, we are collaborating with Robert Klesges, Ph.D., to test booklets inspired by *Forever Free* for preventing smoking relapse among US Air Force recruits following involuntary cessation during basic military training (R01 HL095785; Brandon et al., 2014). Finally, following systematic laboratory research (e.g., Simmons et al., 2004), we have developed a highly-interactive web-based intervention for college student smokers, who are loathe to participate in live, face-to-face counseling (Simmons, Heckman et al., 2013). **In summary, we have considerable experience in the systematic, empirically-driven development of smoking interventions for special populations.**

C.1.4. E-Cigarette Use and Smoking Cessation: Survey Results

In Fall, 2013, we conducted an internet-based survey of e-cigarette users (Harrell et al., 2014). The primary goals of this survey were: (1) to estimate our ability to reach e-cigarette users and recruit them for focus groups and interventions; (2) to assess their interest in quitting smoking and the acceptability of various forms of smoking cessation assistance; and (3) to assess their expectancies regarding e-cigarettes in

comparison to tobacco cigarettes and NRT, a mechanism of change of interest to us. Within 10 days of a local press release, we received 1119 survey responses. Of the dual users, 84% (119) reported that they had made a serious (≥24hr) smoking quit attempt in the past year, and only 6% reported that they had no plans to quit smoking. Also, 76% reported that they would be interested in receiving some treatment to help them quit smoking while using e-cigarettes. Of these, 87% expressed some degree of interest in interventions delivered either via booklets or the internet, as we propose (85% endorsed treatment via smartphone app, which may be a future modality at our disposal.) However, only 37% of dual users reported plans to stop using e-cigarettes eventually, 15% planned to reduce their use, and 48% reported no plans to stop "vaping." Consistent with expectancy theory, users who wanted to quit e-cigarettes rated them as more hazardous to health and less helpful in dealing with stress or providing energy (i.e., potential targets for our intervention). Finally, 29% (305) of the full sample volunteered for focus groups. **These results indicate that we should have little difficulty recruiting for either our focus groups of Study I or the RCT for Study II, especially with the option to recruit nationally for the latter. Data also indicate that the majority of dual users would be open to receiving a smoking-cessation intervention, including one delivered via booklets and the internet.**

C.2. Study I (Specific Aim 1) Methods

C.2.1. Overview

Our research team developed the existing intervention, *Stop Smoking For Good*, that was found to enhance cessation in a general population of smokers (see C.1.2.3). Our team is accomplished in developing and evaluating health materials (e.g., Quinn et al., 2006; Jacobsen et al., 2012; Brandon et al., 2012; Koskan et al., 2012; Simmons et al., 2011) and we will take a systematic approach to adapt and refine these existing booklets (USDHHS, 2008). We will employ a 3-phase process to create a usable, understandable, and acceptable intervention. The final outcome will be a refreshed series of booklets, tentatively named *If You Vape: A Guide to Quitting Smoking*. See Table 2 for a summary of phases and timeline.

Table 2: Study I Phases

PHASES	TASKS/ACTIVITIES TIMELINE	OUTCOME(S)
Phase I	**Conduct Formative Research (Months 1 - 4)** ❑ Conduct individual interviews (n= 28) ❑ Analyze data and identify themes ❑ Construct creative brief to guide adaptation	**Identification of emergent themes and responses to existing booklets** ⇩
Phase II	**Adapt and Refine Booklets (Months 5 - 8)** **Conduct Learner Verification to assess suitability** ❑ Apply and adapt information from Phase I ❑ Draft new booklet and pamphlet content based on feedback ❑ Conduct two pretesting iterations (n=20) o Acceptability - Attraction - Comprehension o Self-efficacy - Persuasion ❑ Revise and modify booklets and pamphlets based on feedback	**Advanced drafts of booklets and pamphlets** ⇩
Phase III	❑ **Final reactions to Draft Booklets from study team and study consultants.**	**Series of smoking cessation booklets and pamphlets for dual users**

C.2.2. Existing Intervention

The starting point for Study I will be the existing Enhanced intervention used in the cessation study described above (see C.1.2.3). At each follow-up, this intervention significantly outperformed Usual Care. This intervention comprised 10 *Stop Smoking For Good* booklets sent separately upon enrollment and at 1, 2, 3, 5, 7, 9, 12, 15, and 18 months. The first booklet provides a general overview about quitting smoking, and each of the remaining nine booklets includes more extensive information on a topic related to maintaining abstinence: *Smoking Urges; Smoking and Weight; What if You Have a Cigarette?; Your Health; Smoking, Stress, and Mood; Lifestyle Balance; Life without Cigarettes, The Benefits of Quitting Smoking,* and *The Road Ahead*. The content of these booklets was based on cognitive-behavioral theory (e.g., Bandura, 1977; Marlatt, 1985) and empirical evidence regarding the nature of tobacco dependence, cessation, and relapse (e.g., Baker et al., 2004). They were originally designed as a means of translating the cognitive-behavioral, relapse-prevention counseling that occurs in a clinic into a written format that would be much more accessible to smokers. Although the focus of the original *Forever Free* booklets was relapse-prevention, they were revised to emphasize both initial cessation and maintenance of abstinence. This intervention maximized both duration

and frequency of contact. In addition to the 10 booklets, we also made contact during non-booklet months to enhance the perceived social support via tri-fold color pamphlets (*A Forever Free Close-Up: How I Quit Smoking*) that reinforce key messages about quitting smoking (e.g., dealing with stress, keeping weight gain in perspective, finding other forms of positive reinforcement). To further induce a sense of social support, the message is communicated via a first-person narrative from a former smoker, incorporating photographs of the purported speaker. All materials were written at the 5-6 grade reading level so as to maximize their accessibility to a wider range of smokers (Meade & Byrd, 1989). The existing *Stop Smoking For Good* booklets and the supportive pamphlets are accessible to reviewers at www.moffitt.org/PQ.

C.2.3. Phase I

Individual interviews will help to identify and explore new content topics for inclusion in the booklets, and gather feedback about the existing *Stop Smoking For Good* booklets in terms of tone, character development, and other important elements of smoking cessation message design for this audience.

C.2.3.1. Sample and Recruitment. We plan to recruit 4 subsets of participants in Phase I: (1) current dual users without interest in quitting smoking; (2) current dual users who have attempted, but not quit smoking; (3) current e-cigarette users who have successfully quit smoking; and (4) former dual users who have quit both products. These subsets represent the continuum from dual use through successful cessation of both products, and will allow us to learn from individuals who have a wide range of smoking and e-cigarette experiences and perspectives relevant to the current study. The final number of participants will be based on the principle of theoretical saturation (Krueger & Casey. 2008). That is, we will conduct additional interviews until no new information is obtained. Each theme will then be assessed in terms of the implications for adapting the booklets to the new audience. . Participants for Study I will be recruited via multimedia advertisements (press releases, daily and weekly newspapers, radio, cable TV, social media, e-cigarette forums, flyers, etc.). The following additional inclusion criteria will be used: ≥18 years of age, able to speak and read English, ≥ 1 year history of daily smoking, ≥ 1 month of e-cigarette use. Screening may occur over the telephone or in person. Participants will be compensated $30.

C.2.3.2. Procedures and Analyses. Participants will complete a brief questionnaire to assess history of tobacco and e-cigarette use and dependence (Foulds et al., 2015), as well as demographic and tobacco history including the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991). Using a structured interview guide, trained interviewers will elicit contributions from participants. Participants will be asked to respond to a series of questions to identify their perspectives about benefits of quitting, barriers to quitting, and how e-cigarettes helped or hindered the cessation process. Interviews will be recorded, transcribed, manually coded for a priori content related to the guide and emergent (new) themes, and then reviewed by members of the research team following the approaches used by Morgan (1996). Codes will be refined until a rate of at least 85% inter- coder agreement is reached. Analysis of verbatim transcripts includes a "mechanical" stage (organizing and dividing the data into a useful scheme) and an "interpretive" stage (identifying criteria for organizing the thematic codes; Knodel, 1993). Results will be used to modify and adapt the existing cessation intervention.

C.2.4. Phase II

The content and format of the *If You Vape* booklets will be developed based upon: (1) the results of our Phase I formative research, (2) the existing *Stop Smoking For Good* booklets, and (3) existing and emerging research and theory regarding both e-cigarettes and use of NRT for smoking cessation. The existing tri-fold color pamphlets (*A Forever Free Close-Up: How I Quit Smoking*) will also be revised to address the special needs of dual users. Finally, two initial brochures, one for each intervention condition, will be developed to provide participants with an introduction to the *If You Vape* booklets and the *Stop Smoking for Good* booklets. Although Study 1 focuses primarily on the formative research, it is important to recognize the value of the other two factors. We are not proposing to develop a *de novo* intervention. Rather, we are proposing to use the findings from the formative research to build upon an intervention that already has demonstrated efficacy with a general population of smokers. We believe that the success of the existing intervention is largely due to its theoretical and empirical basis, so we will maintain that basis for the new booklets. As in our existing materials, significant attention will be given to achieve a reasonable match between logic, motivation, language, and experience— features that enhance receptivity and the likelihood that the materials will be will be used. Integral to the design of the booklets is the communication of concepts in an easy-to-understand, acceptable, relevant, and clear fashion (USDHHS, 2008; Doak et al., 1996; Meade, in press; Card et al., 2011; Castro et al., 2010; IOM, 2004; Nutbeam, 2008). Once initial drafts are generated, we will begin learner verification iterations.

C.2.4.1. Learner Verification Methodology. The learner verification approach strives to reduce miscommunication of messages (Doak et al., 1996). It involves verifying materials with the audience in relation to acceptability, attraction, understanding, self-efficacy, and persuasion via a series of questions relating to the elements to be verified. For example: "What is the main message here? Does anything not make sense to

you about this? Do you think you could do this?" Involving users in the process results in a product that contains "their words."

C.2.4.2. Sample and Recruitment. Because of the formative nature of the proposed research, only small samples at each iterative stage are needed (Doak et al., 1996). Development of the series of educational smoking cessation booklets and pamphlets will include interviews with up to 20 individuals over two iterations. The sample will include only current dual users—the intended audience for Study II, *mirroring that study's inclusion criteria (see C.3.2.)*—who will each be paid $30 per 30-60 minute interview. The educational materials may be mailed or emailed to the participants prior to the interview. Responses will be recorded and transcribed verbatim, and reviewed by the research team. The summarized data will direct modifications for the advanced draft, the expected outcome of Phase II.

C.2.5. Phase III – Final Reactions to the Intervention

This final phase will serve as another feedback loop for improvement and revision. In this last phase, we will obtain final reactions to the new booklets in terms of graphics, layout, and content specific to e-cigarettes and dual use from the study team as well as study consultants who are experts in the field of e-cigarettes.

C.2.6. Expected Content of the Final Intervention

The formative study will guide the adaptation of the current intervention for dual users. We expect that much of the general format and content will remain, but it will be newly targeted to the dual user. At the most apparent surface level, language, photos, and graphics will incorporate e-cigarettes. Additionally, the illustrative vignettes included in the booklets and the personal stories in the supportive pamphlets will be replaced or modified using testimonials from the qualitative research. Both Study I and our e-cigarette experts, Drs. Eissenberg *and Bullen*, will ensure that the language conforms to the current preferences of the population. For example, e-cigarette use is referred to as "vaping" and the e-cigarettes themselves are often called "personal vapers." Deeper content (i.e., specific advice for quitting smoking for dual users) will be informed by: (1) the success and failure experiences shared by dual users in Study I; (2) any emerging empirical literature on smoking cessation by dual users; and (3) relevant research on the best use of conventional NRTs that might generalize to e-cigarettes. For example, if new research continues to show no cessation differences between nicotine and non-nicotine e-cigarettes (Bullen et al., 2013; Caponnetto et al., 2013), we will advise dual users to try using non-nicotine e-cigarette solutions, or at least reduce the nicotine level over time (Lechner et al., 2014). It is possible that the relative benefits and motivations for quitting smoking may differ for dual users, and the booklets could be easily modified to reflect this. If warranted, we may also replace or add additional booklets to emphasize new topics that are particularly relevant to dual users. For example, when we adapted our standard relapse-prevention intervention into a version for pregnant women, on the basis of the research literature and our qualitative findings, we created a new booklet specifically for the women's partners, and another that focused on the transition from pregnancy to postpartum (Quinn et al., 2006). A possibility for the proposed intervention would be to add a new booklet specifically focused on the cessation of e-cigarette use. Regardless, because the long-term health consequences of e-cigarette use remain unknown, we will also infuse the booklets with progressively stronger and more specific advice to discontinue e-cigarette use following smoking cessation. In summary, the intervention will disseminate emerging empirical findings regarding e-cigarettes, in contrast to the currently prevalent misinformation available on the internet and other sources (Cobb et al., 2013).

C.3. Study II – Intervention Trial (Aim 2)

C.3.1. Design Overview

Table 3: *Overview of Study Design: Interventions and Assessments*

ASSESS																					
GENERIC	IG + G	G	G	G	g	G	g	G	g	G	g	g	G	g	g	G	g	g	G		
eTARGET	IT + T	T	T	T	t	T	t	T	t	T	t	t	T	t	t	T	t	t	T		
Month	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**	**21**	**24**
Assessment	B			AF			FF			AF			FF			AF			FF	AF	FF

Legend

ASSESS = Assessment Only; GENERIC = Generic Self-Help; eTARGET = Targeted E-Cigarette Self-Help; Assessments = Assessment Points; IG = Generic *Stop Smoking for Good* initial brochure; IT = Targeted If You Vape initial brochure; G = Generic *Stop Smoking for Good* booklet; T = Targeted *If You Vape* booklet; g = Generic supportive letter and tri-fold pamphlet; t = Targeted supportive letter and tri-fold pamphlet; B = Baseline Assessment;
AF = Abbreviated Follow-up assessments; FF = Full Follow-up assessments. Shading indicates the duration of the intervention.

We propose a three-arm randomized design (*N* = 2900) with the following conditions: (1) Assessment Only (ASSESS; *n* = 580), the no-treatment control; (*2) Generic Self-Help (GENERIC*; *n* = 1160*), which will*

include the Enhanced (non-targeted) cessation booklets from our cessation study and 9 intermittent (non-targeted) motivational pamphlets (C.1.2.3.), and (3) targeted e-cigarette booklets (eTARGET; *n* = 1160), which will be the full intervention developed in Study I, expected to comprise an initial brochure, a series of 10 *If You Vape* booklets and 9 intermittent motivational pamphlets delivered over 18 months. *Importantly, GENERIC and eTARGET will be exactly matched in amount of contact and content.* Assessments will occur at 3-month intervals, over 24 months. An overview of the design is depicted in Table 3.

Specific Aim 2 (the RCT) will be tested with a comparison of smoking-cessation outcomes of eTARGET vs both ASSESS and GENERIC conditions. A secondary outcome will be cessation of e-cigarettes themselves. *The comparison of GENERIC versus ASSESS will address whether an untargeted intervention is sufficient for dual users.* A secondary outcome will be cessation of e-cigarettes themselves. Additionally, the cost-effectiveness of both active interventions will be calculated in reference to ASSESS, as per Specific Aim 3. Secondary analyses will involve surveillance of both tobacco and e-cigarette use over time.

C.3.2. Participants

Participants will be 2900 weekly smokers, recruited throughout the US, with an emphasis on Central Florida (for bioverification; see C.4.1.4) via multimedia advertisements (daily and weekly newspapers, radio, cable TV, social media, e-cigarette forums, etc.). To maximize generalizability, we will have minimal inclusion criteria assessed at the time of the telephone screening: (1) smoking ≥ 1 tobacco cigarette/week over the past year; (2) e-cigarettes use ≥ 1/week over the past month; (3) age ≥ 18 years; (4) not currently enrolled in a face-to-face smoking cessation program; and (5) able to speak and read English. Upon receipt of the baseline, if it is determined that a participant no longer meets the inclusion criteria, they will be withdrawn from the study (see C.4.1.2 for details). At that time, they will be sent a withdrawal letter and provided with a copy of NCI's *Clearing the Air* booklet.

In addition, to reduce leakage of information about differences in treatment conditions among participants, we will limit the number of participants from the same street address to 1, and not allow more than 2 referrals per participant. We will assess whether participants use any other smoking cessation services (e.g., state quitline, websites) or pharmacotherapy so that we can examine their impacts statistically, but we will not exclude smokers who utilize these widely available smoking cessation tools. Participants will be invited to a study examining tobacco and e-cigarette use over time and told that they may also receive materials to help them quit. That is, we will not limit recruitment to treatment-seeking e-cigarette users. (See C.7.1)

We believe that it is feasible to accrue the target N of 2900 during the 18 months we have allocated for accrual. In the previous self-help cessation study (C.1.2.3), we successfully recruited 1874 smokers over 16 months. Although the current study will be limited to smokers using e-cigarettes (dual users), which is a smaller population base, it is nevertheless substantial and growing. Because all contact with participants will be by telephone, internet, and mail, we are not geographically limited. The rate of accrual is limited only by the amount of advertising, staffing levels, and logistic requirements of screening callers and processing baseline data. The tremendous response to our survey (C.1.4) indicates that we can efficiently reach large numbers of potential participants. We have a history of meeting our accrual goals, even with notoriously difficult populations that required adjustments to accrual strategies. Most notably, we have recruited participants from a much smaller segment of the population: 700 women in months 4-8 of their pregnancy who had already quit smoking and were interested in relapse-prevention assistance (Brandon et al., 2012; Lopez et al., 2008).

C.3.3. Study Arms

In this section, we describe the rationale and form of the three intervention conditions. Note that participants in both the GENERIC and eTARGET conditions will have the option of receiving electronic versions of the intervention materials via a link to a website (see C.7.2).

C.3.3.1. Assessment Only (ASSESS). Participants in this condition will not receive any intervention materials. They will participate solely in the repeated assessments. Including this comparison condition controls for the effect of repeated assessments and allows for the most meaningful evaluation of the efficacy effect size as well as the cost-effectiveness of the eTARGET intervention. This condition will also be the primary source of data for the secondary surveillance aim regarding naturalistic changes in smoking and e-cigarette use over time.

C.3.3.2. Generic Self-Help (GENERIC). *This condition will comprise the initial Stop Smoking for Good brochure, 10* Stop Smoking for Good *booklets, and 9 supportive My Story pamphlets delivered over 18 months, as used in our previous cessation study (see C.1.2.3.). It will allow us to evaluate our novel self-help intervention for e-cigarette users (our* If you Vape *booklets) against a matched non-targeted intervention that has demonstrated efficacy for cigarette smokers in general. Such a comparison controls for the possibility that e-cigarette users are sufficiently primed to quit smoking and that even a generic, non-targeted intervention would be effective. This possibility will be directly tested by comparing this condition against both the ASSESS and eTARGET conditions in terms of clinical outcomes and cost-effectiveness.*

C.3.3.3. Targeted Self-Help (eTARGET). Participants in this condition will receive the intervention created as the product of Study I. As described in C.2.6 and shown in Table 3, it is expected to include the initial *If You Vape* brochure, a series of 10 *If You Vape: Guide to Quitting Smoking* booklets, distributed over 18 months, and 9 supportive *My Story* pamphlets, delivered in the months between booklets.

C.4. Assessment

As Table 3 indicates, assessments will occur at baseline and at 3-month intervals thereafter, through 24 months. Assessments will be conducted as we have before (Brandon et al., 2000, 2004), via the mail, but now with an internet option. A tension inherent in clinical trials, particularly trials of minimal interventions for behavior change, involves balancing the value of assessment against the risk of reactance effects. This is a concern in the current study because we posit that contact contributes to treatment effects. Moreover, assessment of specific domains may influence those very domains. For example, assessment of coping skill usage is itself a reminder to use coping skills. Finally, participants who enroll in studies of minimal interventions often will reject the burden of a heavy assessment load, increasing attrition and reducing generalizability. Therefore, in our self-help studies we aim to keep both the frequency and magnitude of assessments to the minimum required to meet the specific aims. Compared to our traditional treatment studies, we must be much more selective in choosing instruments to administer in our self-help studies, and thus we will limit assessments to 3-month intervals.

C.4.1. Assessment Contacts

C.4.1.1. Initial Telephone Contact. At the first telephone contact after a dual user responds to an advertisement or other recruitment effort, the research assistant will collect basic demographic information, a brief tobacco and e-cigarette history, and screen for the inclusion criteria.

C.4.1.2. Baseline Assessment. Dual users who meet inclusion criteria and provide initial verbal consent over the telephone will be sent a bound set of baseline questionnaires or an email link to our survey site. The following questionnaires will be included: (1) a demographic and tobacco history questionnaire including the Fagerström Test for Nicotine Dependence (Heatherton et al., 1991), as well as use of pharmacotherapy and other cessation aids; (2) a questionnaire assessing current and past e-cigarette use that we developed for our recent e-cigarette survey; (3) a continuous measure of readiness to quit, the Contemplation Ladder (Biener & Abrams, 1991); (4) the Stages of Change Algorithm (SOC) (DiClemente et al., 1991); and (5) intentions to quit cigarettes and e-cigarettes. We will also assess three other motivation- related constructs: a situation-specific abstinence self-efficacy scale (Velicer et al., 1990); a recent measure of Abstinence-Related Motivational Engagement (ARME; Simmons et al., 2010), which assesses change in cessation motivation; and a measure of cigarette vs. e-cigarette outcome expectancies that we also developed for our recent survey. To test motivational mechanisms of action, these measures of motivation will be examined as potential moderator variables, with follow-up measures tested as mediators of treatment effects. Finally, we will use 1-item questions to assess overall “commitment” to, and “confidence” about being smoke-free, and 2 questions to assess craving for cigarette smoking.

Inclusion criteria will be evaluated using responses to baseline survey items. Given that participants provided responses during the initial telephone contact that met the inclusion criteria, we created rules for 4 of the 5 inclusion criteria that required strong evidence from the baseline survey for exclusion. The rules acknowledge that participants may mark unintended responses.

Those with the following responses will be excluded based on **Criterion #1** (smoking ≥ 1 tobacco cigarette/week over the past year).

Rule 1) Marked either ‘1-5 days a month’ or ‘No use in the past month’ to item 4 in the ‘Tobacco Cigarettes’ section.

Rule 2) Marked the designated answer to any two or more of the following in the ‘Tobacco Cigarette’ section: a) Item 4a: response of 7 or more days since last cigarette;
b) Item 5: response of ‘no use in the past month’; c) Item 7: response of ‘I do not smoke’;
d) Item 9: response of ‘I do not smoke’; e) Item 10: response of ‘I do not smoke’;
f) Item 11: response of ‘I do not smoke’; g) Item 15: response of ‘I do not smoke’;
h) Item 16: response of ‘I do not smoke’; h) Item 22: response of ‘I do not smoke’.

Those with the following responses will be excluded based on **Criterion #2** (e-cigarettes use ≥ 1/week over the past month).

Rule 3) Marked the designated answer to any two or more of the following in the ‘E-Cigarette’ section: a) Item 1: response of ‘Less than 1 month ago’; b) Item 2: response of ‘No use in the past month’; c) Item 3: response of ‘Not applicable - no use in past month’

Those with the following response will be excluded based on **Criterion #3** (age ≥ 18 years).

Rule 4) Computed difference between date of survey completion and date of birth is less than 18 years.

Those with the following response will be excluded based on **Criterion #4** (not currently enrolled in a face-to-face smoking cessation program).

Rule 5) Marked 'Currently use' to the item assessing in-person counseling or support program.

C.4.1.3. Follow-Up Assessments. Participants will be sent follow-up assessments (by mail or email link) at 3-month intervals through 24 months, as indicated in Table 3. The length of the follow-up (24 months post-enrollment) was calculated by adding the standard 6 months after the end of the eTARGET intervention. We deliberately keep each follow-up assessment brief to minimize participant burden and consequent attrition. Each of these follow-ups will include an assessment of the use of tobacco products, e-cigarettes, pharmacotherapies, and other tobacco cessation aides or services since the previous contact. These data will constitute the Abbreviated Follow-Ups, and will be sufficient for calculating treatment outcomes as well as for the longitudinal tracking of cigarette and e-cigarette usage for the secondary aim. Full Follow-Ups at 6, 12, 18, and 24 months will include most of the questionnaires from the baseline assessment, as well as additional domains, including evaluation of the intervention (Client Satisfaction Questionnaire; Attkisson & Greenfield, 1994), self-reported use of the material (i.e., how much they read, how often they refer back, how much it affected their behavior), current intentions to quit smoking and to quit e- cigarettes, and the three motivation-related scales administered at baseline. The 24 month follow-up will also include an 12-item measure of health outcomes (SF-12™ Health Survey; Ware, J E, Kosinski, M, Keller, S D., 1995), 2001). Research staff will attempt to contact participants to complete any missing data on the completed baseline and follow-up assessments.

C.4.1.4. Biochemical Verification. The decision regarding inclusion of biochemical verification (e.g., saliva, serum, or urine cotinine; breath carbon monoxide [CO]) of self-reported smoking status is difficult and complex (Benowitz et al. 2002). In general, low contact interventions such as we propose tend not to benefit from bio-verification, and trials should avoid assessments that might cause reactivity, a threat to generalizibility. That participants will be recruited from throughout the US makes collection of biosamples from the full sample prohibitively expensive. Considering the low-contact nature of the intervention, potential reactivity, that assessments will be collected by mail and internet, and that there should be little differential in social-desirability demand across conditions, we concluded, consistent with Benowitz et al. (2002) and Velicer et al. (1992), that bio-verification of the *full* subject sample is not warranted. Instead, we will conduct face-to-face interviews and collect breath CO and saliva (for cotinine analysis) on the 10-15% of participants expected to reside within 100 miles of Tampa and who report abstinence at the 12 or 24-month follow-up points (n = ~75-100). We will then be able to use the disconfirmation rates from this sample to estimate adjusted smoking rates for the full sample. To collect biosamples, a researcher will make an appointment to visit the participant at home, work, or other location for a face-to-face interview. Participants will also be provided with the option of coming to the lab to complete the face-to-face interview, and if they elect to do so, they will receive an additional $20. During the interview, the researcher will ask consent to collect the breath and saliva samples. The breath sample will be collected with a portable CO monitor (Micro CO™ by Micro Direct, Inc.), and the saliva sample will be collected in a 2ml tube for immediate cotinine analysis using the NicAlert™ dipstick by Nymox. The CO sample is needed to differentiate smokers from e-cigarette users. Cut-offs of 8 ppm for CO and 10 ng/ml for cotinine will be used (Benowitz et al., 2002). Participants will be paid $20 for the interview and $15 for providing the biosamples. We have used this strategy successfully in past studies and found very low disconfirmation rates (Brandon et al., 2004, 2012).

C.4.1.5. Participant Retention Procedures. We have developed several procedures to minimize attrition in our prior longitudinal self-help studies (Brandon et al., 2000, 2004). As an incentive, we will send participants $10 for completing each abbreviated follow-up, $20 for completing the baseline and each of the full follow-ups (excluding the 24 month follow-up), and $40 for completing the 24 month follow-up., We will also send participants a pre-selected gift (e.g., stylus pen, nail file, etc.) valued at approximately $1 if they return the forms within one week. In addition, participants will receive a bonus payment of $60 if they complete all 9 assessments, or $40 if they complete at least 7 assessments, including the final follow-up. Questionnaires will be constructed in a manner demonstrated to maximize participation (Dillman, 1991). Other procedures include reminder phone calls, emails, text messages, and letters; at baseline, we will request information for a contact person in case we lose contact with the participant.

If participants are unable to be reached using the retention procedures described above, additional methods of contact will be attempted:

1. Internet databases: If mail has been returned to us, indicating that we have a wrong address or the participant has moved, several free and paid services will be used to locate participants. Websites will include whitepages.com, smartpages.com, and Yahoo! People (people.yahoo.com). These services will allow us to search for individuals by name, address, and phone number. We will be able to verify whether or not participants are in the armed forces, incarcerated, or have passed away by using Military.com and state websites like Florida.gov.
2. Facebook: If all avenues of contact have been exhausted, we will utilize the social media platform 'Facebook' in an attempt to contact participants.

Facebook Protocol

A Facebook account will be opened under the study name 'Project EASE.' The profile will contain the study and Moffitt Cancer Center logo, along with a paragraph briefly describing the study. Facebook searches will be initiated using the participant's first and last names. If the first and last names result in a match, we will attempt to further verify we have identified the correct individual by confirming 'current city', 'age', or 'email address'. When we are confident that we have identified the right individual, we will use the internal messaging system of the Facebook platform. An initial message will be sent to the individual asking if they are participating in Project EASE. The message will emphasize that we have exhausted all other means of contact, provide our telephone number and email address, and request that the individual contact us or reply via the internal messaging system regarding their willingness to update their contact information and continue their participation in the study. The message will apologize in advance for possibly contacting the wrong individual. If this was the case, we will additionally request that they simply reply with this respect to ensure they are not to be contacted in the future. If the user does not reply, another message will be sent 14 days later.

C.4.2. Outcome Variables

At each assessment point we will calculate point-prevalence abstinence rates (for tobacco smoking as well as e-cigarette use) using 7-day, 30-day, and 90-day criteria. Point-prevalence measures are best for capturing the dynamic nature of cessation, maintenance, and relapse. The 7-day criterion will serve as our primary outcome index. Continuous abstinence is not feasible because quit dates will be highly variable across participants, and also because one goal of the intervention is to encourage lapsers to quit again (recycle). We need our outcome measures to reflect these changes in smoking status over time. However, the 30-day and 90-day point-prevalence abstinence criteria also reflect more prolonged abstinence than the 7-day criterion usually used in treatment studies (Velicer et al., 1992). We will also compare groups on continuous measures, such as current smoking rate (cigarettes/day), months of smoking during the follow-up period, length of current abstinence period, and latency from quit date to relapse. Outcomes will be reported that account for missing follow-up data using both multiple imputation (MI) and intent-to-treat (ITT) approaches.

C.5. Cost-Effectiveness Analysis (Aim 3)

The relative effectiveness and costs of the intervention compared to standard care will be measured based on the health care system perspective. Using the trial endpoint results, effectiveness will be predicted in terms of smoking cessation and translated into life years and quality adjusted life years (QALY) based on published associations between smoking cessation and long-term health outcomes (Cohen & Fowler, 1993; Torrance, 1986). Costs include the intervention costs, collected prospectively, and lifetime costs of reduced medical expenditures attributable to smoking cessation, that will be modeled using published estimates (e.g., Berman et al., 2013; Cowan & Schwab, 2011; Fishman et al., 2003; Hockenberry et al., 2012; Hodgson, 1992; Oster et al., 1984). No out-of-pocket costs or transfer payments (i.e., increased social security due to longevity) will be incorporated into the analysis, because they do not fall within the system perspective. In addition, costs associated only with research (e.g., mailing of assessments) will be excluded. Monetary values will be inflation adjusted, and all outcomes will be presented in discounted and undiscounted values.

The effectiveness and cost results will also be presented as incremental cost-effectiveness ratios, specifically cost per quitter, cost per life year, and QALY. We will assess the robustness of incremental results between the three study arms using probabilistic sensitivity analysis. In our previous study of *Forever Free* as a relapse-prevention intervention, we found that the cost per non-relapse at 24 months was $186, and the cost per extra QALY was $83 at a 4% discount rate (Brandon et al., 2004). In addition, the parallel incremental costs of supplementing an existing smoking cessation intervention with the *Forever Free* booklets were estimated at $4,225 and $2,385, respectively (Chirikos et al., 2004). Both estimates are well below the $50,000 per QALY typically applied in health policy recommendations, and they compare very favorably to counseling, pharmacotherapy, and telephone quitline interventions (Cromwell et al., 1997; Hollis et al., 2007). These results may refine public health decisions between alternative modalities.

C.6. Data Management and Analysis

C.6.1. Data Management

Data will be input through screens created by the Data Systems Team within Moffitt's Research Computing Support Group (Research IT) and will be subject to computerized range and consistency checks. The data will then populate an Access database, which will also be created and maintained by Research IT. This process will be supervised jointly by the PI and Study Data Manager/Staff Biostatistician. The database will be converted on a monthly basis to a SAS database (SAS Institute, Cary, NC). This database and SAS will be used by the statistician who will provide the PI with reports and summaries on a regular basis and perform the final analyses. To ensure participant confidentiality, unique identifiers will be expunged from this data set.

C.6.2. Sample Size and Study Power Analysis

The primary statistical analyses will assess the effectiveness of the full intervention (eTARGET) in producing smoking cessation compared to the no-treatment control (ASSESS) and the generic smoking cessation booklets(GENERIC). Based on prior published work (Bullen et al., 2013), data from our cessation study (C.1.2.3), and considering that the sample will not be limited to treatment-seekers, we estimate no greater than 15% abstinence by 18 months in ASSESS, with at least 5% increments for GENERIC and eTARGET, respectively. We estimated sample size using GEESIZE version 3.1 (Rochon, 2003) with an AR(1) working correlation structure and coefficient of 0.7; adjusted alphas of .017 (ASSESS vs. eTARGET), .025 (ASSESS vs. GENERIC), and .05 (GENERIC vs. eTARGET) following Holm's procedure (Holm, 1979); and abstinence rates that increase from 6 to 18 months, then remain stable through 30 months. Randomizing 2065 participants based on 1:2:2 relative sizes (413 to ASSESS; 826 to GENERIC, and 826 to eTARGET) ensures ≥80% power for all contrasts. We plan to recruit 580, 1160, and 1160 individuals, respectively, in expectation of 17% attrition after baseline assessment, as observed in our prior study.

We initially planned to recruit 500, 1000, and 1000 individuals, respectively, in expectation of 17% attrition after baseline assessment, as observed in our prior study. Based on return rates of the 3-month survey for the first 575 study participants, we now expect 27.5% attrition after baseline. Therefore, we plan to recruit 2900 individuals (400 more than initially planned) with 580, 1160, and 1160 individuals in the ASSESS, GENERIC, and eTARGET conditions, respectively. This will ensure the same sample size for statistical analysis at the higher-than-expected attrition rate.

C.6.3. Data Analysis Overview

Participants will be randomized into the three conditions using balanced-permuted block randomization with a block size of 10 (2-4-4). Analyses will be conducted with SAS version 9.3 and Mplus Version 7 (Muthén & Muthén, 2008). Frequency distributions and contingency table analyses will be used as a point of departure for more advanced analyses. Multiplicity will be legitimately adjusted as needed for Aim 2, but not for the secondary or exploratory analyses. *We will perform attrition analyses, using survival analysis, to test whether the attrition rate differs across intervention arms, if participants and dropouts differ on key variables, and if such variables moderate attrition differences across arms. The median time to attrition and its 95% confidence interval, will be summarized by intervention arm using the Kaplan-Meier method with log-rank test. Any significant variables on those attrition patterns in multivariable Cox Proportional Hazards (PH) models will be accounted for during multiple imputations as well as in the main analysis.*

To manage missing data, multiple imputation under the Missing at Random assumption will be applied using a Markov Chain Monte Carlo method (Shafer, 1997) via PROC MI in SAS, given the expected large number of non-monotonic missing data patterns. Preliminary analyses will determine auxiliary variables (e.g., baseline measures that predict smoking status at follow-up) to be used. A post hoc approach (Rubin, 1987) will address the influence of Missing Not at Random (MNAR) on smoking status (i.e., missing is due to smoking). Sensitivity analyses will be performed to assess alternative multiple imputation techniques upon the extent of MNAR influences.

C.6.4. Analytic Plan for Addressing Specific Aims.

C.6.4.1. Specific Aim 1 (see C.2.3.2.) and Aim 3 (see C.5.)

C.6.4.2. Specific Aim 2.

Generalized estimating equations (GEE) will be used to fit population-averaged models to handle the longitudinally measured binary outcomes, with the main covariates of intervention conditions, time (months from baseline), and the interaction of condition and time. Potential confounding variables (e.g., group differences in demographic, smoking history, or pharmacotherapy use) that appear despite randomization will be adjusted for in the model. Pair-wise condition and time interval comparisons will be tested using the generalized score statistics from GEE models by utilizing the contrast statements. Further, the generalized linear mixed effects models with a logit link function will be expanded, including the participant-specific intercept and slopes as the random effects in the model. Moderators (e.g., gender, SES, quitting motivation, nicotine dependence, magnitude of e-cigarette use, expectancies)will be tested via interactions with condition and condition x time. *Mechanisms of change associated with treatment*

will be tested (e.g., motivational measures, intervention usage, e-cigarette usage) via mediation analysis, performed using Hayes' (2009) "Indirect" macro within SAS. The approach described above will be used to evaluate the primary outcome of smoking cessation as well as the secondary outcome of e-cigarette cessation.

We will extend our analysis to lapse/recovery models using the Kaplan-Meier method with log-rank test for the stratified sub-groups (e.g., lapsed and recovered groups) to test the effect of intervention condition and Cox PH models controlling potential confounding variables.

To capture proportional shifts in cigarette vs. e-cigarette use, we will create a response variable with multiple levels for each follow-up assessment reflecting the relative level of e-cigarette to cigarette use, referenced against baseline use of each product. The multi-level outcome variable will be fitted using a logistic analysis on the generalized logits to test if the interventions have a significant impact on these shifts.

C.6.4.3. Secondary Aim. This aim is to describe the patterns of cigarette smoking and e-cigarette use among initial dual users at 3-month intervals for 2 years. This process will occur relatively naturalistically in the ASSESS condition. The primary analysis will be completed using a growth mixture model (Ram & Grimm, 2009) applied via Mplus Version 7. Growth mixture models assume each participant has his/her own trajectory of smoking cessation behavior over time. We aim to (1) describe the trajectories for tobacco cigarette and e- cigarette use, and (2) identify distinct subgroups of trajectories over time. The model assessment will be conducted using residuals for the fitted means or covariance, as well as overall model fit indices.

C.7. Study Design Considerations

C.7.1. Should we recruit only treatment seekers? *Limiting recruitment to treatment-seeking (or cessation-motivated) dual users would parallel most conventional intervention trials. However, we decided to recruit dual users more generally into the broader surveillance study (Secondary Aim), but inform them of the treatment arms before obtaining consent. Not only are most dual users cessation-motivated, but other advantages of this approach include: (1) We will be able to test whether our intervention motivates attempts to quit smoking among non-treatment-seeking, non-cessation-motivated dual users. (2) We will be able to test cessation-motivation (Contemplation Ladder) as a moderator variable. (3) A broad recruitment strategy models likely dissemination approaches for a low-cost self-help intervention (i.e., external validity). (4) We avoid appearing to promote e-cigarette as a cessation tool for current smokers (see C.7.3). (5) We increase the generalizabiltiy of the surveillance study of the Secondary Aim.*

C.7.2. Printed versus internet-based materials. In theory, an internet-based intervention offers some substantial advantages: no printing or mailing costs; constant availability; and ease of distribution. However, there are also some advantages of traditional printed materials: potentially greater salience and retrievability of a tangible product; use and portability not dependent on technology; and less affected by economic barriers that may limit internet access. Because our previous efficacy studies that produced strong findings used printed materials, we are hesitant to make a wholesale shift to internet-based content. Doing so would impair our ability to interpret a failure to replicate the previous results. However, we recognize the potential advantages of internet-based delivery of health promotion content. Therefore, for the proposed study we will offer participants the option of also receiving an email with a personalized link to the appropriate booklet and to all earlier booklets in the series. They will receive this email an average of 2-3 days before they receive the printed booklets by US mail. We will collect metadata regarding use of the internet-based documents, namely how many times the link was accessed, and whether the electronic booklet(s) were downloaded , which will allow us to document their use and acceptability. We will also collect evaluations and preferences regarding internet distribution at follow-up to test as potential moderators or mediators of treatment effects. This information should assist us in deciding whether to transition fully to internet-based or mobile content (i.e., smart-phone/tablet apps) distribution in the future.

C.7.3. Will we be promoting or recommending e-cigarette use? We are sensitive to the risk that either our intervention or the study itself could be construed as promoting e-cigarettes as a cessation tool. Given insufficient evidence regarding the safety or efficacy of e-cigarettes, we do not wish to promote their use, and we took several actions to minimize such a perception: (1) We will not recommend or provide e-cigarettes to participants. (2) We will only recruit dual users—smokers who are *already* using e-cigarettes. (3) Reflecting the first two points, our intervention materials are tentatively titled, ***If*** *You Vape: Guide to Quitting Smoking*. (4) Our public recruitment materials will not mention smoking cessation, but only surveillance of dual users. (5) Our intervention will recommend and assist with cessation of e-cigarettes following smoking cessation.

C.7.4. Dealing with the likely change in e-cigarettes during course of study. We recognize the e-cigarette marketplace is rapidly changing with the entrance of the traditional tobacco industry This process is expected to consolidate the market as well as lead to a more consistent product and more sophisticated product marketing. Another anticipated change is the regulation of e-cigarettes by the FDA as well as the passage of state-level restrictions. Meanwhile, e-cigarette technology will continue to evolve. The sum of these trends suggests that the landscape of e-cigarettes and dual use will be different by the end of the study

than it is today. Our response to this likelihood is the following: (1) Our co-investigator, Thomas Eissenberg, Ph.D., PI of a new FDA/NIDA-funded center to study e-cigarettes, stays on the cutting edge of e-cigarette development, and he will keep us informed of any developments that will require modification of our methodology or consideration in the interpretation of results. (2) We will concentrate recruitment within an 18-month period to minimize sample heterogeneity with respect to changes in e-cigarettes. (3) Rapid growth of e-cigarette and dual usage necessitates *immediate* research; the opportunity costs incurred by postponing research to an unknown time when e-cigarette usage and development stabilizes would be considerable.

D.8. Study Timeline

Month	Activity
1 – 12	Conduct formative evaluation (Study 1) to tranform existing *Stop Smoking For Good* booklets into *If You Vape*
13-30	Accrue sample and begin distribution of interventions and follow-up assessments
31-48	Continue distribution of GENERIC and eTARGET intervention and follow-up assessments;
49-54	Complete follow-up assessments through 18 months
55 – 60	Complete final data analysis and prepare reports

Protection of Human Subjects

1.RISKS TO HUMAN SUBJECTS

a. Human Subjects Involvement, Characteristics, Design

In Study I, approximately 92 participants will be recruited. In Phase I, we will recruit: (1) current dual users (of tobacco cigarettes and e-cigarettes) without interest in quitting smoking; (2) current dual users who have attempted, but not quit smoking; (3) current e-cigarette users who have successfully quit smoking; and (4) former dual users who have quit both products. Approximately 48 participants will be recruited across the 4 focus groups. In Phase II, up to 20 current dual users will be recruited for individual learner-verification interviews. In phase 3, 24 participants will be recruited across 2 focus groups. To be eligible for Study I, participants must: a) be ≥ 18 years of age; b) be able to speak and read English; c) have ≥ 1 year history of weekly smoking; and d) have ≥ 1 month of e-cigarette use.

In Study II, we will recruit 2900 dual users and randomize them into the 3 treatment conditions. Inclusion criteria will be: (1) smoking at least one cigarette per week over the past year; (2) using e-cigarettes at least once per week over the past month; (3) age 18 or older; (4) not currently enrolled in a face-to-face smoking cessation program; and (5) able to speak and read English.

b. Sources of Research Material (to be used for research purposes only)

In Study I, research data will be derived from questionnaires measuring socio-demographic characteristics, smoking history, e-cigarette use history, nicotine dependence levels, and participant responses to the focus group and interview guides. In Study II, materials will include questionnaires measuring socio-demographic characteristics, smoking history, e-cigarette use history, nicotine dependence levels, motivation to quit measures, smoking expectancies, follow-up use of tobacco products, e-cigarettes, pharmacotherapies, other cessation aids and services, and breath carbon monoxide and saliva cotinine samples.

c. Potential Risks

Risks are judged to be extremely minimal. The intervention is a self-help approach and the focus groups and assessments are all self-report. Potential risks involve confidentiality and loss of privacy because participants may provide personal information about themselves during the focus groups and on screening or demographic questionnaires. Confidentiality will be maintained by using participant ID numbers on questionnaires, rather than names.

2.ADEQUECY OF PROTECTION AGAINST RISKS

a. Recruitment and Informed Consent

Participants will be weekly smokers recruited via multimedia advertisements (daily and weekly newspapers, radio, cable TV, social media, e-cigarette forums, etc.). Interested participants will be contacted and screened by a trained research assistant who will explain the purpose of the focus groups or interviews (in Study I) and explain the intervention study in detail and obtain verbal consent to participate (in Study II). Our research team has been successful with obtaining a waiver of written informed consent from the Institutional Review Boards (IRBs) of three institutions for our Forever Free RCTs. Research assistants will describe compensation, risks and benefits to participation, and confidentiality of the collected information, including that data will be shared with investigators and Moffitt Cancer Center. In Study II, the baseline questionnaire will include an introductory cover letter that contains a written explanation of the study and includes all the required elements of the informed consent. The letter will explain that returning the completed baseline questionnaire will be considered provision of informed consent. Informed consent and consenting procedures will adhere to the IRB guidelines.

b. Protections Against Risk

Potential risks involve confidentiality and loss of privacy because participants may provide personal information about themselves during the focus groups, as well as on assessment questionnaires. To minimize potential

risks all research assistants will receive training in research ethics. In addition, confidentiality will be maintained by using participant numbers on data, rather than participants' names. Participant data will be available only to research staff. Data will be kept in locked filing cabinets in locked laboratory rooms. Electronic data will be stored in password-protected database. Identifying information will not be reported.

3.POTENTIAL BENEFITS OF THE PROPOSED RESEARCH TO HUMAN SUBJECTS AND OTHERS

The potential risks are judged to be extremely minor. The main benefit of Study II is that participants may receive information to help them quit smoking and maintain abstinence. For participants in Study I or the assessment only condition of Study II, direct benefits of participation will be minimal. Participation may raise awareness regarding e-cigarette use, smoking, and cessation behaviors, and eventually lead to smoking cessation, with associated health benefits.

4.IMPORTANCE OF KNOWLEDGE TO BE GAINED

The proposed treatment development and clinical trial could potentially assist the large population of smokers who have already demonstrated initial action toward smoking cessation by commencing use of e-cigarettes. This naturally-occurring, self-selected, and motivated group may be primed to benefit from a minimal intervention that may enhance their chances of achieving and maintaining tobacco abstinence. The intervention was designed to be easy to disseminate and implement, and cost-effectiveness data should aid stakeholders in making implementation decisions.

5.DATA SAFETY AND MONITORING PLAN

This is an extremely minimal risk study. Nevertheless, the principal investigator, Dr. Brandon, will implement a DSMP to ensure that the expected risk/benefit ratio is maintained throughout the study and that the confidentiality and accuracy of the data are preserved. All members of the study team will receive formal training in research ethics and HIPAA procedures through the University of South Florida IRB, as well as study-specific training provided during research team meetings. The study team will meet weekly to discuss study progress, including participant recruitment and retention, data management, any participant complaints, and confidentiality issues. In addition, study progress will be tracked by Moffitt Cancer Center's Protocol Review and Monitoring Committee (PRMC). The probability of an adverse event occurring in this study is extremely low, given the nature of the study. However, as per IRB policy, any serious or unexpected adverse events will be reported promptly (within 2-5 business days, depending on the nature of the event) to the IRB and the PRMC. A summary of the adverse events that occurred during the previous year will be included in the annual progress report to NIH.

Inclusion of Women and Minorities

Inclusion of Women

Our self-help intervention studies typically attract a sample comprising approximately 60% women, representing women's greater willingness to seek assistance. We expect a similar gender distribution in the proposed study.

Inclusion of Minorities

Study I

The Tampa Bay area is racially/ethnically diverse. Based on similar studies we have conducted with a community sample, and recent data indicating that e-cigarette use rapidly becoming more evenly across racial and ethnic groups (King et al., 2013), we anticipate that 71% of the sample will be Caucasian, 20% will be African American, 1% American Indian/Alaska Native, 1% Pacific Islander, 1% Asian, and 6% other (more than one/unreported). We expect that 11% of the local sample will be Hispanic.

Study II

Based on our previous studies with "Forever Free" self-help interventions with national recruitment, including our cessation study currently in progress (C.1.2.3), as well as data on the racial and ethnic distribution of e-cigarette use (King et al., 2013), we estimate that 64% will be Caucasian, 30% will be African American, 1% American Indian/Alaska Native, 1% Pacific Islander, 1% Asian, and 3% other (more than one/unreported). We expect that 6% of the national sample will be Hispanic.

The "Targeted/Planned Enrollment Table" displays the expected racial and ethnic distributions for each study.

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Smoking Cessation Self-Help for Dual Users of Tobacco Cigarettes and E-Cigarettes (Study I)

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Not Hispanic or Latino		Hispanic or Latino		Tota l
	Femal	Mal	Femal	Mal	
American Indian/Alaska Native	0	1	0	0	**1**
Asia	1	0	0	0	**1**
Native Hawaiian or Other Pacific	1	0	0	0	**1**
Black or African American	10	6	1	1	**18**
Whit	36	24	4	2	**66**
More than One Race	2	1	1	1	**5**
Tota	**50**	**32**	**6**	**4**	**92**

Study 1
of 2

Funding Opportunity Number: PA-13-302. Received Date: 2014-06-16T14:35:12.000-04:00

OMB Number: 0925-0002

Planned Enrollment Report

Study Title: Smoking Cessation Self-Help for Dual Users of Tobacco Cigarettes and E-Cigarettes (Study II)

Domestic/Foreign: Domestic

Comments:

Racial Categories	Ethnic Not Hispanic or Latino		Hispanic or Latino		Tota l
	Femal	Mal	Femal	Mal	
American Indian/Alaska Native	15	10	0	0	**25**
Asia	15	10	0	0	**25**
Native Hawaiian or Other Pacific	15	10	0	0	**25**
Black or African American	44	294	9	6	**750**
Whit	88	592	72	48	**160**
More than One Race	36	24	9	6	**75**
Tota	**141**	**940**	**9**	**60**	**250**

Study 2
of 2

Funding Opportunity Number: PA-13-302. Received Date: 2014-06-16T14:35:12.000-04:00

Inclusion of Children

Smokers ≥18 years of age are eligible for study participation. The NIH defines children as individuals under the age of 21, and therefore children are not excluded. Children under the age of 18 are excluded because their smoking profiles, dependence levels, and cessation motivations are different than adults. Hence, they most likely require smoking cessation materials appropriately tailored for their age group. Moreover, we do not want to appear to reinforce e-cigarette use in any way among smokers below the age of 18.

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