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EAQ171CD

Implementing a Virtual Tobacco Treatment in Community Oncology Practices: "Smoke Free Support Study 2.0"

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STUDY PARTICIPANTS	***ACTIVATION DATE***
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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave and the ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) system. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password. Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the CTSU Regulatory Support System (RSS).		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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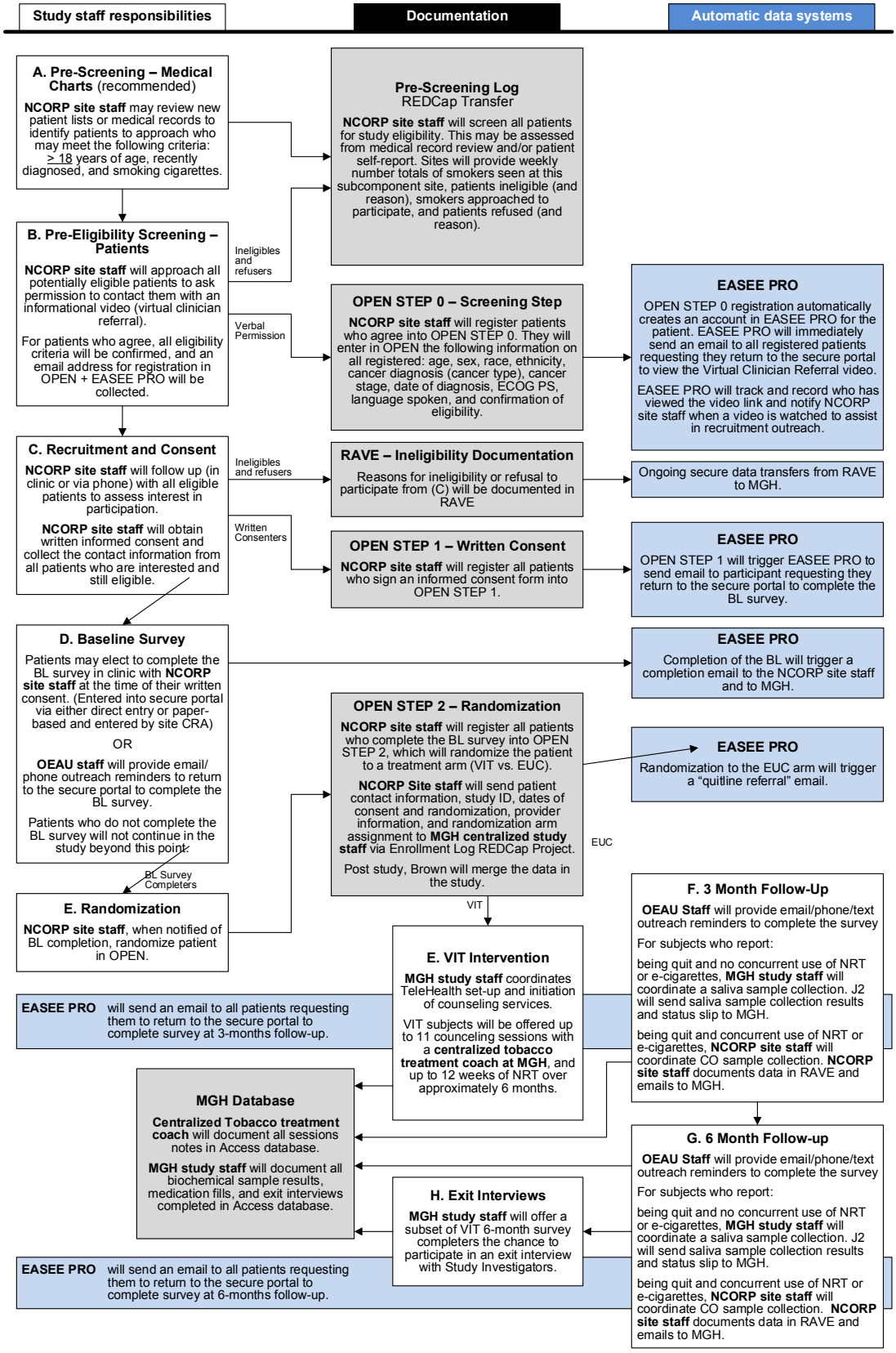
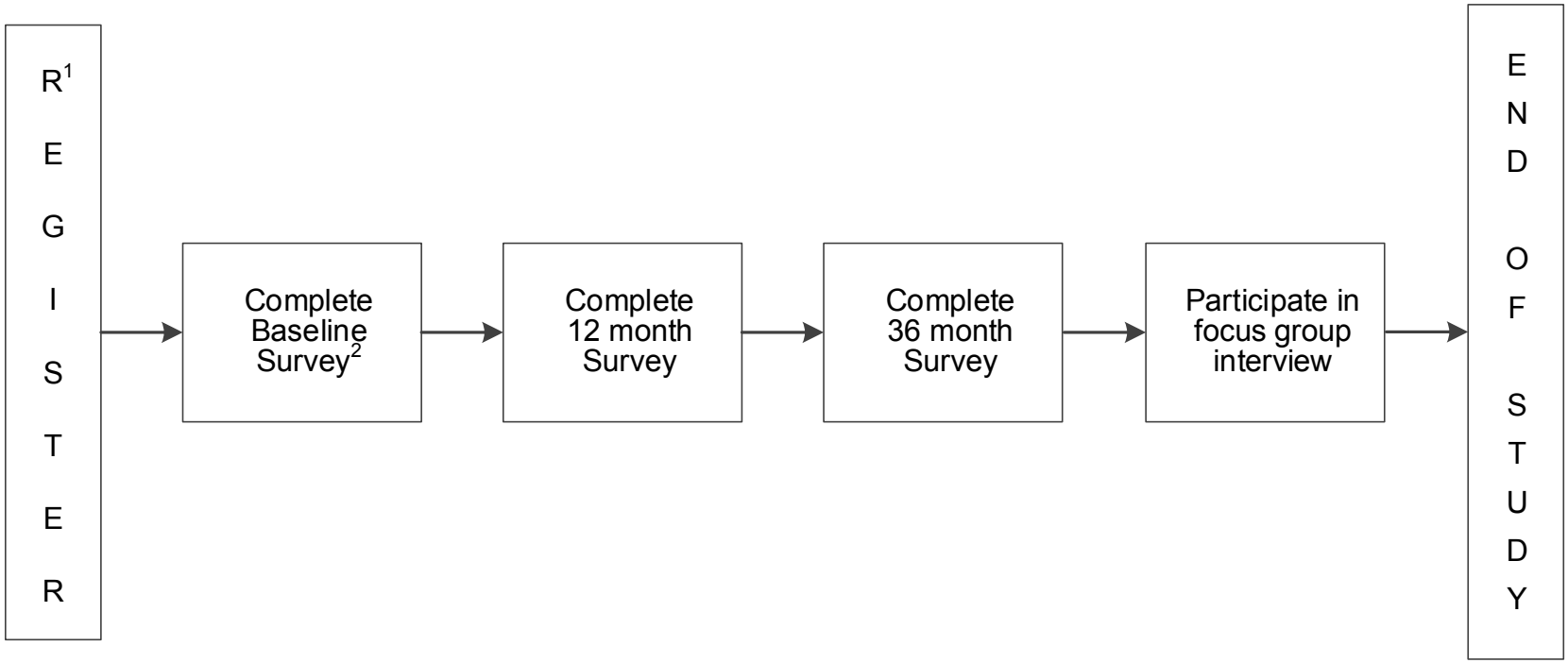
Patient Schema



NCORP Site Staff Schema



1. For each NCORP site, the CCDR lead will identify 8-10 multidisciplinary staff members to participate in this study.
2. Site staff must complete baseline survey prior to first patient enrollment.

1. Introduction

1.1 Study Significance

The landmark 2014 Surgeon General's Report concluded that for individuals with cancer, persistent smoking results in increased toxicity, poor cancer treatment, response, and increased risk for disease recurrence and second primary cancers.[1] Accordingly, in 2016 the Tobacco Control Research Working Group's priorities presented to the NCI's Board of Scientific Advisors emphasized the need to develop and test effective cessation treatments for cancer patients with persistent tobacco use.[22] We propose to conduct the first study to examine the effectiveness and implementation of a virtually-delivered evidence-based tobacco treatment into cancer care for patients at NCORP community sites, including NCORP minority/underserved community sites (>30% of patients are racial/ethnic minorities or rural residents). Since 80% of patients receive their cancer care in the community, [17] and as many community-based oncology networks serve large rural populations and lack resources, this is a tremendous opportunity to examine and implement an evidence-based treatment to an NCI priority population of vulnerable patients. NCORP community sites identified evidence-based cessation services as a priority. In 2016 the NCI-AACR Cancer Patient Tobacco Use Assessment Task Force [23] delineated implementation strategies. Our proposal evaluates 3 of these priorities: evaluation of 1) effective means of delivering tobacco treatment, including motivational approaches and telemedicine; 2) the effects of cessation treatment moderators; and 3) cost-effectiveness.

NCORP community sites provide access to a diverse population of cancer patients making them ideal for studying effectiveness and implementation of tobacco treatment in real-world cancer care settings. The NCI recently launched NCORP to coordinate trials among its community sites, which are organized networks of community-based oncology programs, including minority/underserved community sites. The goal of NCORP is to conduct cancer control research in communities where patients receive their care, with a priority on improving access and evaluating innovative cancer care delivery models, particularly among underserved and underrepresented populations. Our proposal is closely aligned with NCORP priorities

Tobacco use following a cancer diagnosis is prevalent and compromises treatment outcomes. About 10% to 30% of cancer patients are smoking at the time of diagnosis, [5-8, 24, 25] and the majority of cancer patients who smoke at diagnosis continue to smoke following diagnosis.[7,26] Quitting smoking upon cancer diagnosis may improve cancer treatment effectiveness, reduce risk of recurrence and of developing new primary tumors,[1,13-15, 27-30] and improve chances of survival.[5, 31-33] Conversely, continuing to smoke may result in diminished quality of life,[5, 34, 35] treatment delays and increased treatment complications.[6,10-12, 36-44]

National initiatives emphasize the importance of identifying smokers in cancer care settings. In 2011, the Joint Commission and Medicare adopted National Hospital Quality Measures for hospitals to report on how often hospitalized smokers receive cessation advice, counseling, and medication.[45] Smoking status was designated as a core objective in the 2010 "Meaningful Use" EHR documentation.[46, 47] The 2013 AACR released guidelines emphasize the

provision of tobacco cessation services to cancer patients.[48] The American Society of Clinical Oncology (ASCO) recommends cessation counseling to all smokers as a core quality indicator.[49] In 2015 the National Comprehensive Cancer Network (NCCN) published Smoking Cessation guidelines to formalize these initiatives.[2]We propose to implement a virtually-delivered tobacco treatment to help community cancer centers meet national recommendations.

Integrated, evidence-based services are needed, but are lacking, during cancer care. The USPHS Practice Guidelines recommend that evidence-based tobacco treatment – specifically, combined medication and counseling– be delivered to all smokers in health care settings, yet little progress has been made to integrate these guidelines into cancer care.[50] A survey of comprehensive cancer centers found that almost all believed that having a tobacco treatment program is "very important" but only half had any such type of program.[51] This is unfortunate, as cessation closer to the time of diagnosis results in a higher likelihood for continued abstinence,[5, 52-55] effective interventions exist,[5,52-55] and many cancer patients who smoke want to quit smoking.[52, 53, 56, 57] Additionally, little work has been done to explore the delivery and effectiveness of tobacco treatment among racial/ethnic minority cancer patients who are at risk for continued smoking. [3, 58, 59] Lastly, tobacco use remains unaddressed after treatment completion.[60] A recent national study[61] found that smokers treated for cancer were significantly more likely than smokers without cancer to try to quit smoking.

Tobacco use is not being assessed or intervened upon during cancer care. Assessment of tobacco dependence among cancer patients is lacking; [62-64] in particular, rates of smoking assessment are lower in non-academic medical settings (i.e., community settings).[65] Unfortunately, during treatment, many smokers are not advised to quit,[66, 67] and most cancer patients do not get assistance (e.g., medications, counseling) to quit and/or stay quit.[68-70] Only 30%-40% of oncologists provide assistance to help patients quit smoking. [62, 63, 71] Furthermore, tobacco use assessments and cessation support have not been incorporated in most cooperative group clinical trials.[72] Lack of adequate training, lack of expertise in providing cessation treatment, and lack of patient support resources such as dedicated cessation counseling programs, have been reported as leading impediments to implementation of cessation treatment in cancer care. [51, 62, 63]

Cancer patients who smoke have socioeconomic, biologic and psychosocial vulnerabilities. Individuals with lower incomes and education have a higher prevalence of smoking.[73, 74, 75] Dr. Park found that Cancer Care Outcomes Research & Surveillance Consortium (CanCORS) participants who were smoking at diagnosis had less education and more often had public health insurance ($p<.001$).[7] Cancer patients are at risk of financial hardship.[76] A recent study of Medicaid patients demonstrated that barriers to treatment access still exist.[77,78] Cancer patients who report persistent smoking need intensive treatment, often endorsing high rates of nicotine dependence and household smoking.[79] Cancer patients who smoke often experience internalized stigma; [80, 81] smokers who perceive stigma are less likely to disclose their smoking status and receive needed treatment.[82] NCORP community sites enable us to reach vulnerable cancer patients.

Implementation of tobacco treatment into community cancer centers would be facilitated by cost data. A significant barrier to translation of behavioral interventions into practice is failure to conduct analyses of intervention costs.[83]

Emerging health care finance mechanisms that move away from fee-for-service payment (accountable care organization, episode-based payment, etc.) will heighten the demand for cost data. Smoking cessation trials conducted with cancer patients have not examined treatment costs. Our current R01 trial results will contribute the first cost analyses of smoking cessation treatments for cancer patients at the time of diagnosis, but these are limited to comprehensive cancer centers. The proposed trial will extend this work and be the first cost analyses to be conducted in cancer community settings.

Implementation outcomes to be gained from the proposed hybrid-effectiveness trial. In summary, the NCI, ASCO, AACR, and NCCN promote incorporating tobacco treatment into the delivery of cancer care, but this has never been done in community cancer centers. Trial findings will establish the effectiveness and cost of utilizing a virtual strategy to deliver evidence-based tobacco treatment in community oncology settings and provide detailed initial data on implementation processes that will inform subsequent testing of multi-level implementation strategies for broad national dissemination into community cancer care settings.

Building on current work to enhance virtual tobacco treatment delivery. Our preliminary R01 (the Smokefree Support Study 1) data demonstrates that an intensive tobacco treatment, delivered in-person (during outpatient and inpatient cancer center appointments) and via phone, targeted to the needs of recently diagnosed cancer patients (breast, lung, GU, GI, ob/gyn, lymphoma, head and neck, and melanoma), is effective. We believe that face-to-face contact is an important ingredient in patient-counselor rapport. In our previous study, patients had the opportunity to meet counselors in-person during treatments, but the wide geographic distribution of cancer clinics within community-based setting limits the ability for tobacco treatment access and in-person contact. Recent pilot studies reported on the feasibility of using videoconferencing to deliver psychosocial care to cancer patients,[117-119] and behavioral interventions using videoconferencing technology have been found to be as effective as in-person delivery. [120-123] There have been only two studies using videoconferencing to deliver smoking cessation programs, but both required patients to come into clinics to use the technology; both found it to be feasible to deliver and reported high reported patient satisfaction. Dr. Carlson concluded that videoconferencing delivered cessation groups produced quit rates similar to in-person groups.[120] Dr. Richter compared a videoconferencing-delivered program, delivered within primary care clinics, to a telephone-delivered program and found that videoconferencing increased utilization of cessation medication.[124] To our knowledge, our study is the first to offer virtual delivery, via remote videoconference, of a tobacco treatment to cancer patients. We will leverage existing systems; we developed English/Spanish treatment protocols, electronic data capture systems, medication algorithms, cost tracking templates, and motivational interviewing counseling fidelity and supervision materials. The proposed trial improves reach by: 1) using videoconferencing to bring a tobacco counselor (synchronous visits) directly to patients; 2) bringing tobacco treatment into community cancer centers; 3) offering tobacco treatment to diverse patients; and 4) incorporating involvement of cancer clinicians, through delivery of brief videos.

1.2 Background

Dr. Park has conducted multisite tobacco treatment trials with cancer patients and low SES smokers.[85, 125-127] Dr. Park directed an efficacious 24-site RCT to test a smoking cessation intervention for childhood cancer survivors assigned to a telephone-based peer motivational counseling plus NRT patch intervention versus usual care.[125,126] Drs. Park and Rigotti collaborated on an RCT for 607 low-SES, English and Spanish-speaking smokers that compared quitline referral to phone-based motivational counseling calls with a tobacco counselor embedded in the health care system and NRT.[84] The intervention significantly increased tobacco abstinence at 9 months compared to usual care (18% vs. 8%; p<.001). Drs. Rigotti and Park also collaborated on an RCT of a smoking cessation intervention for 397 hospitalized smokers.[95] An intervention using automated calls (IVR) and free NRT was significantly more efficacious compared to quitline referral (26% vs.15%; p<.01). Dr. Park conducted a pilot smoking cessation study which supported the feasibility of an Intensive Treatment (motivational counseling plus varenicline) vs. usual care for patients at the MGH thoracic clinic.[79] Dr. Ostroff led a randomized trial evaluating the efficacy of a gradual smoking tapering intervention combined with nicotine patch in 185 cancer patients awaiting hospitalization for surgical treatment (6-month abstinence was 32%).[128] Dr. Ostroff also co-led a large cluster,randomized trial testing the effectiveness of several systems-level, implementation strategies to improve adherence to tobacco treatment guidelines in community-based public health dental clinics.[129] In June 2016, Drs. Park, Ostroff and Perez participated in a new NCI initiative, SPeeding Research-tested INTerventions which focuses on integrating research trial-based interventions into real-world settings. They conducted 30 interviews with stakeholders to discuss barriers to implementing tobacco treatment training and programs for oncology patients. These interviews confirmed 1) the need for a national tobacco treatment program, 2) the need for tobacco treatment delivery to be specialized for cancer patients, and 3) that oncology clinicians, although strongly supportive of tobacco treatment for their patients, lacked tobacco treatment training experience and time.[130] In September 2016, Drs. Wagner, Park and Ostroff were awarded an NCI supplement to administer the AACR tobacco assessment to 1000 patients (at enrollment, 3 and 6 months) in ECOG/ACRIN NCORP trials to determine the effects of tobacco use on patient's a) physical and psychological symptoms and b) cancer treatment duration, dose intensity, and therapeutic benefit. *These developments strengthen the team's ability to assess implementation of tobacco treatment in cancer care settings.*

1.2.1 Current R01 preliminary findings (Smokefree Support Study 1).

The proposed study was informed by the recently completed RCT which Drs. Park and Ostroff conducted at MGH and Memorial Sloan Kettering (MSK) to assess integration of an Intensive Treatment (IT; 11 sessions of motivational counseling, in-person and phone, plus choice of FDA-approved medication) versus MSK's usual care with recently diagnosed cancer patients (4 sessions of MI counseling plus FDA-approved medication advice).[127]Among patients who are potentially eligible based on chart screen, approximately one-third enrolled; among known eligible smokers who agreed to be screened, 70% enrolled. Based on preliminary analyses as of February 2018, 303 patients were enrolled and randomized to a treatment arm (56%

female, mean age = 58; 82% white, non-Hispanic; 10 % Black; 5.0% Hispanic). This includes patients diagnosed with thoracic, head and neck, GI, GU, breast, lymphoma, melanoma, and ob/gyn cancers. Using intention-to-treat analyses counting non-responders as "smokers" (86% 6-month survey response rate and 87% cotinine validation response rate), cotinine validated 6-month abstinence rates are 19% in the Standard Care group and 33% in the Intensive Treatment group (p<.02). Using intention-to-treat, 57% of Intervention Treatment group participants were adherent to sustained counseling (> 7 sessions), which was associated with increased 6-month quit rates (p<.0001). These data support preliminary effectiveness of the proposed intervention treatment.

1.3 Approach

1.3.1 Design Overview

We propose a hybrid-effectiveness design,[18] Hybrid Type 1 enabling us to test the effectiveness of our clinical intervention while also gathering key information on its delivery and potential for implementation in a real-world situation. This design choice fits the 3 recommended conditions for Hybrid Type 1 use, specifically: 1) strong face validity for the intervention that would support applicability to the new setting (NCORP centers), population (more diverse cancer patients), or delivery method (synchronous videoconferencing); 2) strong base of indirect evidence (data from different but associated populations) for the intervention; and 3) minimal risk associated with the intervention, both its direct risk and any indirect risk through replacement of a known adequate intervention. Our design compares the effectiveness and implementation of Enhanced Usual Care (EUC: Asking about tobacco use, Advising current tobacco users to quit and Referral to NCI Quitline) versus an evidence-based Virtual Intervention Treatment (VIT; Asking about tobacco use, Advising current tobacco users to quit and Referral to a centralized NCORP tobacco coach for a videoconferencing intervention).

1.3.2 Virtual Approach: Referral and Delivery

An IT platform will be used to recruit patients to the study via a Virtual Clinician Referral. Brief, educational videos will be created for patients. Through this virtual clinician referral, clinicians can engage in a supportive collaborative care approach to underscore the importance of cancer patients addressing their tobacco use and encouraging treatment participation.

These brief videos can be accessed via a computer, tablets, or smartphones, and sent via secure email platform. To enhance patient engagement and standardized clinician care delivery, MGH staff will be available to support our brief video development and implementation. Working with the MGH team, we will develop a brief (approximately 1-2 minutes) video that introduces the study and encourages participation in the study. These videos will build on our extensive experience in recruiting and retaining participants in study trials.

In an effort to standardize usual care, a script will be provided to each individual site, and the virtual clinician referral will be recorded by a site-designated oncology provider at each participating NCORP center. These brief videos will introduce the tobacco treatment program and ask about smoking behavior, normalize tobacco use to decrease internalized stigma, advise cancer patients of the importance of quitting/decreasing their smoking, encourage behavioral and medication support, refer patients to the program, and encourage follow-up with the treatment group referral.

1.3.3 Conceptual Framework for Treatment

Our tobacco counseling sessions, which address tobacco use in the context of a cancer diagnosis, combines two theoretical lenses—a coping with illness model and a health behavior change model. The Self-Regulation Model (SRM)[147,148] focuses on the dynamic process between beliefs, emotions and coping, and has been widely used to study patients' coping with cancer. Applying the SRM to a cancer diagnosis, changes in beliefs about cancer outcomes may lead smokers to engage in quitting as a strategy to cope with the cognitive and emotional threat of cancer. If individuals' evaluation of the effects of quitting, physical changes (e.g., breathing has improved) and environmental influences (e.g., smokefree home), make them feel better, then they will stay quit. If quitting smoking decreases a sense of shame and anxiety, this will increase chances of staying quit. The HBM[149] posits that when faced with a health threat, individuals are more likely to change a behavior if they feel the threat is serious, they are at risk, they are able to make the change, and the change would decrease their risk. Applying the Health Belief Model (HBM) to a cancer diagnosis, smokers will be more likely to engage in tobacco treatment and quit if they 1) believe that continued smoking after a cancer diagnosis threatens health, 2) understand that continuing to smoke puts them at risk for poor outcomes, 3) are confident they can quit, and 4) believe quitting will improve outcomes.

1.3.4 Rationale for NRT

The selection of combination NRT is based on the current recommendations for the NCCN Smoking Cessation Guidelines[2] and data from our prior clinical trial demonstrating safety and strong patient preferences. Smokefree Support Study 1 intervention arm participants were offered a choice of NRT (patch and/or lozenge), bupropion sustained release (Zyban, Wellbutrin), or varenicline (Chantix). In preliminary analyses as of February 2018, 80% of Intervention Treatment group participants elected to receive a smoking cessation medication, among which 83% selected NRT. Reported NRT medication side effects have been minor (e.g., tingling sensation on tongue, vivid dreams). Thus, given patient preferences and safety results from the R01 trial, combined with the ability to deliver the NRT via mail, patch and lozenge will be used in this trial. Additionally, NRT is being used by many state quitlines, has successfully been used with cancer patients,[150,151] is available over-the-counter, and is covered by Medicaid and many private insurers. Lastly, the NCCN guidelines concluded that blood[2] nicotine levels

from NRT, including combination NRT, are significantly less than from smoking cigarettes; additionally, there is insufficient evidence that NRT causes cancer in humans or increases risk of myocardial infarction or cardiovascular disease.[51,152,153]

1.3.5 Counseling Approach

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Counselors will contact patients directly (via phone, e-mail, or text messaging) to schedule the virtual counseling sessions. Counseling sessions will be conducted via MGH TeleHealth, which connects providers to patients through virtual HIPAA-compliant videoconferencing technology including: phone, video, email, mobile applications and remote monitoring. These virtual visits are conducted via a videoconference platform that addresses clinical privacy and security (e.g., Zoom, Doximity, or other HIPPA-compliant platform). 2017 Pew findings[154], [155] showed that 74% of adults ages 50-64 (average projected age of proposed study sample) own Smart Phones, and 87% use the internet; thus, a web-based option is a feasible modality.[156]

The VIT session materials have been created at the 8th grade reading level.[160] The counseling will be delivered by a study-designated tobacco treatment coach based at MGH and trained in a Motivational Interviewing (MI) style[161-162], structured according to the 5As format and personalized to participant's cessation readiness and cancer treatment phase (initiation, transitions, surveillance). MI is an empathic and supportive style of treatment1[61] for smoking cessation,[162] proven effective in treating low SES smokers and smokers with medical co-morbidities.[16,85] Dr. Park has effectively used MI to promote quitting among childhood cancer survivors and lung cancer patients.[79,126] MI is particularly effective with cancer patients; 1) MI focuses on building and maintaining self-confidence, and our pilot work showed that cancer patients report low confidence; 2) the main MI tools (e.g., affirmations, reflections) are effective when addressing sensitive topics, such as cancer and smoking-related beliefs (e.g., shame, fear of recurrence), and in delivering sensitive information (e.g., risks of smoking during cancer treatment);[161] and 3) MI skills will encourage and sustain quit motivation.

Of note, the intervention counseling as delivered here is a psycho-educational program, and is not being delivered as clinical care.

2. Objectives

We propose to conduct the first study to examine the effectiveness and implementation of a virtually-delivered, evidence-based tobacco treatment into cancer care for patients in community oncology settings. Our study is designed to compare the effectiveness and implementation of an Enhanced Usual Care (EUC; control group) versus a Virtual Intervention Treatment (VIT; intervention group) for tobacco cessation in newly diagnosed cancer patients who smoke. Trial findings will establish the effectiveness and cost of utilizing a virtual strategy to deliver evidence-based tobacco treatment in community oncology settings and provide detailed initial data on implementation processes that will inform subsequent testing of multi-level implementation strategies for broad national dissemination into community cancer care settings.

2.1 Study Aims:

2.1.1 **Aim 1:** To assess treatment effectiveness, by comparing the proportions of participants in the Enhanced Usual Care (EUC) and Virtual Tobacco Treatment (VIT) study arms abstinent post enrollment.

2.1.2 **Aim 2:** To assess the potential effect of potential moderators (e.g., sociodemographics, medical and smoking history, cancer variables) on treatment effectiveness between the two arms.

2.1.3 **Aim 3:** To assess the processes of implementation and dissemination (acceptability, adoption, appropriateness, treatment fidelity, cost effectiveness, penetration/reach, and sustainability) of delivering tobacco treatment interventions at community oncology sites.

2.2 Primary Objective:

2.2.1 Treatment effectiveness (Aim 1)

To compare the proportions of participants in the Enhanced Usual Care (EUC) and Virtual Tobacco Treatment (VIT) study arms with biochemically-verified 7-day point-prevalence abstinence from cigarettes at 6-months post enrollment.

We will define biochemically-verified 7-day point-prevalence abstinence at 6 month follow-up by:

- saliva cotinine (< 15 ng/ml), or
- expired air CO (< 10ppm)

2.3 Secondary Objectives:

2.3.1 Secondary treatment effectiveness (Aim 1)

Secondary smoking outcomes (5) include:

- Biochemically-verified 7-day point prevalence abstinence at 3-months follow-up
- Self-reported 7-day point prevalence cigarette abstinence at 3- and 6-months follow-up

- Significant reduction (> 50% reduction in reported number of cigarettes per day) in daily smoking from baseline to 3- and baseline to 6-months follow-up
- Continuous (no self-reported smoking since last survey point) and sustained abstinence at 6 months (cotinine-verified at 3-months and 6-months)

2.4 Exploratory Objectives

Aim 2: To assess the potential effect of known and potential moderators on treatment effectiveness between the two arms.

Exploratory analyses will examine the moderator and mediator effects on treatment effectiveness (Aim 2).

Moderators/Mediators of primary interest:

- Sociodemographics: Sex, age, marital status, race/ethnicity, education level, financial burden, health insurance, internet and smartphone access and modality
- Smoking history: Years smoked, daily smoking rate, other tobacco/nicotine use (e.g., cigars, cigarettes), current/past use of tobacco treatments, nicotine dependence
- Cancer variables: Cancer type, cancer stage, treatment, and days since diagnosis
- Site characteristics: Site, geographic location, clinic volume, baseline organizational readiness, site usual care

Additional moderators/mediators to be explored:

- Medical history: ECOG Performance Status, alcohol use
- Quality of life/emotions: Emotional distress, coping, anxiety, depression
- Cancer and smoking beliefs: Stigma, quit motivation, self-efficacy to quit, importance of quitting, perceived benefits of quitting smoking, quit-smoking medication beliefs
- Physical symptoms: Cravings
- Environmental influences: Level of second-hand smoke exposure, perceived social support, perceived provider support

Aim 3: To assess the processes of implementation and dissemination (acceptability, adoption, appropriateness, treatment fidelity, cost effectiveness, penetration/reach, and sustainability) of our intervention at community oncology sites

Guided by Proctor and colleagues' (2011) recommendations for measurement of implementation outcomes, we will explore the following to gain an initial understanding of the implementation process (Aim 3).

Implementation Outcomes

- Acceptability: Patient satisfaction with content/delivery of their randomly assigned tobacco treatment
- Adoption: Site program uptake, changes in organizational readiness to deliver tobacco treatment

- Appropriateness: Perceived fit and relevance of the VIT and EUC interventions from the perspective of representative site staff
- Tobacco Treatment fidelity: Delivery of all components of the Smokefree 2.0 Study Treatment Interventions (EUC and VIT).
- Cost: Incremental cost per quit of the VIT intervention relative to the EUC control over the 6-month follow-up period
- Feasibility: Ease of delivery and suitability for routine care of the VIT and EUC interventions
- Penetration/Reach: Patient participation rate at each site, reasons for study ineligibility and refusal, comparison of sociodemographic and cancer variable characteristics of enrollees and refusers of the study
- Sustainability: Resources needed and preference for a site-based centralized tobacco treatment program

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Using existing staff data collection survey and interview tools as well as synthesis of notes from minutes of monthly meetings with CCDR Leads and study investigators, we will enhance our understanding of the implementation process (Aim 3) by: 1) examining organizational characteristics that influence adoption of tobacco treatment interventions; and 2) identifying and developing strategies to address barriers for implementation of tobacco use assessment and treatment in the trial. This exploratory research will add to the limited knowledge about contextual factors influencing the engagement of community oncology sites in the adoption of tobacco use assessment and treatment; and inform how best to engage community oncology practices in the integration of smoking cessation in cancer care.

3. Participant Selection

3.1 Selection of NCORP Site Staff Participants

In order to achieve Aim 3, we will enroll a subset of staff (n=approximately 110) from a minimum of 11 participating NCORP sites. We are seeking to elicit implementation process perspectives from key stakeholders (clinicians and research administration staff) who would most likely be instrumental in making tobacco use assessment and treatment routine part of cancer care. Guided by his/her knowledge of key stakeholders' roles and responsibilities, the Cancer Care Delivery Research (CCDR) Leader and site PI from each participating site will be responsible for identifying approximately 10 multidisciplinary staff members to complete brief (approximately 15 minute) surveys and participate in focus group interviews (approximately 45-60 minutes). The focus group interview will be conducted approximately 24-36 months after site activation, upon the completion of 36-month follow-up surveys by the site. Although specific site staff participant composition will vary somewhat by site, we envision participation of the CCDR Leader, the Site PI, 2-3 oncology nurses, 2-3 additional medical oncologists and 2-3 additional staff members.

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In terms of eligibility criteria, eligible NCORP site staff participants will be English-speaking, employed at the NCORP site for at least three months, and able to provide informed consent to participate in this study (see Informed Consent for NCORP Staff). The CCDR Lead and Site PI will be responsible for consenting each other and the other staff participants. The CCDR Lead will update the REDCap Roster survey with the dates of consent for each participant. The consent date entered into the MSK REDCap Roster survey will be used as the source documentation by MSK staff to send out the baseline survey to those consented participants. Given the minimal risk, minimal burden and broad relevance of this research to CCDR priorities for enhancing high quality cancer care, we do not anticipate any difficulty recruiting staff participants. In the event that there is staff turnover, the CCDR Leader will be responsible for identifying one or more replacement staff participants who will provide 12 and 36-month follow-up surveys and participate in the focus group interview. Given our assumption that the selected staff represent key site stakeholders and that the quantitative (baseline, 12 and 36-month follow-up surveys) and qualitative data (focus group interview) will be analyzed at the level of the site, some variation in pre- and post-trial participants will is allowable and will not diminish the accomplishment of Aim 3.

3.1.1 Staff Eligibility Criteria

_____ 3.1.1.1 Must be English speaking

_____ 3.1.1.2 Must be employed at NCORP site for at least three months

3.2 Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: NCI Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

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3.2.1 Patient Eligibility Criteria Step 0 and Step 1 (Registration)

3.2.1.1 Inclusion

_____ 3.2.1.1.1 Age ≥ 18 years.

_____ 3.2.1.1.2 Patient presenting with any type of cancer with a date of diagnosis within the past 4 months (124 days) at the time of Step 0 Registration.

Recurrence, diagnosed within the last 4 months, of tumors in patients with past cancer diagnoses will be considered eligible. Patients with a new primary cancer, diagnosed within the last 4 months (124 days) at the time of Step 0 Registration, who have been treated previously for other types of cancer will also be considered eligible. "In situ" cancers, diagnosed within 4 months (124 days) at the time of Step 0 Registration), will also be considered eligible.

_____ 3.2.1.1.3 Patient must be a current smoker. Current smoker is defined as any cigarette smoking (even a puff) in the past 30 days prior to Step 0 Registration.

_____ 3.2.1.1.4 Patient must be fluent in both written and spoken, English or both written and spoken, Spanish.

_____ 3.2.1.1.5 Patient must have telephone, e-mail access, and have access to the internet with a camera-enabled device (e.g.,. smartphone, tablet, computer, laptop with a webcam/camera).

NOTE: The restriction to those with web and e-mail access is based on the primary intention of the study; to assess the implementation of the virtual intervention in the NCORP network.

3.2.1.2 Exclusion (Subject must not meet any of the criteria listed here)

_____ 3.2.1.2.1 Patient has an ECOG performance status of 3 or above, or is deemed medically unable to participate by study investigators or oncology clinician (i.e., referral to hospice).

_____ 3.2.1.2.2 Patient has no intention to receive their cancer care or monitoring at an NCORP community cancer site.

3.2.2 Patient Eligibility Criteria Step 1 (Registration)

3.2.2.1 Patient must still meet all criteria outlined in Step 0

NOTE: The requirement to register within 4 months from cancer diagnosis is determined by the date of the Step 0 registration and not the date of the Step 1 registration.

3.2.3 Patient Eligibility Criteria Step 2 (Randomization)

3.2.3.1 Patient must have completed Baseline Survey in EASEE-PRO within 31 days of the date of Written Informed Consent (Step 1).

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration and Randomization Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;
- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications (e.g., Roster Update Management System (RUMS), OPEN, Rave,);

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- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (i.e., Alliance). Additional information can be found on the CTEP website at <https://ctep.cancer.gov/investigatorResources/default.htm>.

For questions, please contact the RCR ***Help Desk*** by email at <RCRHelpDesk@nih.gov>.

CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol Principal Investigator (PI) (i.e., the investigator on the IRB/REB approval) must meet the following criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status;
- Rostered at the site on the IRB/REB approval (applies to US and Canadian sites only) and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and

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- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Log on to the CTSU members' website at https://www.ctsu.org using your CTEP-IAM username and password
- Click on Protocols in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand

Click on the **ECOG-ACRIN** link to expand, then select trial protocol **EAQ171CD**

Click on Documents, select Site Registration, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above).

Requirements For EAQ171CD Site Registration:

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- Study Chair approval

Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log on to the CTSU members' website → Regulatory → Regulatory Submission

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date

- Type of review (full board vs. expedited)
- Date of review.
- Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on Regulatory at the top of the screen;
- Click on Site Registration;
- Enter your 5-character CTEP Institution Code and click on Go;
- Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB type.

NOTE: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol intervention prior to registration.

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type; and
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. Prior to accessing OPEN, site staff should verify the following:

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- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is provided on the OPEN tab of the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.1 Registration Information Required at **Step 0**

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and Affiliate Name
- Investigator's Name

4.1.3 Patient Identification

- Smoking Status
- ECOG Performance Status
- Cancer Diagnosis
- Verbal Consent
- Patient Demographics
  - Gender
  - Age
  - Race
  - Ethnicity
  - Method of Payment
  - Language
  - Care at NCORP
  - Cancer Stage
  - Email Address

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4.2 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.2.

4.3 Registration Information Required at **Step 1**

4.3.1 Protocol Number

4.3.2 Investigator Identification

- Institution and Affiliate Name
- Investigator's Name

4.3.3 Patient Identification

- Patient Demographics
  - Gender
  - Age
  - Race
  - Ethnicity
- Written Informed Consent

- HIPAA authorization

NOTE: The Registration Information listed in Section 4.3 does not need to be re-entered into OPEN if there are no changes since Step 0.

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Registration Information Required at **Step 2** (Randomization)

4.5.1 Protocol Number

4.5.2 Investigator Identification

- Institution and Affiliate Name
- Investigator's Name

4.5.3 Patient Identification

- Patient Demographics
  - Gender
  - Age
  - Race
  - Ethnicity
  - Method of Payment
  - Baseline EASEE-PRO completed within 30 days of date of written informed consent
  - Previously enrolled in ECOG-ACRIN study

NOTE: The Registration Information listed in Section 4.5 does not need to be re-entered into OPEN if there are no changes since Step 0.

4.6 Stratification Factors

Stratification within site

4.7 Additional Requirements

4.7.1 Patients must provide a signed and dated, written informed consent form in order to continue into Step 1.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.7.2 See Section 10 for submission of biochemical validation of smoking status by saliva samples or collection of CO measurements.

4.7.3 Registration of Patients

Prior to enrollment of the first patient sites must confirm they have completed the following to receive final IRB approval in the CTSU system:

- Baseline surveys must be completed by 10 staff members as outlined in Sections 3.1 and 6.3 of the protocol.
- Brief videos videos must be completed and approved by study staff for the purposes of patient recruitment.

For approval of brief videos and to confirm all baseline surveys have been completed, please email the study alias at smokefreesupportstudy2@partners.org. The study staff will then inform the CTSU that your site is ready for enrollment.

4.7.4 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata::

- A valid and active CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type;

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the accept link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings),and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at

www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.7.4.1 The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

NOTE: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

4.7.5 ECOG-ACRIN Systems for Easy Entry of Patient Reported Outcomes (EASEE-PRO) System

We will use a combination of EASEE-PRO and mailed questionnaires for this study. A proxy or family member can complete the questionnaires on behalf of the patient as long as they can speak English or Spanish. The questionnaires are only available in English or Spanish.

Access to the study in EASEE-PRO is granted to all participants registered to the study through the OPEN registration system with a valid participant email address. Upon registration, an account verification email will be sent to the user with a link to activate their account. The user will be required to enter some verification information (e.g. DOB) in order to activate their EASEE-PRO account. Additionally, site persons with the appropriate roles in RSS will be granted access after IRB approval is obtained. In some studies, this access may allow CRAs to assist the participant accessing baseline surveys, educational materials, or other EASEE-PRO materials.

EASEE-PRO Participant Access:

To access EASEE-PRO, the participant must have an active EASEE-PRO user account. Upon registration to the study in OPEN, an account activation email will be sent to the address entered for the participant in OPEN eligibility checklist. This email address must be a valid email address for the participant. All participants in the **EAQ171CD** Study are required to have access to the internet and a valid email address to participate. (If the patient email address were entered incorrectly in OPEN, the CRA must contact the OEAU (pro-help@stat.brown.edu to manually correct the error.) To activate their account, users must click the link in the email and verify their account before they can login and complete surveys or view web education materials. Once the account is activated, participants may login to the EASEE-PRO system through the OEAU-PRIDE web portal (https://pride.stat.brown.edu/Participant-Login). Upon login, users will be presented with a list of available surveys and materials they can view.

EASEE-PRO CRA Access:

To access EASEE-PRO, the site user must have an active CTEP IAM account (https://eapps-ctep.nci.nih.gov/iam). In addition, site users that are a member of ECOG-ACRIN must have the mapped ECOG-ACRIN roles or explicit Rave roles (Rave CRA) in RSS at the enrolling site. Site users that are not members of ECOG-ACRIN must have the Rave roles on the CTSU roster at the enrolling sites. The Site Administrator or Data Administrator at the enrolling site may assign the appropriate roles from the Site Roles tab on the CTSU website. To login, CRAs will use their CTSU(IAM) credentials on the OEAU-PRIDE web portal (https://pride.stat.brown.edu/CRA-Login) using the familiar IAM interface. No e-learnings are required for use of this site.

The ECOG-ACRIN Outcomes and Economics Assessment Unit can be contacted for Patient Reported Outcome Questions via email at pro-help@stat.brown.edu. An EASEE-PRO instructional guide for both sites and patients can be found on both the E-A and CTSU websites.

Please see below for additional details on the EASEE-PRO system.

1. A secure environment for control of user records, information, and transactions (SECURIT): Provides a secure – limited access point for entering data into the restricted secure PII Database, for management of user data, creating user accounts, and reporting. The SECURIT web management interface requires the secure hypertext transfer protocol (HTTPS) to ensure encryption of transmitted data.
    a) PII database: is a dedicated secure limited access database, used to store protected PII.
        i) Secure: All communications to the PII database through SECURIT are encrypted. The database resides behind a firewall and cannot be reach from outside the OEAU.

ii) Limited access: this database is restricted not only by username and password but is also restricted to specified internal OEAU computers by IP address, so that only authorized users logging in at the OEAU from pre-specified computers may access/enter PII. At no time is outside access allowed to this database.

iii) Protected restricted PII (e.g. SSN) are encrypted at the time of data entry and double data entered for verification. All users regardless of their security level are blinded to this protected data, and it cannot be decrypted without the encryption key, housed in a safe, in a location separate from the OEAU. This type of data is generally collected for long term follow-up where it may be needed to be decrypted for select patients in order to search registries like the national death index to determine survival status of lost participants. In these instances, with appropriate approvals, the Database Administrator will decrypt this data in accordance with the approved retrieval specification.

b) User records: This functionality allows OEAU personnel, using specific computers within the OEAU, to create user records, enter user information into the PII database, and establish user web accounts in the separate user database. Allows the management of users and their data, including the ability to update a participant's preferred contact method, address, and participation status (e.g., no longer wishes to be contacted with respect to the PRO component of the study).

c) Information: This functionality allows the OEAU to record all participant contact, document any changes to the participant, and make any important notes related to the participant. Note that a paper based patient contact form will require completion by the patient. Site staff will need to fax the patient contact forms to the OEAU office. See section 11.2.

d) Transactions: SECURIT provides a reporting and monitoring interface to the PRO database, which is used to store non-PII patient reported survey responses.

i) Allows OEAU to monitor per patient form completion status using the tracking management facility. This facility reports on what data is currently expected from participants, CRAs, and the OEAU interviewers.

ii) Aggregate reporting: this series of reports allows the OEAU to monitor the distribution of patients over data completion methods and form completion methods (both overall and by site).

2. Database utility and control environment (PRO-DUCE): This utility interfaces with the main clinical database containing CRF/trigger data (Medidata RAVE), monitors the clinical database for events (eg., participant registrations, scheduled procedures, and other triggers) and establishes event scheduling. The system sets up e-mail reminders to CRAs,

participants [and SMS text message reminders, when applicable to the study], and OEAU personnel to ensure timely completion of surveys.

3. Web entry systems (PROWESs): a Web site where participants complete online surveys
    a) PROWESs provides a front facing web portal for participants to complete questionnaires and have those results stored in the PRO database.
    b) Secure site using HTTPS and requiring a username and password login.
    c) On login, user is presented with brief instructions; including approx. time for completion, number of questions to be completed in this session, any important information regarding this survey (including help and contact information)
    d) PROWESs is a one-way interface, data cannot be returned from the PRO-DB to the user.
4. Valet Interface and data entry system (PROVIDES).
    a) The PROVIDES system is a web interface that allows site CRAs to act as a valet and enter a participant's responses to a survey into the PRO database should the survey be completed on paper. This allows Site CRAs to enter forms completed by the patient on site.
    b) Secure site using HTTPS and requiring a username and password login.
    c) Which forms can be entered is restricted by username, site affiliation, and role, thus Sites RAs can only enter surveys predesignated as on-site data collection surveys and only for their own patients.
    d) On login, user is presented with brief instructions; is requested to select the protocol, case number, timepoint and verify the case Id by providing the participant birthdate.
    e) PROVIDES is a one-way interface, data cannot be returned from the PRO-DB to the user.

4.7.6 REDCap System to be used for Site Staff Surveys

The site staff roster and survey data collected for this study will be managed through REDCap (Research Electronic Data Capture). REDCap is a free, secure, web-based application designed to support data collection and storage for research studies. REDCap is fully compliant with HIPPA regulations. REDCap is a tool for the creation of customized, secure data management systems including web-based data entry forms, reporting tools, and a full array of security features including user and group based privileges with a full audit trail of data manipulation and export procedures. More specifically, REDCap will be used to distribute and collect the roster, baseline, 12-month follow-up, and 36-month follow-up NCORP site staff surveys. For this study,

the REDCap data management software system will be supported by Memorial Sloan Kettering Cancer Center (MSKCC). REDCap is maintained on MSKCC-owned servers that are kept in a locked server room with appropriate environmental modifications (e.g. proper ventilation, power redundancy and fault tolerance arrangement) and backed up nightly with some back-up tapes stored off-site. The MSKCC Information Systems group is responsible for applying all operating system patches and security updates to the REDCap servers. All connections to REDCap utilize encrypted (SSL-based) connections. Nationally, the REDCap software is developed, enhanced, and supported through a multi-institutional consortium led by Vanderbilt University.

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4.7.7 Qualitative Data

Focus Groups: This data will be stored using qualitative database software (NVivo) located on the MSKCC secure file network.

Patient Exit Interviews: This data will be stored using qualitative database software (NVivo) located on the MGH secure file network.

4.8 Instructions for Patients who Do Not Complete Baseline Survey and/or Do Not Start Assigned Study Intervention

If a patient is registered to Step 1 and does not complete the baseline survey within 30 days, the patient is considered off study and no additional data will be requested and patients will not be available to register to Randomization (Step 2).

5. Methodology

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5.1 Recruitment and Accrual

Participants will be recruited from NCORP Community and Minority/Underserved sites.

Screening may occur in accordance with local site policies and procedures. NCORP site staff may determine the following criteria by screening new patient lists/schedules, medical record reviews, or by approaching patients in clinic or via phone. Sites will provide weekly number totals (via a distributed REDCap survey) of smokers seen at this subcomponent site, patients ineligible (and reason), smokers approached to participate, and patients refused (and reason).

For potentially eligible patients, the site staff will also verbally confirm the following additional criteria (as it is less readily-discernable from chart review), via phone or in clinic (in accordance with local site policies and procedures):

- ECOG performance status (ineligible if 3 or above; eligible if 2 or below or no ECOG listed)
- Cancer diagnosis (type; i.e., lung) and date (subject step 0 registration must be within 124 days of diagnosis date)
- Age (must be 18 years or older)
- Language (must be English or Spanish speaking)
- Confirm they have smoked, even a puff, of a cigarette in the last 30 days
- Confirm they intend to receive their cancer care or monitoring at NCORP site (not a one-time consult or second-opinion)

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- Confirm they have telephone, e-mail access, and have access to the internet with a camera-enabled device (e.g., smartphone, tablet, computer, laptop with a webcam/camera).

The recommended process is as follows: Site staff to review new patient list or schedules, particularly the electronic medical records (EMR) of patients with upcoming visits to identify all patients who are identified as current smokers. This list can either be created using an automated report with information obtained from the relevant EMR fields (e.g., tobacco use) or manually by site staff. It is recommended that this list of potentially eligible patients be generated at least on a weekly basis. If information on the smoking status of patients is either missing or unknown, site staff should ask the patient about their current smoking status and update their record. The total count of current smokers onsite should be documented in the MSK REDCap Survey.

EMRs of current smokers should be reviewed for patients who are adult (≥ 18 years) and newly diagnosed (within past 4 months). Site staff should then approach these patients to confirm smoking status, receipt of care at the NCORP site, and email/web access, as well as any above-listed criteria that were unable to be discerned from chart review.

Only patients who are still eligible after this initial chart review step should be approached about the study. For patients who are deemed ineligible, or whom refuse to be fully screened upon approach, during this screening process, site staff will document reasons in the MSK REDCap Survey (see Section 5.1.1).

For patients who meet study criteria, the site staff will ask the patient if it is okay for central coordinating study staff to contact them with a brief, informational video about the study. Verbal permission may occur per sites usual practice (via telephone or in clinic). For patients who refuse, reasons for refusal will be documented and tracked in the study specific enrollment log. Patients who agree to be contacted about the study will be registered in OPEN (Screening Step 0). Patient contact information and screening characteristics (criteria collected above) will be entered into OPEN. Once a Patient's information is in OPEN, the virtual clinician referral (informational video) will be sent to the email address provided by EASEE PRO. It is highly recommended that site staff have an interested and eligible participant view the video at the time of visit and then also obtain written consent (OPEN Step 1).

Participants may choose to wait to sign consent, but give verbal consent to view the outreach recruitment video. Site staff will then follow-up with all patients who received a virtual clinician referral to assess their interest in participating in the study. Additionally, EASEE-PRO will prompt site staff when a patient has watched the virtual clinician referral video, to help facilitate recruitment efforts. Follow-up attempts may occur at upcoming clinic visits or via phone. It is recommended site staff make at least 3 outreach attempts (e.g., approaches in clinic, or voicemails), unless a refusal or enrollment decision is received first. For those who refuse or are ineligible for the study, reasons will be documented in RAVE and ongoing secure data transfers will be sent to MGH. Otherwise, interested, eligible patients will be given an informed consent form to review and sign, and will be consented to the study by the NCORP site staff.

Once a patient has signed written consent, they will be registered to OPEN Step 1 of the study and be prompted to complete the Baseline Survey in EASEE-PRO. After completion of the Baseline Survey, the patient will then be eligible to register to OPEN Step 2 of the study, which will randomize them to a treatment arm. Following OPEN Step 2, NCORP site staff will send patient contact information, study ID, dates of consent and randomization, provider information, and randomization arm assignment to MGH centralized study staff via the site's Enrollment Log REDCap project. MGH site staff will then email participants' provider an email notification of enrollment in the study.

5.1.1 Screening Procedure and Log

All smokers on new patient lists or schedules should be screened.

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Inclusion criteria are:

- Age >18
- Diagnosed within the past 124 days (Note: patient must still be in the 124 day window at step 0 registration.)
- Primary language English or Spanish
- ECOG performance score < 3

Patients who meet inclusion criteria are approached directly to confirm eligibility. To be eligible patients must:

- have smoked a cigarette in the past 30 days,
- plan to receive care at the site, and

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- have telephone, e-mail access, and have access to the internet with a camera-enabled device (e.g., smartphone, tablet, computer,

laptop with a webcam/camera). Sites will provide the cumulative total number of smokers seen at their site, the number of smokers approached, number of patients who are ineligible and refuse, and reasons for ineligibility and refusal. These totals will be provided to the MSK coordinating center via a REDCap survey.

Eligible patients are asked for consent to be contacted about the study. Those consenting are entered in OPEN and their OPEN ID is recorded. If the patient refuses to be contacted, the reason for refusal is recorded.

For patients who are eligible and provide written consent (OPEN Step 1), the site staff will enter sociodemographic, clinical, and contact data into their site specific REDCap Project Enrollment Log.

The data will be securely exported from REDCap and assessed for completeness at the DCC on an ongoing basis. Complete screens will be stored in the study database at the DCC. DCC staff will provide feedback to the site contact about any data quality issues via password-protected emails. The timing and frequency of the data exports will be coordinated between the site and DCC staff.

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5.1.2 Accrual Target

Sites participating in this trial should anticipate an accrual goal (i.e., patients who complete the baseline survey) of 25 cases per subcomponent site. In recognition of variability of patient flow across NCORPS, please contact the MGH Coordinating Center to discuss more feasible recruitment targets.

5.1.3 Brief Video Development

The original template script will be developed by the study investigative team and vetted by ECOG-ACRIN NCORP PI advisory committee chair. This approved script will be disseminated to participating sites. Sites will follow the brief video instructions on how to record and upload the video to the online study account. Final approval of the brief video will be conducted by Drs. Park, Ostroff, and Wagner. The approved video will be uploaded to the site's study account. The video will then be sent to the patient via the site's patient portal.

5.2 Enhanced Usual Care (EUC) (Arm A)

The EUC reflects the NCCN Smoking Cessation Guideline recommendations[2] and mirrors what is often delivered at cancer centers and community settings: assessment of smoking status, provision of quitting advice, and referral to the national NCI Smokers' Quitline for free counseling. Some participating NCORP community sites might provide additional tobacco treatment, which we will assess and document as well.

All participants randomized to EUC will have received the assessment of smoking status and provision of quitting advice through the screening and recruitment (virtual clinician referral) process, and will additionally be referred to the NCI Smoking Quitline (smokefree.gov). Referrals will be sent via email by EASEE PRO automatically upon randomization to the EUC arm see

supplemental Appendix P). Referrals will also be sent via mailed letter (see EUC Referral Letter Supplemental Appendix Z1A) by the MGH study staff to the address provided by EUC participants.

On an ongoing basis, the NCI Quitline will provide reports on participant engagement (date and duration of Quitline call) with quitline services. This interaction will be documented in Rave.

5.3 Virtual Intervention Treatment (VIT) (Arm B)

The VIT group will be offered up to 11 counseling sessions over approximately 6 months (approximate schedule: 4 weekly sessions through week 4; 4 biweekly sessions through week 12; and 3 monthly sessions through week 24) and up to 12 weeks of free FDA-approved combination NRT (patch and lozenge combined, or may elect to receive either option alone).

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VIT participants will receive their 11 counseling sessions via MGH TeleHealth, which connects providers to patients through virtual HIPAA-compliant videoconferencing technology including: phone, video, email, mobile applications and remote monitoring. These virtual visits are conducted via a videoconference platform that addresses clinical privacy and security (e.g., Zoom, Doximity, or other HIPPA-compliant platform). Participants can use this videoconference platform on their computer, tablet or smartphone. The counseling will be delivered by a study-designated tobacco treatment coach based at MGH. Since the counseling takes place virtually, participants will be emailed handouts that are traditionally provided as hardcopies in person. These handouts, distributed at the end of Session 1, include a pill diary, 11 Reasons for Cancer Patients to Quit Smoking, and Health Benefits When You Quit Smoking.

5.3.1 Terminology

Counseling structure and content: The initial session will last approximately 40 minutes; follow-up sessions will last approximately 15 minutes.

All counseling sessions will be structured in a 5 As, patient-centered format[16] and will include a variety of psycho-educational topics (see Table below).

Session #		Counseling Topics	Cessation Medication
1	Weekly	• Smoking assessment • Barriers to quitting and strategies to enhance readiness • Medication education and assistance	• Introduction to NRT & use
2		• Cancer related care and distress, care team communication • Assess medication adherence and managing side effects • Knowledge about quitting at the time of diagnosis	• NRT question/side effects
3		• Coping with cravings and withdrawal • Introduction to social support • Introduction to mindfulness	• Assess NRT use & 2nd dose
4		• Introduction to Stress management – deep breathing exercises	• Review 2nd dose/NRT fit
5	Bi-Weekly	• Introduce beginning with appreciations	• Assess

Session #		Counseling Topics	Cessation Medication
		• Values clarification exercise • Smoke free home and car • Nicotine and addiction • Pleasurable behaviors	adherence during treatment
6		• Smoking associated stigma and negative self-talk • Stress Management 2 – battery exercise • Weight gain concerns • Review values clarification exercise	• Assess adherence during/post treatment
7		• Risk of other forms of tobacco • Types of social support • Stress management 3 – stress signs and coping	• Assess adherence during/post treatment
8		• Rewards and financial costs of smoking • Sleep and self-care • Picturing positive change • Breath awareness	• Review NRT completion
9	Monthly	• Fear of recurrence • Managing physical symptoms	• Discuss if any continued NRT
10		• Managing slips and relapses during following treatment • Stress management 4 – single pointed focus exercise	• Discuss if any continued NRT
11		• Review overall smoking progress • Finalize smoking goals, relapse prevention • Post treatment Support	• Discuss if any continued NRT

During the initial session, the tobacco counselor:

1. introduces the study and provides an overview of the goals and structure of the program;
2. gathers a comprehensive smoking history;
3. assesses participants' concerns about smoking;
4. offers a personalized message to quit smoking;
5. assess participants' importance and confidence to quit and pros and cons for quitting and continuing to smoke; and
6. evaluates participants' readiness to quit.

The tobacco counselor tailors participants' quit plan based on their quit stage, which falls into one of 3 branching logics:

1. not ready to quit or make changes;
2. not ready to quit, but ready to make changes; and
3. ready to quit.

The tobacco counselor assists the participant in setting a goal for the week and schedules a follow-up session for the next week. Participants then receive 3 weekly sessions, 4 biweekly sessions, and 3 monthly (booster) sessions. The structure of each follow-up treatment session mirrors the initial weekly sessions, wherein the

tobacco counselor assesses quit progress and cancer care treatment, examines importance and confidence to quit, monitors and intervenes on medication use, and tailors quit advice and strategies based on participants' quit readiness; however, each session also introduces novel topics identified to be relevant concerns among cancer patients who are trying to quit

5.3.2 Provision of medication: Nicotine Replacement Therapy (NRT)

At the initial counseling session, the tobacco counselor will discuss use of NRT. Using a decision tree (see Appendix VII and Appendix VIII) the tobacco counselor will review contraindications of the patch and lozenge. The lead CRA and oncology clinicians will be informed, via password protected emails sent by the tobacco counselor, that over-the-counter nicotine replacement therapy (patch/lozenge) medication was dispensed as a means of collaborative care; this is the standard of care for nicotine replacement therapy. This method was reviewed by the ECOG-ACRIN regulatory officer and MGH IRB and it was determined that oncology clinician notification prior to treatment was not needed. The coordinating site staff will inform the NCORP oncology provider of the NRT assignment and participants will be offered an initial 4-week supply of nicotine replacement patches and lozenges. Although use of medication will be promoted, it is not required for study participation. Medication will be administered according to the USPHS guidelines[16]. Two 4-week refills will be discussed with the patient and dispensed accordingly. Side effects will be monitored and discussed weekly with the MPIs. Treating clinicians will be contacted for NRT-related questions/concerns. The tobacco counselor will adjust the NRT dose to control withdrawal symptoms and minimize adverse effects. NRT will be housed at the MGH and mailed to participants by MGH study staff. NRT has been safely distributed through quit lines in this way. [85, 127] NRT kits will include instruction and patient information sheets in English and Spanish written for a 6th grade reading level. Use of NRT will be supported during each session.

5.4 Patient Assessments (Arms A & B)

Patients assigned to both arms will complete surveys in the EASEE-PRO system at the following time points:

- Baseline (Supplemental Appendix A)
- 3 months (Supplemental Appendix B)
- 6 months (Supplemental Appendix C)

The baseline survey (Supplemental Appendix A) should take approximately 20 minutes to complete. The 3 month (Supplemental Appendix B) and 6 month (Supplemental Appendix C) survey should each take approximately 15 minutes to complete. While the preferred method of follow-up data collection is participants completing the surveys through the EASEE-PRO system, study staff may contact participants to assist with data collection over the telephone. If the study participant prefers a paper copy of the survey, study staff may mail participants surveys to be completed and returned.

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5.5 Adverse Event Reporting Requirements

All adverse event grades described throughout this protocol and all reportable adverse events will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.5.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.5.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans [(in this protocol Nicotine Replacement Therapy (NRT)], whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol agent (NRT), using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to the Nicotine Replacement Therapy (NRT)
Unlikely	The AE is *doubtfully related* to the Nicotine Replacement Therapy (NRT)
Possible	The AE *may be related* to the Nicotine Replacement Therapy (NRT)
Probable	The AE is *likely related* to the Nicotine Replacement Therapy (NRT).
Definite	The AE is *clearly related* to the Nicotine Replacement Therapy (NRT)

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent (NRT). An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol (please refer to Section 8) or drug package insert.

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5.5.3 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at http://ctep.cancer.gov, so that ECOG-ACRIN and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the FDA (1-800-FDA-1088)

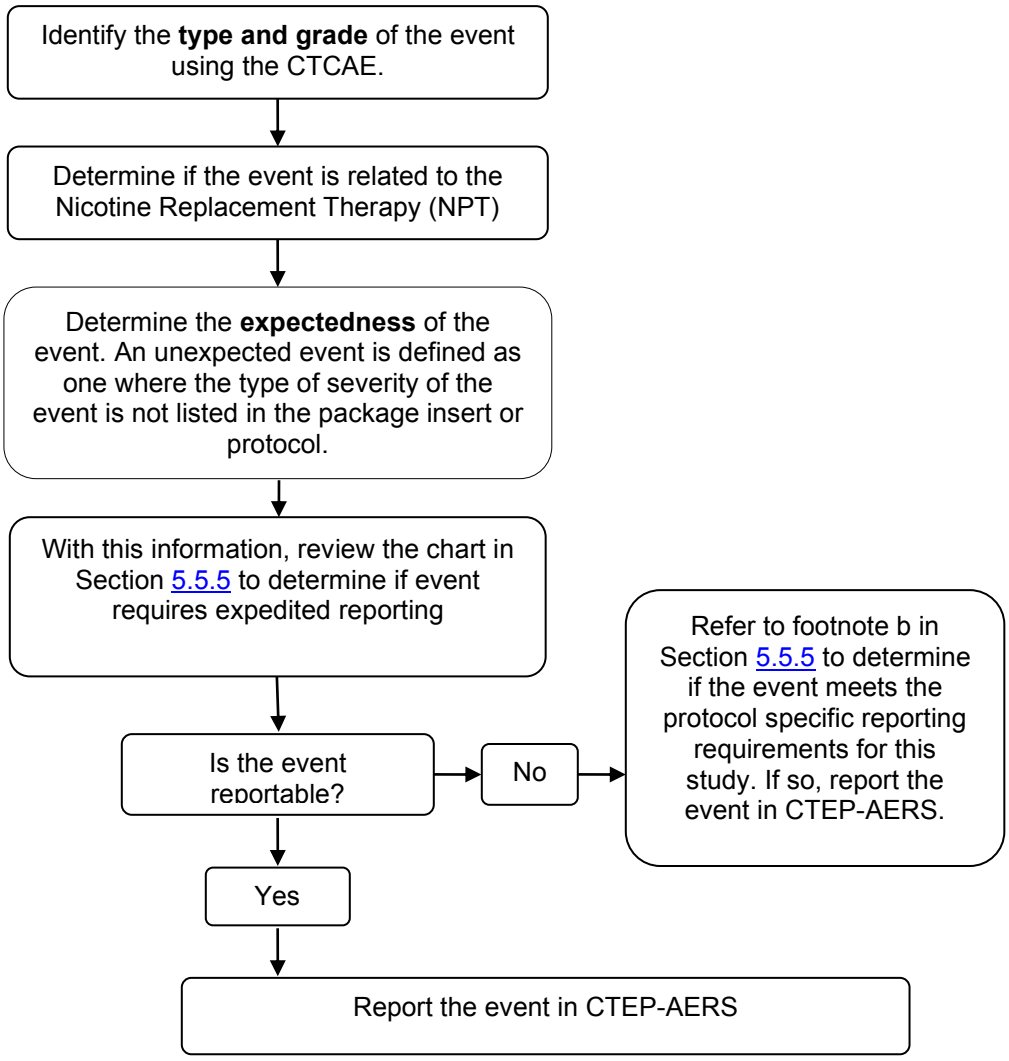
For this study, an electronic report MUST be submitted via CTEP-AERS immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the FDA (800-332-0178) in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EAQ171CD and outline the specific expedited adverse event reporting requirements for study EAQ171CD.

5.5.4 Steps to determine if an event is to be reported in an expedited manner – Arm B only



5.5.5 Expedited Reporting Requirements for Arm B on protocol EAQ171CD

Commercial Agents: Over-The-Counter Nicotine Replacement Therapy (NRT) - patch/lozenge

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only (NPT) – Arm B

Attribution	**Grade 4**		**Grade 5[a]**		**ECOG-ACRIN and Protocol-Specific Requirements**
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death while on study treatment (NRT) or within 30 days of the last dose of NRT requires both routine and expedited reporting, **regardless of causality**. Attribution to NRT or other cause must be provided.

NOTE: A death due to progressive disease of the patient's cancer should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be included within the CTEP-AERs report.

NOTE: **Any death that occurs > 30 days after the last dose of NRT and is attributed possibly, probably, or definitely to the NRT must be reported within 7 calendar days of learning of the event**.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

5.5.6 Other recipients of adverse event reports and supplemental data

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.6 Duration of Intervention

Patients assigned to Arm B will receive up to 12 weeks of NRT. NRT will be dispensed in 4-week increments.

Patients assigned to Arm B will receive counseling for approximately 6 months.

Patients will receive protocol counseling and NRT (if randomized to Arm B) unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EAQ171CD Forms Packet.
- Patient withdraws consent.

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5.7 Duration of Study and Follow-up

Patients in this study may be followed for up to one year.

6. Measurement of Effect

6.1 Biochemical Samples

6.1.1 Primary effectiveness outcome

The primary outcome is 7-day point-prevalence tobacco abstinence at 6-months follow-up, confirmed biochemically by saliva cotinine or expired air CO. Point-prevalence is biochemically verifiable and highly correlated with continuous and sustained abstinence.[168]

6.1.2 Secondary effectiveness outcome

7-day point-prevalence tobacco abstinence at 3-months follow-up is a secondary effectiveness outcome, confirmed biochemically by saliva cotinine or expired air CO. Point-prevalence is biochemically verifiable and highly correlated with continuous and sustained abstinence.[168]

6.1.3 Definition of biochemically-confirmed quit

6.1.3.1 **Saliva samples**

Saliva samples will be collected from all subjects who report being quit at 3- and/or 6-month follow-up who do not report concurrent NRT or e-cigarette use. Saliva samples will be tested for cotinine, which is a chemical the body makes when exposed to nicotine.

6.1.3.1.1 Saliva cotinine scores of < 15ng/ml[167, 168] will be considered biochemically-confirmed quit.

6.1.3.2 **Expired air CO samples**

Expired air CO breath tests will be offered to all subjects who report being quit at 3- and/or 6-month follow-up who also report concurrent NRT or e-cigarette use. The expired air tests will show carbon monoxide levels in the breath.

6.1.3.2.1 Expired air CO samples with a reading of < 10ppm[168] will be considered biochemically-confirmed quit.

6.2 Patient assessments

6.2.1 Secondary smoking outcomes are commonly used in tobacco cessation trials and in our previous work.[127] Reduction in smoking is important as most adult smokers reduce smoking as they try to quity[206]; self-reported smoking status will additionally be used as it has been reported that deception of smoking status classification among cancer patients is low.[207]

6.2.1.1 Self-reported quit status

Patients will be asked on the 3- and 6-month follow-up surveys, how long it has been since they last smoked a cigarette, even one or two puffs. “Current smoker” will be defined as smoking a cigarette, even one or two puffs, in the past 7 days. (See Supplemental Appendices B: 3-

month Survey and C: 6-month Survey). This will be used to generate secondary outcomes of self-reported 7-day point prevalence abstinence, continuous and sustained abstinence (See Section 2.3 for definitions).

6.2.1.2 Significant reduction in daily smoking

Patients will be asked at baseline, 3-, and 6-month follow-ups, in the past 30 days, (1) on how many days they smoked cigarettes, and (2) how many cigarettes per day they typically smoked. “Significant reduction” will be defined as a > 50% reduction in cigarettes per day from baseline to 3- and 6-month follow-ups. (See Supplemental Appendix A: Baseline Survey)

6.2.2 Exploratory objectives – Moderators and Mediators: We will collect information on the following baseline factors and modifiable characteristics that may affect the association between treatment group and effectiveness outcomes. The following factors have been selected from the theoretical models, the Self-Regulation Model (SRM)[147,148] and the Health Belief Model (HBM)[149], that have informed this intervention, as well as based on our previous research.[127]

6.2.2.1 **Sociodemographics**

Patients will be asked information about their sociodemographic characteristics (i.e., sex, age, marital status, race/ethnicity, education level, health insurance) at baseline. Financial burden will be assessed using 3 items from Dr. Park’s national health insurance survey.[205]

6.2.2.2 **Medical history**

Alcohol use

Patients will be asked about alcohol use using the Alcohol Use Disorders Identification Test (AUDIT-C), [194] a three-item brief screening test for heavy drinking or alcohol dependence.

6.2.2.3 **Smoking history**

Patients will be asked information about their smoking history (i.e., # of years smoked, daily smoking rate, 24-hour quit attempts, other tobacco/nicotine use, current and past use of tobacco treatments) using items adapted from the Cancer Patient Tobacco Use Questionnaire (C-TUQ), developed by the NCI-AACR Cancer Patient Tobacco Use Assessment Task Force designed to capture information about tobacco use for cancer patients and survivors. [195, 196]Nicotine dependence will be assessed using the 2-item Heaviness of Smoking Index from the Fagerstrom Test for Nicotine Dependence (FTND), which has predictive validity with the FTND. [171-173]

6.2.2.4 Quality of life and emotions

Emotional distress will be assessed using the NCCN's one-item Distress Thermometer that asks the respondents to rate their current level of distress on a scale ranging from "0" (No distress) to "10" (Extreme distress).[174,175]

Coping will be assessed using a 1-item, 10-point scale asking how the subject has been able to cope with the current stress in their life, ranging from "0" (Not at all able) to "10" (Very much able).

Anxiety will be assessed using the PROMIS Item Bank Emotional Distress-Anxiety-Short Form 4a which was developed for the general adult population and which evaluates anxiety symptoms (e.g., "My worries overwhelmed me") over the past 7 days on a 5-point Likert scale with raw scores ranging from 4-20. [188, 198]

Depression will be assessed using the PROMIS Item Bank Emotional Distress-Depression Short Form 4a which was developed for the general adult population and which evaluates depression symptoms (e.g., "I felt hopeless") over the past 7-days on a 5-point Likert scale with raw scores ranging from 4-20. [188, 198]

If a patient is determined as at acute risk, the study investigators will reach out to the patient's oncology team immediately to recommend a visit to the emergency room.

The tobacco counselors will be trained to assess suicidality and be supervised by licensed psychologists to assess the best real-time approach to the safety issues that may arise.

We will include a standard disclaimer at the end of each study survey that stipulates that survey responses are not reviewed in real time. We will also provide guidance for individuals who feel that they need additional psychosocial support and possibly mental care:

"We do not review these surveys in real time. Many individuals in a similar situation may feel distressed, and the study investigators encourage you to speak to your cancer care team to find out about local psychosocial support services. Your well-being is important to us. The American Psychosocial Oncology Society (APOS) helpline and chat services are available to anyone who may need psychosocial support for coping with cancer and its treatment (1-866-APOS-4-HELP). If you are feeling highly depressed or anxious, you may call and speak to a professional hotline counselor at 800-273-8255."

6.2.2.5 Cancer beliefs

Cancer stigma will be measured using the Internalized Stigma and Constrained Disclosure subscales of the Lung Cancer Stigma Inventory (LCSI). These subscales have

been modified in wording for use in the general cancer population. The LCSI has preliminary psychometric evidence demonstrating reliability and validity. [199, 200] Items assess to what degree the subject has experienced certain situations since their cancer diagnosis (i.e., "I have been careful who I've told about my cancer"), and are scored on a 5-point Likert scale ranging from "Not at all" to "Extremely".

6.2.2.6 Smoking beliefs

Quit-smoking medication beliefs will be assessed using a modified version of the Attitudes about Nicotine Replacement Therapy Scale (ANRT-12)[201], which asks about the subjects' thoughts on the benefits of using nicotine replacement therapy (i.e., "NRT is easy to use") on a 5-point agreement scale ranging from "1" (Strongly disagree) to "5" (Strongly agree).

Self-efficacy to quit and importance of quitting will be assessed using two 1 item, 10-point measurements[161] ranging from "0" (Not confident at all; or; Not important at all) to "10" (Very confident; or; Very important).

Perceived benefits of quitting smoking will be evaluated using 5 questions about the benefits of quitting for decreasing risk for second primary cancer or recurrence and increasing cancer treatment efficacy, scored on a scale from "0" (Not at all) to "10" (Very much) (i.e., how much does quitting smoking reduce your chances of developing your cancer again?").[87]

Quit-smoking medication beliefs will be assessed using a modified version of the Attitudes about Nicotine Replacement Therapy Scale (ANRT-12)[201], which asks about the subjects' thoughts on the benefits of using nicotine replacement therapy (i.e., "NRT is easy to use") on a 5-point agreement scale ranging from "1" (Strongly disagree) to "5" (Strongly agree).

Stigma will be assessed using a 6-item scale measuring stigma related to being a smoker, which has been modified from a previously used measuring smoking related stigma among smokers with comorbid behavioral health conditions.[208] Items ask how strongly subjects agree or disagree with statements such as "I have avoided telling others that I am a smoker" or "I have worried that others will view me unfavorably because I am a smoker".

6.2.2.7 Physical symptoms

Cravings will be assessed using a single item from the Mood and Physical Symptoms Scale (MPSS)[202] which evaluates urges to smoke over the last 24 hours on a scale from "0" (Not at all) to "5" (All the time).

6.2.2.8 **Environmental influences**

Level of second-hand smoke exposure will be assessed by evaluating the number of smokers in the household and existence of a household smoking policy using 2 questions from the 2008 National Social Climate Survey of Tobacco Control.[187]

Perceived social support will be assessed using the PROMIS Item Bank Emotional Support 4a Short Form[188] [203] which was developed for the general adult population and which evaluates perceived feelings of being cared for and valued as a person (e.g., "I have someone who will listen to me when I need to talk") on a 5-point Likert scale ranging from "1" (Never) to "5" (Always).

Perceived provider support will be assessed using the Patient Reported Oncology Provider 5As Delivery, a Yes/No scale asking subjects if their cancer doctor or nurse has delivered any of the 5A's (i.e., "Advised you to quit smoking cigarettes") in a recent consult. [204]

6.2.3 Exploratory objectives – implementation outcomes: We will assess patient satisfaction with the proposed virtual treatment delivery modality and intervention content. Patient feedback will be taken into consideration in further refining of intervention protocols, and is important for gathering key information on intervention delivery and potential for implementation in real-world situations.

6.2.3.1 **Acceptability**

Satisfaction with various aspects of the tobacco treatment program will be evaluated through participant survey responses and post-treatment interviews.

6.2.3.1.1 Surveys

At the 6-month survey (Supplemental Appendix C), participant satisfaction will be assessed using a mixture of multiple-choice question items: (1) To what extent has the tobacco treatment program met your needs? (2) Did you get the kind of smoking cessation assistance that you wanted; (3) How helpful was the smoking cessation assistance?; (4) How would you rate the quality of the assistance you received? (5) Would you recommend this program?; as well as open-ended free-text items about aspects of the program they found the most/least helpful, challenges faced to participation, and any recommendations for additional topics or programs that would have improved their experience at this time.

6.2.3.1.2 Semi-Structured Individual Patient Interviews

Following completion of their 6-month follow-up surveys, 40 intervention VIT participants will be randomly selected (based on smoking status) to participate in in-depth exit interviews. Using a semi-structured interview guide, study staff will conduct these virtual interviews. All participants will be asked open-ended questions about a) program engagement: (1) What did you think of the clinician video that you received encouraging you to enroll in the study?, (2) reasons for it being helpful or not; b) counseling: (1) What counseling components/NRT did you find the most helpful? Why?; (2) What counseling components/NRT did you find the least helpful? Why?; c) NRT medication dose and access: (1) Please tell me if you used any NRT medication. How much? How difficult/easy was it to access?; d) logistics and overall impressions: (1) What were some of the challenges you faced to participating?, (2) Probe: virtual assessments, mailed NRT, etc.; e) videoconferencing delivery: (1) Please tell me about your experience connecting with your tobacco counselor via a virtual screen. What did you like about it? Dislike about it? Difficulties to using the program? Benefits to using the program?; and f) cessation advice and assistance received from oncology care team.

6.2.4 Patient Remuneration

Patient participants will receive $20 in gift cards for each survey completed (baseline, 3 months, and 6 months; 3 total possible). Subjects who complete a biospecimen sample (saliva or CO breath test) will receive $40 in gift cards for each sample completed (3mo., and 6mo; 2 total possible). Subjects who are randomly selected for an exit interview will be provided $20 in gift cards for participation (1 possible). Therefore, subjects have the opportunity to receive up to $160 in remuneration. (See Supplemental Appendices G-M for Patient Remuneration Letters). The central coordinating site (i.e., MGH) will be responsible for managing the disbursement of gift cards directly to participants.

6.3 NCORP Site Staff Assessments

At the practice (organizational) level, little is known about the acceptability of integrating tobacco treatment delivery into routine oncology care. In this trial,

implementation outcomes will be assessed with mixed methods using qualitative (focus group interviews) and quantitative (surveys) data to be collected from a subset of Site PI, CCDR Leader, and other oncology clinicians and research administrative staff from each participating NCORP site (See Section 3.1). As shown in the NCORP Site Staff Schema (p 7), surveys will be collected at baseline (pre-patient participant enrollment, and then again at approximately 12 and 36 months following baseline).

Rev. Add4

The NCORP Site Staff assessments will be managed by Dr. Ostroff and her study designated research assistant. The baseline, 12 and 36 month follow-up surveys will be collected using REDCap, (Research Electronic Data Capture), a data management software system supported by the Memorial Sloan Kettering Cancer Center (MSKCC) Information Systems group.

Staff Survey of Site Characteristics, Organizational Readiness and Perceived Tobacco Treatment Feasibility, Acceptability and Appropriateness:

As described in Section 3.1, the CCDR Leader and site PI from each participating NCORP site will identify a subset of approximately 10 clinicians (nurses, oncologists) and administrative staff (site coordinators, support staff)] to provide data about the implementation of tobacco use assessment and treatment. Data collection will include qualitative (focus group interviews) and quantitative (survey) research methods. The baseline site staff surveys will be administered prior to the first site patient enrollment. Post surveys will be conducted approximately 12 and 36 months post the baseline survey. The group interview will be conducted at the 36-month follow-up as well. (See Supplemental Appendices D: Baseline Site Staff Survey, E: 12-month Site Staff Survey, F: 36-month Site Staff Survey).

The content of the mixed methods data collection will focus on several implementation outcomes including Appropriateness, Feasibility, Acceptability, and Sustainability. The focus group interviews will last for approximately 45-60 minutes, and the surveys will require approximately 15 minutes for completion. Site staff participants will be remunerated $100 incentive in total for completion of each wave of pre- and post-trial surveys ($20 per survey) and focus group interview ($40).

6.3.1 NCORP Site Characteristics:

At the time of site registration, the CCDR Lead or their designee(s) will complete the site rostering survey. This survey requests that applicable CTEP IDs be grouped into larger practice groups with shared providers, populations served and services offered. For each practice group, the CCDR Lead or their designee(s) will complete items regarding practice characteristics including safety net designation, minority/underserved NCORP status, geographic site location, practice volume, provider mix and ownership, and tobacco cessation services that are available for patients treated at each practice group.

6.3.2 Organizational Readiness for Implementing Tobacco Use Assessment and Treatment:

Organizational readiness for the treatment of tobacco use in the context of cancer care and the feasibility of implementing the various

components of the tobacco treatment interventions (EUC and VIT) will be assessed by participating staff pre- and post-trial. Perceptions of site organizational readiness will be measured using the 7-item Organizational Readiness for Implementing Change (ORIC, Shea et al 2014) measure assessing two subscales, change commitment and change efficacy, on a 5-point ordinal scale ranging from 'Agree' to 'Disagree'. A total organizational readiness score, and subscale change commitment and change efficacy score are created. [144,145]

6.3.3 Perceived Tobacco Treatment Feasibility, Acceptability and Appropriateness:

Staff participants will also rate perceived feasibility, acceptability and appropriateness of the various tobacco treatment interventions being tested in this trial (Weiner et al, 2017) on a 6-point ordinal scale ranging from 'Strongly Disagree' to 'Strongly Agree' Aggregate and intervention-specific summary scores for tobacco treatment feasibility, acceptability and appropriateness are derived. The NCORP Staff Survey will take approximately 20 minutes to complete and will be administered at baseline, defined as after site registration and before the first patient is registered, and at approximately 12 and 36 months after site registration (See Supplemental Appendices D: Site Staff Baseline Survey, E: Site Staff 12-month survey and F: Site Staff 36-month survey).

6.3.4 Focus Group Interview

The focus group interview will assess implementation processes including barriers and facilitators for sustaining tobacco treatment as routine cancer care practice in the NCORP site. The question probes for our implementation-focused focus group interviews will be guided by the Consolidated Framework for Implementation Research (CFIR)20 and will address the 1) the intervention, 2) inner setting, 3) outer settings, 4) individuals involved, and 5) the process for sustaining tobacco treatment following trial completion.

The focus group interview will be conducted using videoconference software (e.g., Zoom, Doximity, or other HIPPA-compliant platform). enabling audio recording of the focus group interview for subsequent coding of primary implementation themes. The focus group interviews will be scheduled at the convenience of the NCORP staff participants and is expected to take about 45-60 minutes to complete. Focus group interviews will take place at the end of the trial (after patient participant enrollment is closed and 36-month follow-up surveys completed)

Rev. Add2

Focus group Interviews will be recorded, transcribed and analyzed using NVivo qualitative software. Content analyses will be conducted by the two RAs and overseen by Drs. Park and Ostroff. The coders will meet to develop the thematic framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high level of reliability (Kappa= >0.80) is established. Drs. Ostroff and Park will provide an expert review of the analyses.

The qualitative and quantitative findings will provide detailed initial data on implementation processes that will inform subsequent testing of multi-level implementation strategies for broad national dissemination into community cancer care settings.

Rev. Add4

6.3.5 Monthly Meeting Minutes Data

We will conduct content analysis of monthly meeting minutes with CCDR Leaders and other NCORP site staff to summarize engagement of participating sites. We will explore indicators of engagement (quantity and quality) by documenting the proportion and representativeness of participating stakeholders (Site PIs, CCDR leads, oncology nurses) engaged in monthly meetings, how (approaches used and level of engagement) and when (which parts of the research process) stakeholders engage, and what they did to facilitate integration of tobacco assessment and treatment in cancer care delivery (strategies for identifying current smokers).

Rev. Add3

6.4 Cost

We will assess NCORP staff time required to screen all patients for smoking status and identify all current smokers. Each CCDR Leader will fill in costs, including local staff effort (time x base salary) related to eligibility screening. This data will be collected via the weekly Patient Screening Log (Appendix Z2D) All staff time costs will be estimated based on national average wages by job type.

Counseling delivery costs will include the counselor's time, including efforts to contact patients, as well as supervisors' time, all of which will be tracked within study databases.

Rev. Add2

NRT delivery costs will be estimated using national average retail prices. Overall costs will be standardized per randomized study participant across sites for the cost-effectiveness.

6.5 Treatment fidelity/adaptations

We will collect data about EUC fidelity by asking patients at follow-up whether they were advised to quit by their oncology providers and whether they were referred to the Quitline or other tobacco cessation counseling services. All trial participants will be given a Smokefree Study 2.0 brochure about the NCI Quitline providing instructions to call for tobacco treatment. The MGH Coordinating Center will be responsible for providing and documenting distribution of the Quitline brochure to all Smokefree Study 2.0 Trial participants. The Quitline call center routinely asks participants to identify how they found out about the Quitline. For the duration of this trial, the Quitline will record whether callers identify the Smokefree Study as the source of referral. In addition, the Quitline routinely collects limited demographic information, including caller's telephone number, which will serve as the caller identifier allowing us to link the Quitline database with Smokefree Study 2.0 participants. Twice yearly, the MGH Coordinating Center will send an Excel list of Smokefree Study 2.0 participant study IDs with corresponding telephone numbers to the NCI Quitline Call Center requesting lookback for any caller NCI Quitline contact within the past 6 months. In other words, a data manager from the NCI Quitline Call Center will review the data every 6 months to see if a person who entered the study on Smokefree has also contacted the NCI Quitline. The MGH Coordinating Center will record the

date(s) and duration of Quitline contact into Smokefree Study 2.0 Access database. The NCI Quitline will be listed in the Research Authorization.

For VIT intervention participants, the number of contacts, session content and completion, and NRT dispersal will be documented. For EUC participants, information on the number of quitline sessions and NRT dispensed will be obtained from quitline vendors. MGH research staff will also record the percentage of virtual clinician referral videos (brief videos) opened. Patient engagement will be assessed by documenting dispensal and patient-reported NRT use. All of the treatment fidelity of this data will be monitored by MGH research staff and recorded in an Access database (see MGH protocol).

Rev. Add3

Following Stirman and colleagues' recommendations (2013),[165] we will track any intervention modifications (e.g., counselor adherence to the VIT manual, medication changes).

6.6 Reach and Adoption

Site coordinators will document the percentage of all current smokers who participate at each site. Using a Patient Screening Log (Appendix Z2D), we will assess the number of eligible patients who were approached and the number of eligible patients who enrolled. Reasons for ineligibility, refusal, and characteristics of refusers, ineligibles, and drop outs will be documented. Consistent with the hybrid effectiveness implementation trial design, we will collect characteristics of ineligibles and refusers to inform future dissemination efforts such that we can evaluate the critical question of whom we are not reaching for tobacco treatment.

The MGH RA will track uptake and utilization on the sites that are engaged in study activities (i.e., participation in monthly calls and patient program enrollment).

7. Study Parameters

7.1 Patient surveys and samples schedule

Item	Baseline	3 months follow-up	6 months follow-up
Baseline survey (Supplemental Appendix A)	within 30 days of enrollment		
Vital status update		-14 days of target date	
3 month survey (Supplemental Appendix B)		within -7 to +49 days of target date	
3 month sample (saliva)[1]		within 30 days of 3mo survey completion	
3 month sample (CO)[1]		within 30 days of 3 mo survey completion	
Vital status update			-14 days of target date
6 month survey (Supplemental Appendix C)			within -7 to +90 days of target date (VIT subjects: must occur *after* counseling session 11 has a final status)
6 month sample (saliva)[1]			within 30 days of 6 mo survey completion
6 month sample (CO)[1]			within 30 days of 6 mo survey completion
Interview			within 90 days of 6 mo survey completion

[1] Participants who self-report smoking abstinence of at least 7 days at month 3 and/or month 6, on either the survey or during survey outreach, will be requested to provide saliva for cotinine assessments (Section 10.1). Saliva samples will be tested only for cotinine. To avoid false-positives, participants who report use of NRT or e-cigarettes within the last week will be offered the opportunity to instead complete an expired air CO sample (Section 10.2)

7.2 Site staff surveys schedule

Rev. Add3

Item	Baseline	12 - 15 months post Baseline Survey	Approximately 36 months post Baseline Survey
Baseline survey (Supplemental Appendix D)	Prior to first patient enrollment		
12-month survey (Supplemental Appendix E)		X	
36-month survey (Supplemental Appendix F)			After last patient is enrolled
Focus Group Interview			To be held after initiation of 36 month survey collection

Rev. Add4

7.3 Randomization groups schedule (approximate)

	Week	EUC (Control)	VIT (Intervention)
Randomization	0	Quitline referral email	TeleHealth test call
Month 1	1		Session 1 + 1st medication fill
	2		Session 2
	3		Session 3
	4		Session 4
Month 2	5		Session 5 + 2nd medication fill
	6		
	7		Session 6
	8		
Month 3	9		Session 7 + 3rd medication fill
	10		
	11		Session 8 + 3 month follow-ups
	12	3 month follow-ups	
Month 4	13		Session 9
	14		
	15		
	16		
Month 5	17		Session 10

	Week	EUC (Control)	VIT (Intervention)
	18		
	19		
	20		
Month 6	21		Session 11 + 6 month follow-ups
	22		
	23		
	24	6 month follow-ups	
Study completion			Exit interviews

Rev. Add2

7.4 Data collection schedule during eligibility screening, recruitment, and enrollment

	Pre-screen[4]	Step 0[5]	Step 1[5]	Step 2[5]
Sex [2]		X		
Age* [2]		X		
Race [2]		X		
Ethnicity [2]		X		
Language* [2]	X	X		
Cancer diagnosis* [2]		X		
Cancer stage [1,2]		X		
Date of diagnosis* [2]	X	X		
Smoking status* [3]	X	X		
Care at NCORP site* [3]		X		
Email/web access* [3]	X	X		
ECOG PS* [1]	X			
Reasons for ineligibility [2]	X	X	X	
Reasons for refusal [3]	X	X	X	
Contact information [3]			X	
Randomization group				X

* Characteristics from eligibility criteria

1. Will only be collected if the information is available
2. May be patient self-reported or pre-screened from medical records
3. Must be patient self-reported
4. This data will be transmitted via MSK REDCap survey.
5. This data will be entered in OPEN, RAVE and REDCap Enrollment Log.

7.5 Data collection schedule for patient enrollees (surveys)

	Baseline	3 Mo.	6 Mo.
Patient Enrollees			
Point-prevalence tobacco abstinence		X	X
Self-reported tobacco abstinence		X	X
Cigarettes per day	X	X	X
24-hr quit attempts		X	X
Sociodemographics	X		
Smoking history	X	X	X
Cancer variables	X		
Medical history	X		
Quality of life	X	X	X
Cancer and smoking beliefs	X	X	X
Physical symptoms	X	X	X
Environmental influences	X	X	X
Acceptability			X

7.6 Data collection schedule for site staff (surveys)

	Baseline[1]	12 Month	36 Month
Site Staff			
Adoption	X	X	X
Appropriateness	X	X	X
Treatment fidelity	X	X	X
Cost		X	X
Feasibility	X	X	X
Site characteristics	X	X	X
Penetration/reach		X	X
Sustainability	X	X	X

Rev. Add3

1. Site staff must complete baseline survey prior to first patient enrollment

Rev. Add4

2. CCDR Leads will complete Site Characteristics at approximately 12 and 36 Month Follow-up (Appendices E and F)

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

8.1 Nicotine trans-dermal patch (NSC #5065)

8.1.1 Description

Nicotine transdermal patches are supplied as transdermal patches for application to the skin containing nicotine as the active ingredient. The patches are available in dose concentrations of Nicotine 21mg delivered over 24 hours; Nicotine 14mg delivered over 24 hours; or Nicotine 7mg delivered over 24 hours.

Depending on specific commercial product, the patch may also contain the following inactive ingredients (not all inclusive) ethylene vinyl acetate-copolymer, polyisobutylene and high density polyethylene between clear polyester backings. Please refer to commercial package insert" as necessary.

8.1.2 Pharmacology

Mode of Action:

Absorbed systemically; binds to nicotine receptors thereby reducing withdrawal symptoms (including nicotine craving) associated with smoking cessation.

Absorption: 68%

Duration: 24 hr

Peak plasma time: 8-9 hr

Peak plasma concentration: 5-17 ng/mL (average)

Elimination Half-life: 3-4 hr

Excretion: Urine

8.1.3 Storage and Stability

Store at 20-25°C (68-77°F).

8.1.4 Administration

See package insert for complete details for specific product used.

Dosing is determined by the number of cigarettes smoked daily when the patch is started.

>10 cigarettes per day **AND** weight >45 kg

- Start with the highest dose nicotine patch (21 mg/day) for six weeks, followed by 14 mg/day for two weeks, and finish with 7 mg/day for two weeks.

≤ 10 cigarettes per day **OR** weight < 45 kg

- Start with the medium dose nicotine patch (14 mg/day) for six weeks, followed by 7 mg/day for two weeks.

Patient is advised to pick "quit day" and begin using nicotine transdermal patches on that day and simultaneously stop smoking. They may continue to smoke if not immediately able to/willing to stop smoking, however every effort should be made to decrease the amount smoked while on replacement therapy, as continued smoking can increase adverse effects. It is important for patients to complete the full program, but some may need to use NRT for longer periods to keep from smoking.

Apply to clean, dry, non-hairy area of skin (typically upper arm or shoulder), being sure to rotate sight placed. Do not use the same sight for two consecutive applications. Try to not repeat any sight more than once in a 7 day period.

Apply new patch upon awakening and wear patch for 24 hours. In the event patient experiences vivid dreams or insomnia, remove patch before bedtime.

Do not cut patch, as this will result in uneven administration of medication and can increase risk of adverse effects and decrease efficacy.

After removing a patch, fold in half placing the sticky ends together, place in its original pouch, and discard out of the reach of children and pets. The patch still contains small amounts of nicotine which are poisonous children and pets.

8.1.5 Availability/How Supplied

Nicotine transdermal patches are FDA approved for smoking cessation aid and are commercially available.

8.1.6 Side Effects

There are no significant safety concerns associated with using more than 1 over-the-counter (OTC) nicotine replacement therapy (NRT) simultaneously or at same time as another nicotine-containing product (including cigarettes), however the potential for nicotine overdose is increased if patient continues to smoke. Every effort should be made to decrease the number of cigarettes smoked to zero while using replacement therapy.

Below are the most commonly reported adverse events related to nicotine transdermal patch. Please refer to the package insert/investigator’s brochure for the comprehensive list of adverse events.

Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea), headache, insomnia, vivid dreams, and application site irritation.

Contact your doctor if you experience these side effects and they are severe or bothersome.

The incidence of developing dependence on nicotine replacement is considered to be very low. Smokers may worry that they will become dependent on nicotine replacement, but nicotine dependence rarely

occurs. Nicotine replacement therapy has not been shown to increase or cause development of cancer.

Use of nicotine transdermal patches may not be appropriate in the following populations and should be carefully monitored by a physician

- non-smokers, occasional smokers, and children under 18 years of age (see Warnings),
- known hypersensitivity of the skin, allergy to nicotine or any patch components,
- generalized skin disorders,
- recovery phase of acute myocardial infarction, unstable or worsening angina pectoris, severe cardiac arrhythmias, and recent cerebrovascular accident.

Pregnancy and Breastfeeding:

Transdermal nicotine is considered US FDA Category D. The adverse effects on fetal and maternal health caused by cigarette smoking are clearly established. Nicotine freely passes into the placenta and is found in both amniotic fluid and umbilical cord blood (Luck & Nau, 1984; Hibberd et al, 1978). Nicotine is readily transferred to the fetus throughout pregnancy; the fetus is actually exposed to higher nicotine concentrations than the mother (Luck et al, 1985). The use of cigarettes or nicotine gum during the third trimester of pregnancy has been associated with diminished breathing movement in the fetus. There are no conclusive data to support different pregnancy categories for the various nicotine replacement therapy (NRT) products (Lyman & Raebel, 2001).

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known."

8.1.7 Potential Interactions

There is increased risk of nicotine overdose in patients who continue smoking while using a nicotine replacement therapy, or those utilizing more than one form of nicotine replacement therapy. Caution should be used to prevent overdose, and smoking should be completely discontinued while using therapy.

Signs and symptoms of nicotine overdose may include:

abdominal or stomach pain, cold sweat, confusion, convulsions (seizures), disturbed hearing and vision, drooling, extreme exhaustion, pale skin, rapid heartbeat, and tremors. Contact your doctor if you experience any of these symptoms.

8.1.8 References

1. Product Information: NICORDERM CQ - nicotine patch, extended release. GlaxoSmithKline Consumer Healthcare Holdings (US)

LLC. U.S. National Library of Medicine. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed March 28th 2018

2. Product Information: HABITROL STEP 1- nicotine transdermal system patch patch, extended release; HABITROL STEP 2- nicotine transdermal system patch patch, extended release; HABITROL STEP 3- nicotine transdermal system patch patch, extended release. Dr. Reddy's Laboratories Inc. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed March 28th 2018
3. Rigotti NA. (2017). Pharmacotherapy for smoking cessation in adults. In J. A. Melin (Ed.), UpToDate. Retrieved March 29, 2018, from https://www.uptodate.com/contents/pharmacotherapy-for-smoking-cessation-in-adults?search=nicotine%20replacement%20therapy&source=search_result&selectedTitle=1~31&usage_type=default&display_rank=1

8.2 Nicotine Polacrilex Lozenge (NSC #741859)

8.2.1 Description

Nicotine Polacrilex Lozenges are a form of Nicotine Replacement Therapy that deliver nicotine to your body, temporarily relieving craving and nicotine withdrawal symptoms when you quit smoking. The lozenges are available in dose concentrations of 4mg or 2mg.

Depending on specific commercial product, may also contain the following inactive ingredients (not all inclusive): aspartame, calcium polycarbophil, flavor, magnesium stearate, mannitol, potassium bicarbonate, sodium alginate, sodium carbonate, xanthan gum. Please refer to commercial package insert" as necessary.

8.2.2 Pharmacology

Mode of Action:

Absorbed systemically; binds to nicotine receptors thereby reducing withdrawal symptoms (including nicotine craving) associated with smoking cessation. Nicotine lozenges deliver nicotine at a lower and steadier rate compared to smoking cigarettes through the oral mucosa as opposed to the skin or gastrointestinal tract.

Excretion: Urine

8.2.3 Storage and Stability

Store at 20-25°C (68-77°F).

Keep lid tightly closed and protect from light

8.2.4 Administration

See package insert for complete details for specific product used.

Dosing is determined by the time to patients' first cigarette after waking up.

Smokers who smoke first cigarette within 30 minutes of waking up:

- Use one 4-mg lozenge every 1 to 2 hours for weeks 1 to 6, followed by one 4-mg lozenge every 2 to 4 hours for weeks 7 to 9, then one 4-mg lozenge every 4 to 8 hours for weeks 10 to 12.

Smokers who smoke their first cigarette > 30 minutes after waking up:

- Use one 2-mg lozenge every 1 to 2 hours for weeks 1 to 6, followed by one 2-mg lozenge every 2 to 4 hours for weeks 7 to 9, then one 2-mg lozenge every 4 to 8 hours for weeks 10 to 12.

Patient is advised to pick "quit day" and begin using nicotine polacrilex lozenge on that day and simultaneously stop smoking. They may continue to smoke if not immediately able to/willing to stop smoking, however every effort should be made to decrease the amount smoked while on replacement therapy, as continued smoking can increase adverse effects. It is important for patients to complete the full program, but some may need to use NRT for longer periods to keep from smoking.

Place the lozenge in your mouth and allow the lozenge to slowly dissolve (20 - 30 minutes). Avoid chewing or swallowing the lozenge. Patients should also avoid eating or drinking 15 minutes before using or while the lozenge is in your mouth.

Patients may experience a tingling sensation in their mouth when using the lozenge. While using the lozenge occasionally move the lozenge from one side of your mouth to the other until completely dissolved.

To improve your chances of quitting, use at least 9 lozenges per day for the first 6 weeks

Avoid using more than one lozenge at a time or continuously use one lozenge after another since this may cause hiccups, heartburn, nausea or other side effects. Do not use more than 5 lozenges in 6 hours or 20 lozenges per day.

8.2.5 Availability/How Supplied

Nicotine polacrilex lozenges are FDA approved for smoking cessation aid and are commercially available.

Product is supplied as a 2 mg or 4 mg oral lozenge or troche.

8.2.6 Side Effects

There are no significant safety concerns associated with using more than 1 over-the-counter (OTC) nicotine replacement therapy (NRT) simultaneously or at same time as another nicotine-containing product (including cigarettes), however the potential for nicotine overdose is increased if patient continues to smoke. Every effort should be made to decrease the number of cigarettes smoked to zero while using replacement therapy.

Below are the most commonly reported adverse events related to nicotine lozenge. Please refer to the package insert/investigator’s brochure for the comprehensive list of adverse events.

Gastrointestinal symptoms (nausea, vomiting, abdominal pain, diarrhea, unpleasant taste), arthralgia, jaw pain, myalgia, dizziness, lightheadedness, headache, insomnia, hiccups

Contact your doctor if you experience these side effects and they are severe or bothersome.

The incidence of developing dependence on nicotine replacement is considered to be very low. Smokers may worry that they will become dependent on nicotine replacement, but nicotine dependence rarely occurs. Nicotine replacement therapy has not been shown to increase or cause development of cancer.

Use of nicotine polacrilex lozenges may not be appropriate in the following populations and should be carefully monitored by a physician:

- non-smokers, occasional smokers, and children under 18 years of age (see Warnings),
- known hypersensitivity of the skin, allergy to nicotine or any patch components,
- generalized skin disorders,
- recovery phase of acute myocardial infarction, unstable or worsening angina pectoris, severe cardiac arrhythmias, and recent cerebrovascular accident.

Pregnancy and Breastfeeding:

Nicotine Polacrilex is considered US FDA Category C. The adverse effects on fetal and maternal health caused by cigarette smoking are clearly established. Nicotine freely passes into the placenta and is found in both amniotic fluid and umbilical cord blood (Luck & Nau, 1984; Hibberd et al, 1978). Nicotine is readily transferred to the fetus throughout pregnancy; the fetus is actually exposed to higher nicotine concentrations than the mother (Luck et al, 1985). Nicotine use during the third trimester of pregnancy has been associated with diminished fetal breathing movements possibly due to decreased placental perfusion.

If you are pregnant or breast-feeding, only use this medicine on the advice of your health care provider. Smoking can seriously harm your child. Try to stop smoking without using any nicotine replacement medicine. This medicine is believed to be safer than smoking. However, the risks to your child from this medicine are not fully known.

8.2.7 Potential Interactions

There is increased risk of nicotine overdose in patients who continue smoking while using a nicotine replacement therapy, or those utilizing more than one form of nicotine replacement therapy. Caution should be used to prevent overdose, and smoking should be completely discontinued while using therapy.

Signs and symptoms of nicotine overdose may include:

abdominal or stomach pain, vomiting, cold sweat, confusion, headache, convulsions (seizures), disturbed hearing and vision, drooling, extreme exhaustion, pale skin, rapid heartbeat, and tremors. Contact your doctor if you experience any of these symptoms.

8.2.8 References

1. Product Information: NICORETTE- nicotine polacrilex lozenge. GlaxoSmithKline Consumer Healthcare Holdings (US) LLC. U.S. National Library of Medicine. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed March 29th 2018
2. Product Information: NICOTINE, oral lozenge, nicotine polacrilex, oral lozenge. Meijer Distribution Inc, Grand Rapids, MI. U.S. National Library of Medicine. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed March 29th 2018
3. Product Information: NICORETTE (R), nicotine polacrilex. Lakeside, Cincinnati, OH, 1991. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed March 29th 2018
4. Product Information: COMMIT(TM) oral lozenge, nicotine polacrilex oral lozenge. GlaxoSmithKline Consumer Healthcare, LP, Pittsburgh, PA, 2003. https://dailymed.nlm.nih.gov/dailymed/index.cfm. Accessed March 29th 2018

9. Statistical Considerations

9.1 Estimated Effect Size

Based on our current trial preliminary findings (Preliminary Studies) and previous trial with low SES smokers, [85] we conservatively estimate 7-day point-prevalence tobacco abstinence at 6-month follow-up will be 15% for the standard care group and 32% for the intervention group. This estimate is based on our current trial, which has a higher intensity control group.

9.2 Power calculation:

9.2.1 Aim 1. Primary effectiveness outcome.

The study will have 80% power to detect a 17% difference in 7-day point-prevalence tobacco abstinence with a two-sided significance level of 0.01 with 280 participants.

Numeric Results for Testing Two Proportions using the Z-Test with Unpooled Variance

H0: P1 - P2 = 0. H1: P1 - P2 = D1 ≠ 0.

Target Power	Actual Power*	N1	N2	N	P1	P2	Diff D1	Alpha	
0.80	0.80400	117	117	234	0.2700	0.1000	0.1700	0.0100	
0.90	0.90042	148	148	296	0.2700	0.1000	0.1700	0.0100	
0.80	0.80014	78	78	156	0.2700	0.1000	0.1700	0.0500	
0.90	0.90167	105	105	210	0.2700	0.1000	0.1700	0.0500	
0.80	0.80045	126	126	252	0.2900	0.1200	0.1700	0.0100	
0.90	0.90130	161	161	322	0.2900	0.1200	0.1700	0.0100	
0.80	0.80185	85	85	170	0.2900	0.1200	0.1700	0.0500	
0.90	0.90186	114	114	228	0.2900	0.1200	0.1700	0.0500	
0.80	0.80184	140	140	280	0.3200	0.1500	0.1700	0.0100	
0.90	0.90061	178	178	356	0.3200	0.1500	0.1700	0.0100	
0.80	0.80115	94	94	188	0.3200	0.1500	0.1700	0.0500	
0.90	0.90119	126	126	252	0.3200	0.1500	0.1700	0.0500	
0.80	0.80095	148	148	296	0.3400	0.1700	0.1700	0.0100	
0.90	0.90146	189	189	378	0.3400	0.1700	0.1700	0.0100	
0.80	0.80289	100	100	200	0.3400	0.1700	0.1700	0.0500	
0.90	0.90024	133	133	266	0.3400	0.1700	0.1700	0.0500	
0.80	0.80043	159	159	318	0.3700	0.2000	0.1700	0.0100	
0.90	0.90101	203	203	406	0.3700	0.2000	0.1700	0.0100	
0.80	0.80088	107	107	214	0.3700	0.2000	0.1700	0.0500	
0.90	0.90015	143	143	286	0.3700	0.2000	0.1700	0.0500	

* Power was computed using the normal approximation method.

9.2.2 Aim 1. Secondary effectiveness outcome 1.

For biochemically-confirmed 7-day point prevalence abstinence at 3-months, with a sample size of 140 in each arm then smallest detectable difference will be 18% with 80% power and a Bonferroni corrected alpha of 0.002 using and an estimated control rate of 20%.[209, 210]

9.2.3 Aim 1. Secondary effectiveness outcome 2.

For self-reported 7-day point prevalence abstinence at 6-months, with a sample size of 140 in each arm then smallest detectable difference will be 22% with 80% power and a Bonferroni corrected alpha of 0.002 using and an estimated control rate of 31%.

9.2.4 Aim 1. Secondary effectiveness outcome 3.

For self-reported 7-day point prevalence abstinence at 3-months, with a sample size of 140 in each arm then smallest detectable difference will be 22% with 80% power and a Bonferroni corrected alpha of 0.002 using and an estimated control rate of 28%.

9.2.5 Aim 1. Secondary effectiveness outcome 4.

For continuous abstinence, with a sample size of 140 in each arm then smallest detectable difference will be 21% with 80% power and a Bonferroni corrected alpha of 0.002 using and an estimated control rate of 20%.

9.2.6 Aim 1. Secondary effectiveness outcome 5.

For sustained abstinence, with a sample size of 140 in each arm then smallest detectable difference will be 19% with 80% power and a Bonferroni corrected alpha of 0.002 using and an estimated control rate of 13%.

9.3 Estimate of drop-outs/loss to follow-up:

We estimate that 10% of participants will die within 6-months of enrollment, so an additional 10% (n=28) will be recruited.

9.4 Total Sample size:

308 patient participants.

9.5 Plans for handling missing data:

At the outset, we will examine the frequency distributions of all variables. Data from all sites will be pooled for analysis, after confirming there is no significant heterogeneity among sites or adjusting as needed. We will compare the baseline characteristics to assess whether randomization distributed covariates evenly. Outcome analyses will be intent-to-treat; we will classify participants who are lost to follow-up and those who do not provide a saliva or an expired air sample as current smokers. We will determine whether there is differential dropout in the groups and consider developing probability-of-completion weights189 to obtain unbiased estimates of treatment effect. We will assess whether data are missing at random. We will perform sensitivity analysis using: 1) a complete case analysis and 2) multiple imputation for missing data.[190]

9.6 Plans for analyzing the primary objectives: treatment effectiveness (Aim 1)

The primary objective is to compare the proportions of participants in the study arms with 7-day point-prevalence abstinence from cigarettes at 6-months post enrollment. We will define 7-day point-prevalence by saliva cotinine (< 15 ng/ml) or expired air CO (<10 ppm). All participants who report being quit and no NRT or e-cigarette use will be requested to provide saliva samples, expired air CO will be measured in participants who report being quit and report concurrent NRT or e-cigarette use. If a participant is lost to follow-up or does not provide a saliva or CO sample, they will be considered a current smoker. The primary analysis will be performed from an intent-to-treat perspective. Chi-square tests will be used to compare the outcomes between treatment groups. Outcomes will be considered different with $p<0.01$.

As a randomized study, it is hoped that the two groups will be balanced between potential confounders. Appropriate comparisons between the groups will be performed (chi-squared tests, t-tests, etc.) to identify any potential confounders that were not balanced. If significant areas of imbalance are identified, logistic regression modelling will be performed to adjust for potential confounding.

9.7 Plans for analyzing the secondary objectives: secondary treatment effectiveness (Aim 1)

The 5 secondary objectives (defined in Section 2.3) include various ways of measuring abstinence at different times of assessment. In order to adjust for multiple comparisons, differences will be considered significant at 0.01/N=0.01/5=0.002 level.

Similar to the primary objective is to compare the proportions of participants in the study arms with 7-day point-prevalence abstinence from cigarettes at 3-months post enrollment. We will define 7-day point-prevalence by saliva cotinine (< 15 ng/ml) or expired air CO (< 10 ppm). All participants who report being quit and no NRT or e-cigarette use will be requested to provide saliva samples, expired air CO will be measured in participants who report being quit and report concurrent NRT or e-cigarette use. If a participant is lost to follow-up or does not provide a saliva or CO sample, they will be considered a current smoker. Chi-square tests will be used to compare the outcomes between treatment groups.

Another secondary objective is to compare the proportions of participants in the study arms that self-report cigarette abstinence at 3-months. The participant will be asked, “In the past 7 days, have you smoked a cigarette, even a puff.” With the answer recorded as “Yes” or “No”. If the self-report response is unavailable, the participant will be considered a current smoker. Chi-square tests will be used to compare the outcomes between treatment groups. The process will be repeated using self-reported cigarette abstinence at 6-months.

Another secondary objective is to compare the proportions of participants in the study arms that report a continuous abstinence at 6 months. The participants will be asked, “How long has it been since you last smoked a cigarette (even one or two puffs)?” at 6 months. If the response is more than or equal to 3 months (e.g. time since previous survey), the participant will be considered having a continuous abstinence at 6 months. If the self-report response is unavailable, the participant will be considered not having a continuous abstinence at 6 months. Chi-square tests will be used to compare the outcomes between treatment groups.

Another secondary objective is to compare the proportions of participants with sustained abstinence at 6 months. To qualify as a sustained abstinence at 6 months, the participant must qualify as biochemically-verified 7-day point prevalence cigarette abstinence at 3 and 6 months, using the definition above. If either measure is not available the participant will not be considered sustained abstinence at 6 months. Chi-square tests will be used to compare the outcomes between treatment groups.

Generalized Estimating Equations (GEE) approach will be used to study the treatment effect over time, incorporating 3 & 6 month follow-up data. This will take into account the repeated measures structure of observations within the same individuals over time and allow for analysis of incomplete data across time.

9.8 Plans for analyzing the exploratory objectives:

9.8.1 Aim 2: To assess the potential effect of known and potential moderators on treatment effectiveness between the two arms.

We will export the moderator effects on treatment effectiveness.

There are 2 outcomes collected at 2 time points and 2 outcomes at 1 time point:

- Biochemically-verified 7-day point prevalence abstinence at 3- and 6-months follow-up
- Self-reported cigarette abstinence at 3- and 6-months follow-up
- Continuous abstinence at 6 months (no self-reported smoking since last survey point)
- Sustained abstinence at 6 months (biochemically-verified abstinence at 3 and 6 months)

The moderators of primary interest are:

- Sociodemographics: Sex, age, marital status, race/ethnicity, education level, financial burden, health insurance, internet and smartphone access and modality
- Smoking history: Years smoked, daily smoking rate, other tobacco/nicotine use (e.g., cigars, cigarettes), current/past use of tobacco treatments, nicotine dependence (2-item “Heaviness of Smoking Index” from the FTND)
- Cancer variables: Cancer type, cancer stage, treatment, and days since diagnosis
- Site characteristics:
  - Site, geographic location, clinic volume,
  - baseline organizational readiness (9-item survey for readiness to implement NCCN Guidelines for Smoking Cessation using Weiner’s Organizational Readiness for Implementing Change (ORIC) survey[144,145])
  - site usual care (recorded on the 2017 landscape survey)

Additional moderators to be explored:

- Medical history: ECOG Performance Status, alcohol use (3 items form the AUDIT-C)

- Quality of life/emotions: Emotional distress, coping, anxiety, depression
- Cancer and smoking beliefs: Stigma, quit motivation, self-efficacy to quit, importance of quitting, perceived benefits of quitting smoking, quit-smoking medication beliefs
- Physical symptoms: Cravings
- Environmental influences: Level of second-hand smoke exposure, perceived social support, perceived provider support

For each of the 6, we will test the effects of these moderators listed above on the outcomes. We test the effects of these moderators in logistic regression models to determine their association with tobacco abstinence. Once a parsimonious multivariate model is developed, treatment arm will be included to test for the effect of the intervention on the moderators. Interactions between the treatment arm and the moderators will assess the relationship between the moderators and the treatment group on the effectiveness outcomes.

Also, GEE will be used to look at longitudinal models.

Multiple comparisons will be accounted for by considering Bonferroni adjustments.

9.8.2 Aim 3: To assess the processes of implementation and dissemination (acceptability, adoption, appropriateness, treatment fidelity, cost effectiveness, penetration/reach, and sustainability) of our intervention at community oncology sites.

To gain an initial understanding of implementation processes, for Aim 3 we will follow Proctor and colleagues' recommended taxonomy for measurement of implementation outcomes[19]. Specifically, we will measure acceptability (satisfaction with content/delivery), adoption (program uptake), appropriateness (relevance), cost, and treatment fidelity/adaptation and penetration (reach) and sustainability. These implementation outcomes will be assessed with mixed methods using qualitative and quantitative data to be collected from patients, tobacco treatment counselors, NCORP oncology PIs and provider clinicians/staff, and EHR documentation.

We will use descriptive statistics to summarize implementation outcomes (Acceptability, Adoption, Appropriateness, Fidelity, Cost, Penetration and Sustainability) and conduct treatment group comparisons (i.e., Acceptability).

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We will explore organizational readiness and site level engagement using existing quantitative and qualitative data respectively. In order to examine the generalizability of the study findings to the full NCORP network of cancer care delivery sites, we will use the most recent (2017) existing NCORP Landscape data to conduct preliminary analyses comparing participating and nonparticipating sites on relevant site characteristics.

9.8.2.1 Acceptability

Satisfaction with various aspects of the tobacco treatment program will be evaluated through participant survey responses and post-treatment interviews with a subset of patient participants. Patient Surveys. At the 6-month surveys, participant satisfaction will be assessed:

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1 To what extent has the tobacco treatment program met your needs?;
2 How satisfied were you with the smoking cessation assistance received?;
3. How helpful was the smoking cessation assistance?;
4. Would you recommend this program?

Proportions of participants answering these questions will be compared between the arms using chi-squared tests.

9.8.2.2 Adoption

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Using the baseline, 12- and 36-month staff surveys, we will conduct paired t-tests and chi-square test to assess pre/post changes in organizational readiness (ORIC) and tobacco treatment delivery practices.

9.8.2.3 Appropriateness

To measure perceived fit and relevance, we will report on the 12- and 36-month staff surveys and interviews of NCORP PIs, clinicians, and staff about the VIT's a) suitability, b) applicability, and c) match for their patients and site, as well as d) perceptions of site usual care content and implementation.

9.8.2.4 Fidelity

We will evaluate the use and effectiveness of brief videos on enrollment using the Fisher's exact test: brief videos open (y/n) and enrollment (y/n). Using participant self-reported survey data, counselor process data, and quitline data, we will evaluate study treatment and non-study treatment (i.e., site-specific usual care, outside resources) utilization. We will dichotomize medication and counseling use into low vs. high (≥ 8 weeks of NRT; ≥ 8 sessions) levels of treatment utilization.[191] Within each group, we will use chi-square tests and ANOVAs to explore the association between participant characteristics and treatment utilization. We will use chi-square tests to compare the association of treatment utilization (brief videos open, level of medication and counseling use) on smoking outcomes. To predict smoking outcomes, we will use logistic regression models, which will include medication and counseling use levels, adjusting for confounders.

9.8.2.5 Cost

We will calculate the incremental cost per quit of the intervention relative to EUC over the 6-month follow-up period as follows: (total per-person costs of intervention – total per-person costs of EUC)/(cessation rate with the intervention – cessation rate with EUC).[192] Cessation rates will be based on the primary outcome. Statistical uncertainty in cost and effectiveness inputs will be incorporated into the incremental cost per quit comparisons using Monte Carlo simulation methods allowing us to determine whether these ratios are significantly different from zero and allowing us to assess the proportion of simulation outcomes above or below relevant thresholds. The robustness of the cost-effectiveness ratio estimates will be further examined in sensitivity analyses in which each parameter is varied, singly and in combination, through plausible ranges. We will also generate “best case” and “worst case” analyses. Using Wilcoxon rank sum tests and trend tests (Cochran–Armitage), we will explore patient and site characteristics associated with implementation outcomes. We will also collect cost data on EUC components including staff time required to assess smoking status and refer current smokers to this tobacco treatment trial.

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9.8.2.6 Penetration

We will compare proportion of smokers who participate at each NCORP site using chi-square tests. We will analyze data collected from the study sites’ screening logs maintained in REDCap (see Appendix Z2D). This procedure is outlined in Section 5.1. We will compare patient characteristics between enrollees and refusers and screenees from DCP-001 using univariate analyses (chi-square or Fisher’s exact tests and Wilcoxon rank sum tests) to examine the associations of patient characteristics (e.g. sociodemographics, medical and smoking history, cancer treatment, when available) with enrollment (Y/N).

9.8.2.7 Sustainability

We report on interviews with the NCORP site PIs/clinicians/staff to assess sustainability. Specifically, we report on: a) challenges likely to be encountered in providing cessation medications, b) challenges likely to be encountered in providing cessation counseling, c) resources needed to maintain delivery of tobacco treatment and d) preferences for a site-based centralized tobacco treatment program.

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9.8.2.8 Organizational readiness

We will use staff survey data collected at baseline and follow-up to explore the association between organizational readiness and site characteristics, and whether there are differences in organizational readiness

by professional/specialty groups, practice type, etc. Within site/practice level analysis will examine aggregate ORIC scores stratified by survey respondent type (e.g., CCDR leads, medical oncologists, oncology nurses) and how organizational readiness differs across these individuals. Organizational readiness will be operationalized as an ORIC survey score from the 12-item ORIC survey which uses a five-point Likert scale ranging from 1 (disagree) to 5 (agree). Seven items represent the change efficacy subscale and five items represent the change commitment subscale. Change efficacy scores will be calculated from five items assessing expertise, coordination, ability to manage site politics, ability to handle challenges, organizational supports, and tracking implementation progress. Change commitment scores will be computed from the five items assessing staff commitment, determination, motivation and the ability to do whatever it takes to implement tobacco use assessment and treatment. Predictors of baseline organizational readiness will be implementation context variables such as NCORP site designation, organizational, clinical staff, and population characteristics, and the capacity to provide cancer care delivery services. Additional determinants of organizational readiness, particularly, change valence, a determinant of change commitment211 – how staff perceive tobacco treatment interventions and informational assessment, a determinant of change efficacy211 – staff perceptions of resource availability and situational factors favorable to implementing tobacco treatment interventions will be explored in multivariable models. Baseline, 12-and 36-month ORIC survey scores will be analyzed for longitudinal changes in change efficacy and commitment over the course of the study period.

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9.8.2.9 Site level engagement

We will carry our content analysis of monthly meeting minutes. Data will be stratified by representation of stakeholders in monthly meetings (Who); at what point in the project stakeholders are engaged (When); how stakeholders engage in the research project e.g., consultations, advisors/experts, information, recruiting or retaining participants, dissemination efforts (How and how much); and the impact stakeholders have on the project (What). Engagement interactions will be quantified into high, moderate and low levels of engagement. We will then assess the association between engagement level and organizational and clinical characteristics (i.e., organizational, clinical, patient population, characteristics) and capacity to provide cancer care delivery services (i.e., smoking cessation and treatment services).

Qualitative data from focus groups described in Aim 3 will be used to examine the process of engaging community oncology sites in community engaged research (CEnR), evaluate facilitators and barriers to engagement, and identify implementation strategies to facilitate engagement and the adoption of tobacco treatment at the sub affiliate level. Guided by the CFIR20 we will use domains depicting engagement (inner setting, process, characteristics of individuals) and select constructs within the domains20 to examine determinants of engagement, select appropriate implementation strategies to facilitate engagement, and to understand where those strategies can be employed in the implementation process.

Data will be analyzed using an inductive approach and the constant comparative method.212 Using a three-stage analytical approach,213 we will begin with open coding, data immersion and marginal remarks. Axial coding will then be used to allow for the identification of relationships between codes. Finally, selective coding will be used for the integration of all codes into core categories/themes. We will code for 1) facilitators and barriers to engagement and 2) implementation strategies to facilitate engagement and the adoption of tobacco treatment interventions within the CFIR domains and constructs. Independent coding with clear documentation of thematic development followed by assessing for inter-rater reliability (alpha >.80) among coders and iterative data processing will ensure that the qualitative results are confirmable. Strategy domains such as the action, action target, and implementation outcome affected will be described.

9.9 Gender and Ethnicity for Patients

Based on previous data from NCORP reports the anticipated accrual in subgroups defined by gender and race is:

Racial Categories	**DOMESTIC PLANNED ENROLLMENT REPORT**				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	2	3	0	0	5
Asian	8	8	0	0	16
Native Hawaiian or Other Pacific Islander	2	2	0	0	4
Black or African American	12	14	3	2	31
White	110	103	13	17	243

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
More Than One Race	4	5	0	0	9
Total	138	135	16	19	308

9.10 Gender and Ethnicity for Site Staff

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	1	0	0	2
Asian	3	3	0	0	6
Native Hawaiian or Other Pacific Islander	1	1	0	0	2
Black or African American	4	5	1	1	11
White	39	36	5	6	86
More Than One Race	1	2	0	0	3
Total	49	48	6	7	110

9.11 Study Monitoring

This study will be monitored by the ECOG-ACRIN Data Safety Monitoring Committee (DSMC). The DSMC meets twice each year. For each meeting, all monitored studies are reviewed for safety and progress toward completion. When appropriate, the DSMC will also review interim analyses of outcome data. Copies of the toxicity reports prepared for the DSMC meetings are included in the study reports prepared for the ECOG-ACRIN group meeting (except that for double blind studies, the DSMC may review unblinded toxicity data, while only pooled or blinded data will be made public). These group meeting reports are made available to the local investigators, who may provide them to their IRBs. Only the study statistician and the DSMC members will have access to interim analyses of outcome data. Prior to completion of this study, any use of outcome data will require approval of the DSMC. Any DSMC recommendations for changes to this study will be circulated to the local investigators in the form of addenda to this protocol document. A complete copy of the ECOG-ACRIN DSMC Policy can be obtained from the ECOG-ACRIN Operations Office.

10. Specimen Submission and Analysis

Participants who self-report smoking abstinence of at least 7 days at month 3 and/or month 6 (Supplemental Appendix B or C), on either the survey or during survey outreach, will be requested to provide saliva for cotinine assessments (Section 10.1). EASEE PRO triggers a notification to MGH and/or NCORP site staff based on the following criteria: 1) smoking status; 2) NRT use; and 3) e-cigarette use. Saliva samples will be tested only for cotinine. To avoid false-positives, participants who report use of NRT or e-cigarettes within the last week will be offered the opportunity to instead complete an expired air CO sample (Section 10.2). Saliva cotinine results will not be provided to the site or the patients. The expired air CO sample results may be shared with the patient by site staff at time of the measure, at the discretion of the physician.

Smokerlyzers® will be deployed as needed to the centralized site coordinator or administrator. We will include a mailing label for them with a pre-stamped address to ship it back to us. Saliva kits will be mailed directly to the patient by MGH. Only one Smokerlyzer® will be distributed to each site. To request a Smokerlyzer®, please contact the study team.

Questions may be directed to the Smokefree Support Study team at 617-643-4765 or SmokefreeSupportStudy2@partners.org.

10.1 Saliva Cotinine Assessments

For this trial, saliva will be submitted to J2 Laboratories to assay and tested for cotinine levels. J2 Laboratories is a premier forensic drug and alcohol testing and clinical diagnostic laboratory located in Tuscon, AZ that has successfully partnered with the study team for previous saliva cotinine testing (Smokefree Support Study 1). Saliva sample testing results will be sent to the EAQ171CD research staff at Massachusetts General Hospital (MGH). The results will not be returned to the participant or the institution.

The saliva sample will be tested only for cotinine to determine the study participant's exposure to cigarette smoke and nothing else. Saliva samples will be destroyed after they are assayed for cotinine. No samples will be retained for additional research purposes.

10.1.1 Saliva Submission

Saliva assessments are requested from patients who self-report smoking abstinence of at least 7 days and who do not report the use of NRT or e-cigarettes within the last week. Saliva kits will be shipped directly to the patient by MGH for all subjects who report being quit on 3- and/or 6-month follow-up surveys.

If a sample is designated insufficient for testing by the lab, MGH will notify the participant, who will be offered the opportunity to complete additional samples.

NOTE: To avoid false-positives, participants who report use of NRT or e-cigarettes within the last week will be offered the opportunity to instead complete an expired air CO sample (Section 10.2).

10.1.1.1 Saliva Cotinine Collection Kits

Participants who complete a saliva cotinine sample will be provided with $40 in remuneration to thank them for their time.

The collection kit contains:

a. 1 plastic tube

b. 1 plastic insert

c. 1 cotton swab

d. 1 cap to the tube

e. Plastic bag

f. Instructions for the patient regarding the collection and submission of saliva. An example of the instruction sheet is in Appendix II

g. Smoking Status Slip – MGH Research Staff will **COMPLETE THE *ECOG-ACRIN Participant ID* field prior to giving the kit to the patient.**

h. Pre-paid packaging: FedEx package and pre-paid airbill with MGH return address only.

10.1.1.2 Saliva Collection

The instructions for the collection and submission of the saliva are provided within the kit.

1. Prior to distributing the saliva collection kit to the participant, MGH Research staff will COMPLETE THE *ECOG-ACRIN Participant ID* with the EAQ171CD patient ID on the ***Saliva Smoking Status Slip*** (**Appendix III**).
2. BEFORE USING THE KIT the participant is not to eat, drink, chew gum, or have anything in their mouth for at least 15 minutes before using the kit
3. Collecting the saliva –
   a. Pop open the cap. The participant is to take out the cotton swab, Leaving the plastic insert inside the tube
   b. The swab is placed under the tongue for at least 4 minutes

      Participant is not to chew, suck on, or play with the swab
   c. After at least 4 minutes, the wet swab is placed back into the tube
   d. Put the cap firmly on the plastic tube
4. After collection of the saliva
   a. Put the sealed tube in the plastic bag

b. Put the bag with the kit in the prepaid, pre-addressed envelope

c. Complete the ***Saliva Smoking Status Slip.*** Indicate the date and time of the saliva collection and respond to the brief questions. Place the slip in the package with the kit.

NO PARTICIPANT IDENTIFYING INFORMATION other than the EAQ171CD patient ID is to be provided with the sample.

5. Sample shipment:

Using the pre-paid shipping label provided with the kit, samples are to be shipped to:

Processing Department
J2 Laboratories, Inc.
3640 N. 1st Ave, Suite 130
Tucson, AZ 85719

It is recommended that the sample can be mailed the day of collection. If it cannot be mailed the day of collection, the sample is to be placed in a fridge or freezer until it can be mailed.

After completing the kit, participants may simply drop the packaged sample in the nearest FedEx dropbox.

10.2 Expired CO Assessments

As CO samples must be completed in-person, samples will be completed with a member of the local research staff at the site at which the subject was recruited and is receiving their cancer care. The NCORP site research staff will be trained in safe and proper use of the CO monitor and test results interpretation. With the aim of decreasing participant burden, samples may be completed at an existing clinic visit in accordance with patient preferences.

Sites will be provided with an Expired CO Smokerlyzer® which will be used for all participants on EA171CD requiring an expired CO assessment.

Prior to first assessments, contact the Smokefree Support Study team at 617-643-4765 to receive training on the use of the Smokerlyzer®, including use of the required software or app.

For each assessment, follow the *Test Instructions* and operation manual provided. Quick summary of instructions are:

- Fill in the patient ID, date and time of assessment on the ***Expired CO Smoking Status Slip*** (Appendix IV)
- Have the participant complete the questions on the ***Expired CO Smoking Status Slip***
- Obtain the CO assessment, following the instructions provided with the instrument
    - The participant should be standing, to allow proper exhalation

- The participant is to inhale as deeply as possible and hold their breath while the display counts down 15 seconds. If they are unable to do so, please see the manual on how to address this.

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- At the end of the countdown, the participant is to blow slowly into the mouthpiece until their lungs are empty
- Record the results of the assessment on the ***Expired CO Smoking Status:*** ppm, and %COHb

The results of the CO expiration assessment results and the participant's answers to the ***Expired CO Smoking Status Slip*** are to be entered into mediDATA Rave. It is requested that the actual form be uploaded to Rave as well. Site staff should please also scan or send the Expired CO Smoking Status Slip to the MGH Research team via secure email. A copy of the results may be given to the participant using the *Smokerlyzer® breath CO Test Results*, a copy which is provided in Appendix IV.

11. Patient-Reported Outcomes and Quality of Life Administration

11.1 Data Collection Approach for Patient Reported Outcomes

We will use a combination of EASEE-PRO and mailed questionnaires for this study as described in Section 4.7.5. A proxy or family member can complete the questionnaires on behalf of the patient as long as they can speak English or Spanish. The questionnaires are only available in English or Spanish.

EASEE-PRO's PRODUCE sub-system allows for the collection and notification of study critical events. This allows EASEE to interface with a variety of systems and use external APIs to retrieve data necessary for study operations.

11.2 Questionnaire Administration Process

At the time EASEE-PRO account activation, patients will be asked to complete paper-based Patient Contact Information Form. The form collects information used to maintain contact with the participant over the course of the study, including name, home address, phone number, and may include the name of a primary (or other) physician to whom requests for patient location may be made and a close friend or family member.

This form is retained in the study participant's chart at the site and is not submitted to the ECOG-ACRIN RAVE database; the completed form is faxed to the central ECOG-ACRIN Outcomes and Economic Assessment Unit (OEAU) located at Brown University so that the participants can be contacted for the Patient Reported Outcomes (PRO) portion of the study. The contact information is stored in a dedicated SQL database (PII-DB) and IS NOT accessible by ECOG-ACRIN database. The OEAU RA will not have access to the main ECOG-ACRIN database that contains clinical data.

11.2.1 Patient Contact Information Form

On the Patient Contact Information Form, patients will be asked for telephone numbers and addresses to facilitate contacting for completion of questionnaires. Patients will be asked if they would like text message reminders of survey availability as well as email reminders. While the default survey administration method will be on-line, questionnaires will be sent by mail as requested by the patient or

as needed by the study personnel. Administration of questionnaires, both web-based and paper will be coordinated by the OEAU. Administration of the questionnaires will be triggered based on completion of study milestones marked by submission of forms in RAVE and EASEE-PRO.

Patients will be prompted to complete web-based forms via an email prompt (push notifications or SMS as applicable to the study). These notifications will include a link to the web site for questionnaire completion. Questionnaires will be completed on line using a unique patient account. The web site will reference a toll-free phone number and email address that patients can use to reach the OEAU staff should they have questions or need assistance. All data will be stored on a secure server. Patients who do not complete the web questionnaires within 3 working days of the initial request e-mail will receive up to 3 additional reminders, each 3 days apart. These reminders, like the initial notification, will provide a link to the website for the current surveys, ask the participant to confirm that they have been able to access the web site, and provide both the e-mail address and the toll free help number for support.

If patients still have not responded within 14 days of the original e-mail, the OEAU Research Associate may attempt to telephone the patient and administer the questionnaire over the telephone. The OEAU may send a questionnaire in the mail if the on-line version is not completed. If questionnaires are telephone-administered, they will be marked as such in the database. All surveys, while desired within 3 days of the event, will remain available for participants until either the surveys are completed or they are off-study. Since the completion date is recorded for all surveys, the study team will be able to make relevant determinations for inclusion of this data in specific analyses. However, after telephone follow-up, no additional or extraordinary means will be employed to collect overdue/missing questionnaires.

11.2.2 Mailed questionnaire completion

Mailed questionnaire packets will include a letter introducing the study and include a study-specific toll-free phone number that patients can use to reach the OEAU staff should they have questions or need assistance, questionnaires, and pre-addressed, stamped envelopes for return mailing to the OEAU. If patients do not complete the paper questionnaire within 10 working days of the date of the mailing, the OEAU RA may attempt to telephone or text the patient. If the patient has not received the paper questionnaires, additional questionnaires will be sent after confirming the correct mailing address. If the questionnaire is available to the patient, the OEAU RA will urge the study patient to complete and return the questionnaire. If the patient has still not responded within 20 working days of the original mailing, the OEAU may attempt to telephone the patient and telephone administer the questionnaire. If questionnaires are telephone-administered, they will be marked as such in the data base.

11.3 Patient Reported Outcomes/Quality of Life Assessment Schedule

PATIENT COMPLETED SURVEYS	
Survey time point	Survey items
Baseline survey:	Cigarettes per day Sociodemographics Smoking history Cancer variables Medical history Quality of life Cancer and smoking beliefs Physical symptoms Environmental influences
Follow-up survey: administered at 3 months and 6 months after baseline survey	Point-prevalence tobacco abstinence Self-reported tobacco abstinence Cigarettes per day 24-hr quit attempts Smoking history Quality of life Cancer and smoking beliefs Physical symptoms Environmental influences Acceptability (only at 6 months)

12. Electronic Data Capture

Please refer to the EAQ171CD Forms Completion Guidelines for the forms submission schedule. Data collection will be performed in Medidata Rave, EASEE-PRO, and REDCap.

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

Patient individual and NCORP PI/Clinician/Staff Focus Group Interview Analyses: Data analyses will occur coincident to data collection so that we can ascertain if thematic saturation (the point at which no new data are generated) has been achieved for each strata (treatment group, site). Interviews will be recorded, transcribed and analyzed using NVivo qualitative software. Content analyses will be conducted by the two RAs and overseen by Drs. Park and Ostroff. The coders will meet to develop the thematic framework, categories, and coding plan. To ensure coding reliability, coding discrepancies will be resolved through discussion and comparison of raw data. Coding will continue until a high level of reliability (Kappa=>0.80) is established. Patient individual interview results will be analyzed by strata comparisons. NCORP site participants' focus group interviews will be analyzed according to appropriateness and feasibility.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed for the main portion of the study.

13.1 Waivers of Consent

13.1.1 Screening

Per 45 CFR 46.117c, a waiver of documentation of consent for the screening of study eligibility and recruitment of smokers is justified for the following reasons

- screening eligibility review of medical records by clinical research staff does not affect the rights or welfare of subjects because medical record information is screened to establish preliminary eligibility prior to approaching a potential subject,
- screening eligibility review of medical records cannot practicably be done with the waiver due to the number of services participating in which the patients may be eligible. Screening eligibility decreases the burden on patients of introducing a research study to patients who can easily be identified through screening activities as not eligible for a research study,
- screening eligibility review of medical records involves no more than minimal risk because the person accessing the information has undergone training in confidentiality of medical records, and the records are viewed solely to screen for eligibility criteria and only minimal information found in the screening process will be recorded for research purposes.

13.1.2 Waiver of elements of informed consent – site staff

We request a waiver of specific elements of consent regarding medical treatment, medical risks, and injury to site staff participants. This study does not involve medical treatment of site staff, and these elements of informed consent would not apply to site staff participating in the individual staff surveys and focus group interviews. We have therefore removed these sections from the model consent form. Omission of this information does not constitute greater than minimal risk and would not adversely affect the site staff participants.

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