Integrating Tobacco Treatment Into Cancer Care: A Randomized Controlled Comparative Effectiveness Trial

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Study Protocol for a Randomized Controlled Comparative Effectiveness Trial

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Abstract

Background: Despite the well-established risks of persistent smoking, 10-30% of cancer patients continue to smoke after diagnosis. Evidence based tobacco treatment has yet to be integrated into routine oncology care. The study protocol paper describes the manualized treatment interventions, evaluation plan, and overall study design of comparing the effectiveness and cost of two treatments across two major cancer centers.

Methods/Design: A two-arm, two-site randomized controlled comparative effectiveness trial is testing the hypothesis that an Intensive Counseling (IC) intervention is more effective than a Standard Care (SC) intervention in helping recently diagnosed cancer patients quit cigarette smoking. Both interventions include 4 weekly behavioral counseling sessions and a recommendation for use of FDA-approved smoking cessation medication. The IC intervention condition includes an additional 4 biweekly and 3 monthly counseling sessions as well as dispensal of the recommended FDA-approved smoking cessation medication at no cost. The trial is enrolling patients with suspected or newly diagnosed cancer who have smoked a cigarette in the past 30 days. Participants are randomly assigned to receive the SC or IC intervention. Tobacco cessation outcomes are assessed at 3 and 6 months. The primary study outcome is 7-day point prevalence biochemically validated tobacco abstinence.

Discussion: This trial will answer key questions about delivering tobacco treatment interventions to newly diagnosed cancer patients. If found to be efficacious and cost effective, this treatment will serve as a model to be integrated into oncology care settings nation-wide, as we strive to improve treatment outcomes and quality of life for cancer patients.

Key Words: Smoking Cessation, Tobacco Treatment, Cancer Patients, Randomized Controlled Trial, Motivational Interviewing, Pharmacotherapy

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Introduction

Smoking is responsible for approximately one in five deaths each year in the United States [1,2]. Thirty percent of cancer deaths in the United States in 2015 will be caused by tobacco use [3]. Persistent smoking following a cancer diagnosis is associated with diminished effectiveness of cancer treatment, increased risks of recurrence and second primary cancer diagnoses [4-10], decreased overall survival [11-14], diminished quality of life [11,15,16], and increased complications from surgery, radiation, and chemotherapy [17-23].

Despite the risks of persistent smoking, approximately 10% to 30% of cancer patients continue to smoke after a cancer diagnosis [11, 24-26]. Studies utilizing national datasets, have shown that approximately 1 in 10 cancer survivors smoke [27-29]. Currently, tobacco treatment is not well-integrated into cancer care. Several leading oncology organizations have identified this as a missed opportunity for addressing this important modifiable behavior associated with poorer cancer outcomes [30-32], however, many cancer patients who smoke are not asked about their smoking status, are not advised to quit [33, 34], and do not get proper assistance to quit or stay quit [35, 36]. These findings are notable, as many cancer patients who smoke want to quit smoking [37-41]. A recent prospective study among participants from the Cancer Prevention Study-II Nutrition Cohort reported high rates of quitting behavior among smokers with cancer in the 2-4 years following a cancer diagnosis [14]. Patient, physician and system level factors impede the delivery of effective tobacco cessation programs during cancer care [35, 42-44]. Only half of NCI-designated comprehensive cancer centers, in 2009, had any type of tobacco treatment program [45].

The 2008 U.S. Public Health Service Treating Tobacco Use and Dependence Clinical Practice Guideline (PHS) recommends that evidence-based tobacco treatment, including combined medication and multiple counseling sessions, be delivered to all smokers in health care settings [46]. Unfortunately, little progress has been made with integrating these guidelines into cancer care settings. With few exceptions [47], smoking cessation studies with cancer patients have been limited by very small sample sizes and delayed tobacco treatment initiation [48]. It is critical to start tobacco treatment as close to the time of diagnosis as possible, since the closer cessation is to the time of diagnosis, the higher the likelihood for continued abstinence [11, 37, 38, 49, 50] which, in turn, improves cancer treatment outcomes.

Thus, the primary study aim is to compare the effectiveness of two tobacco treatments integrated into cancer care in producing tobacco abstinence at 6 months. We hypothesize that the IC will significantly increase the proportion of smokers with biochemically-confirmed, 7-day point-prevalence tobacco abstinence at 6 months compared to the SC. Secondary aims are to: a) explore mechanisms through which each treatment promotes abstinence; b) understand variations in abstinence outcomes by subpopulation; c) examine components of treatment that promote abstinence; and d) identify the percentage and associated characteristics of smokers who enroll and adhere to tobacco treatment. Lastly, we will compare the cost per quit within each treatment group.

Design and Methods

Study design

The Smokefree Support Study is an ongoing two-site, randomized controlled trial comparing the effectiveness of an Intensive Counseling (IC) versus Standard Care (SC) in helping recently diagnosed cancer patients become smokefree.

Conceptual framework

In order to guide the development of a tobacco treatment intervention in the context of a cancer diagnosis, we combine a coping with illness model and a health behavior change model. The Self-Regulation Model (SRM), a framework widely used to study patients' coping with cancer [51, 52], focuses on the dynamic process between beliefs, emotions and coping. It postulates that individuals form illness representations (e.g., What is it?) that guide their behavioral responses to an illness and then engage in strategies (e.g., What can I do that will make me feel better?) to reduce distress. Illness representations can be influenced by environmental (e.g., others' smoking in the home) and physical (e.g., shortness of breath) factors. Parallel processing between illness beliefs and emotions leads to a coping response (e.g., quitting) and subsequent monitoring of the success of coping efforts. Applying the SRM to a cancer diagnosis: Changes in beliefs about cancer outcomes (e.g., quitting smoking reduces risk of treatment complications) may lead to engagement in quitting as a strategy to cope with the cognitive and emotional threat of cancer. Furthermore, if individuals' evaluation of the effects of quitting, physical changes (e.g., breathing and pain have improved), and environmental influences (people are no longer smoking in their home) make them feel better, then they will be more likely to stay quit. If quitting smoking

decreases an individual's sense of shame and related anxiety, this will increase the chances that he/she will stay quit. The Health Belief Model (HBM) [53] has been widely used to study smoking cessation, and it focuses on health beliefs that underlie behavior change. The HBM 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 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 is a serious threat to their health; 2) understand that continuing to smoke puts them at risk for poor outcomes (i.e., treatment complications, cancer recurrence); 3) are confident that they can quit; and 4) believe that quitting will reduce their risk of poor outcomes.

Setting

Participants are being recruited from two academic medical centers - the Massachusetts General Hospital (MGH) Cancer Center located in Boston, MA and the Memorial Sloan Kettering Cancer Center (MSKCC) located in New York City, NY. This trial is currently open to enrollment and began enrolling subjects in November of 2013.

Inclusion/Exclusion criteria

Study inclusion and exclusion criteria are detailed in Table 1. In brief, adult cancer patients who are identified as current smokers and are undergoing cancer treatment at MGH or MSKCC, have phone access, and are English and Spanish (MGH only) speaking are eligible for study participation. Criteria have been selected to be as inclusive as possible. Of note, patients are eligible if they are willing to discuss changing their smoking behavior; patients are not required to be willing to quit upon enrollment. Patients with psychiatric disorders are eligible as long as there are no indications of current uncontrolled illness. Advanced stage of disease is not an exclusion criterion unless it is determined by an oncology clinician that the patient is medically unable to participate.

Table 1. Study inclusion and exclusion criteria

Inclusion criteria
• New* patient, opting to receive cancer care at a participating cancer center
• Suspected or newly diagnosed thoracic, breast, genitourinary, gastrointestinal, head/neck, lymphoma, melanoma or gynecological cancer
• Age ≥18 years English or Spanish speaking (MGH only)
• Has smoked a cigarette, even a puff, in the last 30 days
• Willing to consider trying to quit smoking
Exclusion criteria
• Non-English or non-Spanish speaking
• No regular access to telephone
• Medically ineligible (ECOG >2, active dementia, referral to hospice care, or too sick to participate as determined by the treating oncology clinician or study investigators)
• Current, active, untreated psychiatric illness (bipolar disorder, manic-depressive disorder, schizophrenia, schizoaffective disorder, or a psychotic disorder)
• Suicidal ideation-related hospitalizations within the past year
• Endorsement of current suicidal intent
• No intention to receive cancer care at a participating cancer center
• Insufficient literacy or comprehension
• MSKCC only: Already receiving tobacco treatment through the existing TTP service

*Patient is attending approximately one of their first 4 visits or are within 3 months of their initial visit date with their primary oncologist at a participating institution. Additionally, patients will be considered new if they 1) are seeking a second opinion and are opting to receive cancer care at a participating institution; 2) have local and distant recurrence of tumors with past cancers diagnoses; or 3) are diagnosed with a new form of cancer other than a previously treated type of cancer.

Recruitment

Eligible patients are identified and recruited by distinct mechanisms at the two participating institutions: The MGH in Boston, MA and the MSKCC in New York City, NY.

MGH. Potential participants are identified using multiple recruitment approaches, including 1) collection of a smoking status intake form; 2) screening of daily clinic patient lists; and 3) direct provider referrals. Specifically, new patients attending an MGH clinic in the thoracic, gastrointestinal (GI), genitourinary (GU), breast, head/neck, lymphoma, gynecological, or melanoma disease center answer a 2-question smoking status screener with multiple choice response options to the questions: “Do you now smoke cigarettes every day, some days or not at all?”, and “About how long has it been since you last smoked a cigarette, even a puff?” Screener questions are included on written clinic intake forms, attached as a stand-alone form in new patient charts or administered by a research staff member. Hard copy forms are collected daily, reviewed, and entered into a screening database by the study Research Assistant (RA). Potentially eligible patients are further identified from new patient lists circulated by each disease center as well as from oncologist referrals. A full electronic medical record review is conducted on patients with newly diagnosed or suspected cancer who report having smoked a cigarette, even a puff, in the prior month and who are $\geq$ 18 years of age. Full electronic medical record review includes screening

for all eligibility criteria, as appears in Table 1. If a patient is deemed eligible based on the electronic medical record review, a member of the patients' oncology care team is contacted to confirm medical eligibility and study suitability as well as obtain permission to introduce the study to the patient. For patients with an upcoming visit scheduled to the cancer center, a member of the research staff visits the patient during their appointment to introduce the study and provide a study information flyer. A patient can then decide at that time to enroll, refuse, or request to be contacted at a later date by a research staff member.

For patients who do not have an appointment scheduled for the near future, research staff mails a study information flyer and an opt-out letter co-signed by the study principal investigator (PI) and the study clinic liaison. The opt out letter instructs patients to contact research staff, via telephone number or email, within 7 days of receipt of the letter if they do not wish to participate. If a patient does not contact the research staff within 7 days, then a research team member calls the patient to discuss study participation.

MSKCC. Eligible patients at MSKCC are identified through either 1) routine referrals to the Tobacco Treatment Program (TTP) or 2) clinic-based identification of smokers in the outpatient thoracic, GI, GU, breast, head/neck, lymphoma, gynecological, and melanoma clinics. At MSKCC, it is the standard of care for all patients to be screened for smoking status (e.g., In the past 30 days, have you smoked cigarettes or used any other forms of tobacco [cigars, pipe, smokeless tobacco, electronic cigarettes]?), and patients who report current tobacco use (i.e., every day or some days) are automatically referred to the MSKCC TTP. MSKCC research staff screen the electronic medical records of all patient referrals to determine study eligibility; subsequently, all eligible patients are mailed an introductory letter that briefly explains the study and provides the RA's contact information so that they may contact the research team member to opt in or out of the study. The MSKCC tobacco treatment specialist (TTS) attempts to reach each eligible referral three times. If the TTS is unable to reach the patient, an RA makes three additional contact attempts (phone or face-to-face in clinic).

As stated above, patients are also recruited face to face through the MSKCC outpatient thoracic, GI, GU, breast, head/neck, lymphoma, gynecological, and melanoma clinics. To aid the physicians in identifying eligible participants, the clinic-designated RA reviews the daily clinic roster to identify patients who may be eligible for study participation. S/he then contacts the patient's physician either via e-mail and/or face to face in clinic so as to prompt the physician of the potential eligibility of this patient for study participation. The physician then confirms eligibility and advises the RA of when best to approach the patient for possible consent to this study. After

receiving physician approval, the RA approaches newly identified smokers as well as follow-up patients referred to the TTP who have not been reachable by phone. Potentially eligible patients who are approached in clinic are provided a study information sheet. All patients who express interest in study participation are asked to complete an eligibility screener with the RA before beginning consent procedures.

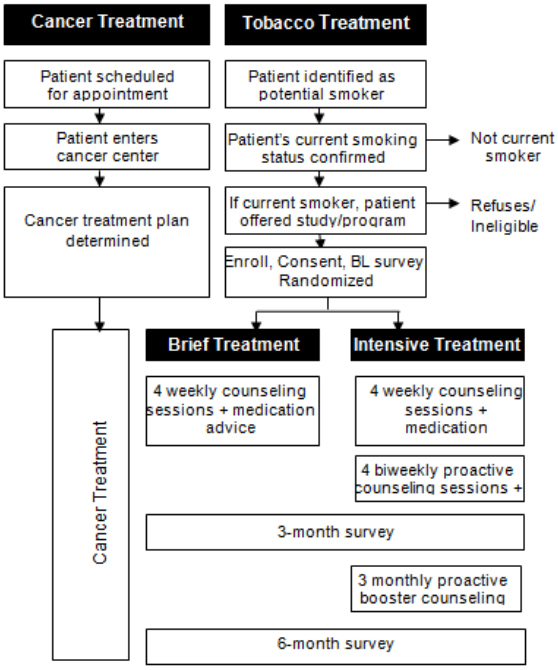
Enrollment

In order to minimize patient burden, consent and baseline procedures are typically scheduled in conjunction with an upcoming oncology visit. If a patient is unable to sign consent at the time of approach, a future appointment is scheduled with the patient to complete consent and baseline study procedures with the RA. Consent procedures are also completed via phone, followed by mailed consent, for patients who may not have upcoming appointments.

Assignment to treatment group

Participants are randomly assigned in a 1:1 fashion to either the SC or IC treatment arm using a computer-generated schedule of randomization IDs and treatment assignments in blocks of 6, stratified by study site and tumor type. After completing informed consent and baseline assessment procedures, the initial counseling session is scheduled to take place either in person or by telephone. Randomization to treatment arm occurs toward the end of the initial session, prior to discussion of cessation medication, when the TTS opens the assigned opaque, sealed randomization envelope. Both patients and the TTS remain blinded to study assignment until this point.

Figure 1: Study Design



Tobacco treatment interventions

Prior to receipt of counseling, all participants receive a study folder containing an informational sheet summarizing the benefits of quitting smoking for cancer patients, medication instruction sheets for bupropion, varenicline, patches and lozenges, a fact sheet outlining the current state of knowledge regarding e-cigarettes, and a monthly calendar for participants to monitor and track their cessation medication use.

Participants assigned to the SC group receive a total of 4 cessation counseling sessions plus medication advice. Participants randomized to the IC arm receive the same four sessions as the SC group. In addition, IC participants receive (1) extended counseling support and (2) up to 90 days of FDA-approved smoking cessation medication at no cost (Figure 1: Study Design). The counseling overview and session topics are shown in Table 2. Participants may withdraw from trial participation at any time, and they may be withdrawn by the investigators in the event of a referral to hospice or declining performance status (ECOG >2).

Counseling session format and content

All counseling sessions follow a motivational interviewing (MI) style, tailored according to stage of readiness. Utilization of an empathic MI style helps patients maintain motivation during a difficult time, such as initiating cancer treatment. MI is a particularly salient strategy for newly diagnosed cancer patients for several reasons: First, MI focuses on building and maintaining self-confidence, and our pilot work showed that this population reports low confidence; Secondly, the main MI tools (open-ended questions, affirmations, reflections, and summarizing statements) are effective when addressing sensitive topics, such as cancer and smoking-related beliefs (e.g., shame, fear of recurrence) and in delivering smoking information (e.g., risk/benefits of quitting in relation to cancer treatment). MI also utilizes a sensitive and effective strategy, known as "Elicit Provide Elicit," to convey health benefits [54]. Finally, MI skills can be used to encourage and sustain quit motivation by eliciting ideas and forming action plans, such as how to cope with cravings, cancer treatment or medication effects, adhere to medications, create smoke-free

Table 2. Counseling Overview

		Session #		Counseling Focus
Standard of Care				
	Intensive Treatment	1	Weekly	• Smoking assessment • Barriers to quitting and strategies to enhance readiness • Medication education and assistance
		2		• Cancer related care and distress, care team communication • Assess medication adherence and managing side effects • Knowledge about quitting at the time of diagnosis
		3		• Coping with cravings and withdrawal • Introduction to social support
		4		• Introduction to Stress management – deep breathing exercises
		5	Bi-weekly	• Introduce beginning with appreciations • Values clarification exercise • Smokefree home and car • Nicotine and addiction
		6		• Smoking associated stigma and negative self-talk • Stress management 2 – battery exercise • Weight gain concerns • Review values clarification exercise
		7		• Risk of other forms of tobacco • Types of social support • Stress management 3 – stress signs and coping
		8		• Rewards and pleasurable activities • Sleep and self-care • Breath awareness
		9	Monthly	• Fear of recurrence • Managing physical symptoms • Stress management 4 – single pointed focus exercise
		10		• Financial costs of smoking • Managing slips and relapses during/following treatment
		11		• Review overall smoking progress • Finalize smoking goals, relapse prevention • Post treatment support

homes, and learn mood management strategies.

The counseling session format is structured around the 5As format (Table 3), standardized, and tailored based on motivation to quit. The TTS Asks participants about their smoking status and progress; Advises participants to quit; Assesses participants' motivation, confidence, and readiness to quit; Assists participants in making a quit plan while addressing medication dosing and side effects; and Arranges for follow-up by summarizing the treatment plan and emphasizing treatment adherence. The first four counseling sessions occur weekly over a one-month period, and participants have the option to complete sessions in-person in coordination with their treatment schedule, or by phone. Participants may call or email the TTS if questions arise between sessions. All sessions close with a summary of session content and participant goals, a recap of participants' reasons for quitting/cutting back, a plan for the next call, and a reminder of assigned homework. The TTS documents each session in the electronic health record (EHR).

Table 3. Counseling session format

5As	Topics
Ask	Explore smoking history
Advise	Discuss the importance of quitting smoking in the context of a cancer diagnosis, benefits of quitting smoking prior to cancer treatment, and protecting self and loved ones from second hand smoke exposure (SHSe) Conduct motivational interviewing procedures that focus on decreasing SHSe
Assess	Evaluate readiness to quit (quitting importance and self-efficacy while facing a cancer diagnosis) using baseline survey responses
Assist	Make a quit plan in the context of a cancer diagnosis and treatment Discuss medication dosing and side effects
Arrange	Follow-up with summary of treatment plan and emphasize adherence to treatments

Initial counseling session. The initial counseling session lasts approximately 40 minutes. During this session, the TTS: 1) introduces the study, and provides an overview of the goals and structure of the program; 2) gathers a comprehensive smoking history, including past quit attempts and medication trials; 3) assess participants' concerns about smoking; 4) summarizes information gleaned and offers a personalized message to quit smoking; 5) assesses participants' importance and confidence to quit as well, as their pros and cons for quitting and continuing to smoke; and 6) evaluates participants' readiness to quit. For participants who are not ready to quit or make changes, the TTS focuses on addressing ambivalence and increasing motivation to quit by helping participants identify their specific barriers to quitting and by encouraging participants to keep a daily diary of their smoking rate and pattern. Keeping in line with MI principles, the TTS utilizes a patient-centered approach with setting cessation goals and does not counter resistance to quitting or making changes. The TTS 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. For participants who are not ready to quit but are willing to make changes, the TTS offers additional strategies, including assisting with different approaches to cutting back and creating a smokefree home/car. Participants who are ready to quit are offered each strategy aforementioned; in addition, they are assisted with setting a quit date and taking appropriate steps to prepare to quit. The TTS also discusses strategies to cope with cravings. The TTS assists the participant in setting a goal for the week and schedules a follow-up session for the next week.

Medication advice. Regardless of quit stage, all participants are offered medication advice to assist cessation efforts. A participant's medical history, prior quit and smoking cessation medication experiences, as well as attitudes toward medication, are considered when making medication recommendations. The TTS provides a general overview of the function, limitations, risks and benefits and usage guidelines for FDA-approved medications, and they use a Cessation Medication Decision Aid flowsheet to guide medication recommendation based on participants' history and preference. Subsequently, the TTS offers assistance with obtaining medication for patients who express interest. In order to facilitate communication with other providers, the TTS documents their medication recommendation as well as patients' preferences and interests in taking any of the smoking cessation medications in the patient's EHR.

Weekly follow-up counseling sessions. Following the initial counseling session, participants are offered 3 weekly proactive follow-up sessions. Sessions follow a similar format as the initial visit, wherein the TTS checks in on participants' smoking progress, cancer care status, level of quit confidence and importance, and level of distress. Further, the TTS assesses and intervenes on the use of cessation medications; specifically, the TTS monitors adherence, problem-solves barriers to medication use, and addresses medication concerns and side effects. Session time is also spent reviewing progress on goals set, which the TTS uses to help participants' reflect on content discussed in prior sessions. Session-specific modules are introduced to briefly discuss and assist with themes often impacting cessation behavior, such as stress and social support. Further tailoring of treatment occurs when the TTS checks in on quitting goals and targets their action plan based on participants' quit stage, which falls into one of four quitting goal branches: 1) does not want to quit; 2) now wants to quit or has tried to quit; 3) has quit but experienced lapse or relapse; and 4) has quit and stayed quit. Each branching logic is designed to meet participants where they are in terms of quit readiness, minimizing confrontation and maximizing intervention points based on their level of motivation to quit and cessation progress. Specifically, the TTS spends time assessing barriers to quitting and weighing the pros and cons for participants' who remain ambivalent;

identifying and assisting with triggers and cravings for participants who are preparing to quit or who have recently quit; and assisting with withdrawal symptoms for participants who have quit and may be at risk for relapse. The fourth session, the final session for SC participants, closes with a review of goals and accomplishments and a referral to the state quitline.

Extended counseling support. For the IC group, extended counseling consists of 7 additional counseling sessions. Participants receive 4 proactive biweekly sessions delivered over a 2-month period, and 3 monthly booster sessions; altogether, they receive ongoing counseling over a span of 6 months. The structure of each follow-up treatment session mirrors the initial weekly sessions, wherein the TTS 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. Specifically, the TTS may help participants with the following: 1) evaluation of values in the context of smoking behavior; 2) assistance with smoking-associated stigma and negative self-talk; 3) help with stress management, including identification of energy-depleting factors and reinforcement of stress-relieving activities; 4) overview of the risks of other forms of tobacco use; 5) promote effective use of different sources of support to help cope with cancer care and cessation efforts; 6) discuss the utility of reward systems for progressive steps toward quit goal; 7) assistance with maintaining adequate sleep and other aspects of self-care; 8) managing pain and physical symptoms; 9) discussing financial costs of smoking; and 10) preparing for relapse and long-term quit maintenance. All sessions reinforce the import of regular participation in counseling sessions, and all session highlight the value of maintaining adherence to cessation medications. All sessions also emphasize the importance of helping participants' identify things they are thankful for (appreciations) in the context of ongoing disease and treatment-related stressors and difficulties.

Smoking cessation medication. Participants who are randomized to the IC arm during the initial session receive the same information as the SC arm in regards to the risks and benefits of concurrent cessation medication use and counseling; however, participants in the IC arm receive an initial 4-week supply of free FDA-approved smoking cessation medication (varenicline, bupropion sustained release [SR] or nicotine replacement therapy [NRT]) of their choice, with the option to renew the medication twice for free for up to 90 days. Medications are administered according to the PHS guidelines [46]; specifically, participants opting to use varenicline or bupropion SR receive the same dose regardless of smoking level, and NRT dose is adapted to

level of smoking as needed for light smokers. Participants also receive a medication-monitoring calendar to keep a log of doses taken while enrolled in the study, to help promote and assist with smoking cessation medication adherence. Although participants are not required to select a medication during the initial visit, medication planning and problem-solving is revisited at each subsequent session; IC participants have up to 4 weeks to decide to initiate medication use and 3 months to change medication type if they do not respond to or tolerate their initial medication choice. Side effects are monitored by the TTS and discussed during weekly group supervision with the site PI.

MGH-specific medication dispensing procedures. Prior to dispensing the study medication, the TTS contacts the patient's treating oncologist for their approval and signature. Upon receipt of oncologist approval and script, the study site RA mails the study medication to the patient or provides the patient with the medication in-hand during one of their upcoming clinic appointments. The study psychiatrist reconciles patient medication requests within their EMR on a biweekly basis.

MSKCC-specific medication dispensing procedures. MSKCC clinical research procedures require a prescribing clinician to sign consent with each patient for all studies on which prescription medication is made available to patients. Therefore, patients randomized to the IC group who choose to take varenicline or bupropion SR are asked to sign an additional consent form at MSKCC. This consent is obtained by the MSK TTS after participants receive their initial counseling session, and it describes the purpose and risks of varenicline and bupropion SR use in this study. The TTSs at MSKCC commonly prescribe cessation medications independently within their scope of advanced practice nursing; as such, the MSK TTS also electronically prescribes study medications to patients randomized to the IC arm who elect to take cessation medications, and all study medications are dispensed from the hospital pharmacy. Patients with upcoming clinic appointments are able to pick up the medications at one of the two out-patient pharmacy dispensaries located on the MSKCC campus; alternatively, patients can opt to have the MSKCC pharmacy mail cessation medications to their home addresses.

Quality Assurance

Our treatment fidelity protocol abides by recommendations of the Treatment Fidelity Workgroup of the NIH Behavior Change Consortium (BCC). Specifically, the BCC cites monitoring the following 5 areas to ensure that studies reliably and validly test behavioral interventions [55]: 1) Design. We ensure that the treatment-assigned intervention (counseling and medication dose) is offered to participants through weekly team meetings,

which includes review of TTS documentation; 2) Training. All study TTSs are experienced, certified tobacco treatment specialists with expertise in smoking cessation medication and counseling for medical patients. Each underwent intensive training in tobacco treatment (including an online course and week-long in-person training provided by the Tobacco Treatment Specialist Training and Certification Program at the University of Massachusetts Medical School or Rutgers Tobacco Dependence Program), MI skills training, counseling protocol training, and specialized didactics on the deleterious health outcomes of smoking for cancer patients and managing cancer patients' distress (e.g., mood & stress management skills). The site PIs have conducted mock MI sessions with each tobacco specialist, guided by a modified MI Integrity scoring sheet [56], which includes acceptability thresholds [57, 58] to ascertain TTS readiness to begin MI counseling. In addition, to further ensure adequate training and protocol preparedness, each TTS listened to supervised cases, practiced each manualized session internally and completed 3 pilot cases prior to intervening with study participants. In addition to these measures, the TTSs a) meet weekly by phone with Drs. Park and Ostroff for group supervision and b) record all counseling sessions, of which 15% are randomly selected and reviewed for adherence by Drs. Park and Ostroff; 3) Treatment Delivery. For each session, the TTSs document the content covered, participant data (e.g., confidence, quit importance), and their impressions (participant's receptivity); all data are stored in an Access database. For suicidality concerns, the study PIs, both licensed clinical psychologists, contact patients to assess safety and, if needed, consult with the study psychiatrist and internist regarding significant psychiatric or medication concerns; 4) Receipt of treatment. At the end of each session, the TTS summarizes content covered, reviews participant goals for tobacco abstinence and medication adherence, and elicits participant's understanding of treatment; and 5) Enactment of treatment skills/knowledge. Participants set treatment goals and check-in on their progress during each follow-up session.

Assessments

Participants complete assessments three times during the study period, either by mail, electronically (through the secure web application, Research Electronic Data Capture [REDCap]), or administered over the phone in accordance with their preferences. The baseline survey is completed following informed consent and prior to initiating counseling; follow-up surveys are completed 3 and 6-months following baseline survey completion. Research staff send three and six-month follow-up survey reminder letters approximately one month prior to participants' survey due date; additionally, they initiate survey outreach attempts (e.g., phone calls, mailed

and electronic surveys) approximately two weeks prior to the target assessment time point. Participants who report smoking abstinence of at least 7 days during the 3 and 6-month follow-up are mailed a saliva collection kit with instructions for use and a pre-addressed, pre-stamped return envelope. Saliva samples are then sent to J2 Laboratories (Tucson, AZ) for cotinine assay. Participants who report smoking abstinence but would likely have elevated salivary cotinine levels due to use of nicotine-based smoking cessation medication or e-cigarettes are asked to complete, in-person, an expired air carbon monoxide sample. Participants are remunerated $20 for the baseline survey, $40 for each follow-up survey and $50 for each cotinine or expired air sample provided.

Participant surveys

Data collection includes the following domains: Sociodemographic questions, including *s*ex, age, race/ethnicity, marital/partner status, educational attainment, insurance coverage, employment status, caretaking responsibilities, language, religious affiliation, and family obligation as a perceived referent and support system, are collected from the baseline survey and the electronic medical record.

Table 4. Data Collection

Variable	EHR	Participant baseline survey	Participant follow-up survey	Tobacco treatment Specialist
Smoking outcomes			x	x
Sociodemographics	x	x		
Smoking History	x		x	x
Medical History	x			x
Emotions		x	x	
Cancer Beliefs		x	x	
Smoking Beliefs		x	x	
Physical Symptoms		x	x	
Environment		x	x	x
Cancer Treatment	x			
Tobacco Treatment			x	
Patient Satisfaction			x	

Smoking history. Questions include age at smoking initiation, the number of cigarettes smoked per day (historically, and in the past 30 days), number of minutes after wake until a cigarette (addiction), date of last cigarette, use of other tobacco products (including menthol, pipe, cigar, chewing tobacco, dip snuff, and e-cigarettes), frequency and reason for use of e-cigarettes, number of 24-hour quit attempts, longest time without a cigarette, presence of withdrawal symptoms, smoking cessation medication use and side effects, and use of alternative methods to help quit smoking (e.g., internet or phone-based program, hypnosis). Nicotine dependence is evaluated using a 2-item Heaviness of Smoking Index [59]. The index considers the time to first cigarette after waking and the daily consumption of cigarettes. Scores range from 0 to 6 with higher scores indicating higher addiction levels.

Medical history. A medical record review completed at baseline gathers information about cancer tumor types, stage, cancer treatment modality, treatment and diagnosis dates, and comorbid conditions.

Health Belief and Self Regulation Model Constructs. *Emotions*: Emotional distress is measured using the National Comprehensive Cancer Network (NCCN) Distress Thermometer, a one-item instrument assessing level of distress, from 0 or “no distress” to 10 or “extreme distress” in the past two weeks [60, 61]. The Stress Analog

Scale, a one-item instrument, measures participants' ability to cope with stress, from 0 or "not at all able" to 10 or "very much able" in the past two weeks. Anxiety and depression symptoms within the past two weeks are assessed using the General Anxiety Disorder Scale (GAD-7) [62] and the Patient Health Questionnaire-9 (PHQ-9) [63], respectively. Each are rated on a 4-point Likert scale from "not at all" to "nearly every day." The Perceived Stress Scale-4 (PSS-4) is a four-item generalized measure of the degree to which a respondent appraises situations in the past month as stressful [64]. The PSS-4 is scored on a 5-point scale from 0 "never" to 4 "very often."

Cancer Beliefs – Stigma. The Lung Cancer Stigma scale, a 5-item questionnaire scored on a 5-point scale from "strongly disagree" to "strongly agree," measures the extent to which shame is internalized [65].

Smoking Beliefs. Readiness to quit smoking is assessed with a one-item,10-point contemplation ladder with responses that range from "I enjoy smoking so much I will never consider quitting no matter what happens" to "I have quit and I am 100% confident that I will never smoke again" [66]. One item scored on an 11-point scale ranging from 0 or "not at all important" to 10 "very important" assesses participants' perceived importance of quitting smoking [67]. Five items scored on an 11-point scale ranging from 0 or "not at all" to 10 or "very much" assesses participants' perceived benefits of quitting smoking as they relate to their perceptions of the severity of their cancer, cancer therapy, and risk of recurrence [67]. Self-efficacy to resist smoking urges is assessed with an 11-item measure scored on an 11-point scale ranging from 0% or "no confidence at all" to 100% or "absolutely confident". Items were adapted from the 46-item Confidence Scale [68].

Physical Symptoms. Cancer symptom severity over the past two weeks is assessed with three stand-alone scales for fatigue, pain, and nausea [69]. The items are scored on an 11-point scale ranging from 0 or "no" levels of the symptom to 10 or "extreme" levels of the symptom. Sleep is assessed with two stand alone questions about hours of actual sleep and sleep quality during the past month [70]. One item is a fill in the blank with average hours of sleep per night. The other item is scored on a 1-4 scale ranging from 1 or "very bad" to 4 or "very good" overall sleep quality. One item from the Mood and Physical Symptom Scale is used to measure participants' urge to smoke in the past 24 hours [71]. This item is scored on a 6-point scale ranging from 0 or "not at all" to 5 or "all of the time."

Environmental Influences. Four items evaluate the level of second hand smoke exposure (SHSe) by asking participants about the number of people in the household who smoke, the smoking status of their spouse or partner, and the rules about smoking in their household and car [72]. Household smoking is scored with one 3-

point scale ranging from “no one is allowed to smoke anywhere” to “smoking is permitted anywhere.” Car smoking is scored on a 4-point scale ranging from “no one is allowed to smoke in my car” to “people are allowed to smoke in my car at any time.” Perceived social support is measured using the Partner Interaction Questionnaire (PIQ), a 20-item instrument divided into 2 subscales consisting of 10 positive behaviors and 10 negative behaviors scored on a 5-point scale from 0 or “never” to 4 or “often” [73]. An adapted 8-item instrument using 4 positive behaviors and 4 negative behaviors is used in this study. Four items of the Medical Outcomes Study (MOS) Social Support Survey, scored on a 5-point scale from 1 or “none of the time” to 5 or “all of the time” [74], are used to explore the types of support that patients with chronic conditions receive from others. Six items were derived from the Hospital Consumer Assessment of Healthcare Providers and Systems (HCAHPS) survey to assess the quality of the patient experience received from the participants’ oncology care team [75]. Items are scored on a 4-point scale from 0 or “never” to 4 or “always”. Seven items were derived from the Department of Health and Human Services to assess patient reported oncology provider communication [76]. Items are scored on a dichotomous scale of either 0 or “no” or 1 or “yes.”

Quality of Life. The EuroQol 5-Dimensional 5-Level Quality of Life survey (EQ-5D-5L) is a standard measure of current health consisting of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [77]. Each dimension is rated on a 5-point scale with responses ranging from “no problems” to “unable” or “no” to “extremely”. It was specifically designed to facilitate cost analyses.

Cost

Cost-effectiveness will be assessed using cost per quit as the outcome. We will examine the costs of implementation were this program to be implemented in a clinical setting; the major costs to be collected include training and responsibilities of the TTSs, consulting program physicians and the clinical supervisor, as well as the cost of the smoking cessation medications and general program equipment and space (Table 5).

Table 5. Cost data collection domains

Resource	Description	Source of resource data	Source of cost data
Tobacco Treatment Specialist (TTS)	Training (tobacco treatment specialist course, basic skills for working with smokers online course, motivational interviewing training), Supervision (weekly team meetings), Intervention delivery (pre-session preparation, cessation counseling, EHR note documentation, call attempts, database documentation)	Study records	Human resources data
Program Physician(s)	Medication reconciliation, psychiatric consultation, medication side effect consultation	Study records	Human resources data
Clinical Supervisor and Program Director	Training (motivational interviewing skills, mock cessation counseling), treatment fidelity (weekly group supervision meetings, review of randomly selected recordings, review of randomly selected EHR record documentation)	Study records	Human resources data
Smoking Cessation Medications	Up to a 3-month supply of FDA-approved smoking cessation medications provided to IC patients	Study records	Red Book, 2016
Equipment and Space	Hospital workspace, telephone use, folders, labels, stickers, phone cards, printing costs (paper and ink), mailing costs (envelopes and postage)	Study records	Study records

Outcome Measures

Intervention effectiveness: Smoking cessation

The primary outcome is verified 7-day point prevalence tobacco abstinence at 6-month follow-up. Participants are asked, “in the past 7 days, have you smoked a cigarette, even a puff?” This is verified by biochemically confirmed saliva cotinine (evaluated at both <10 and <15ng/ml), or <10 ppm expired air carbon monoxide (CO) for participants concurrently using NRT or e-cigarettes. The secondary outcome measures include biochemically confirmed point prevalence abstinence at 3 months, self-report outcomes, significant reduction, and 24-hour intentional quit attempts. We chose point prevalence abstinence since it is biochemically verifiable and highly correlated with continuous and sustained abstinence [78].

Treatment use and adherence

The treatment outcomes may be mediated by factors associated with smoking cessation medication usage and treatment adherence. Secondary outcome measures include: (1) the proportion of participants who use smoking cessation medications; (2) duration of medication use measured in number of days; (3) number of counseling sessions; and (4) length of counseling sessions.

Tobacco Treatment. Participants are asked about smoking cessation medication use over the past 3 months, including duration of treatment and side effects, at each of the follow-ups. Additionally, participants are asked about the use of non-study pharmacological and behavioral tobacco treatments (e.g.,nicotine gum, nicotine

nasal spray, nicotine inhaler, quitline, internet program, in-person quit smoking support, text messaging support, hypnosis, acupuncture). Smoking status screening and treatment by oncology providers via the 5As model of behavioral change is evaluated by a patient-reported measure consisting of 7 yes-no questions [76] at 3- and 6-months.

Program Satisfaction

Participant satisfaction with the program is assessed with five multiple choice questions: (1) "To what extent has the Smokefree Support Study program met your needs?" (4-point scale ranging from "none of my needs have been met" to "almost all of my needs have been met"); (2) Did you get the kind of smoking cessation assistance that you wanted? (4-point scale ranging from "no, definitely not" to "yes, definitely"); (3) "How would you rate the quality of the smoking cessation assistance that you received?" (4-point scale ranging from "poor" to "excellent"); (4) "How helpful has the Smokefree Support Study been for you?" (5-point scale ranging from "not at all helpful" to "very helpful"); (5) "If a friend were in need of similar help, would you recommend the Smokefree Support Study to him or her?" (4-point scale ranging from "no, definitely not" to "yes, definitely"). Furthermore, participants are asked seven open-ended questions: (1) "What about the Smokefree Support Study did you find the most helpful? Why?"; (2) What about the Smokefree Support Study did you find the least helpful? Why?"; (3) What were some of the challenges you faced to participating in this program?"; (4) Please list any recommendations (e.g., additional topics, skills to include) of how we can improve the Smokefree Support Study?"; (5) What other kinds of programs would have been helpful to have around the time of diagnosis?"; (6) What kinds of programs would be helpful for you now?"; and (7) "Is there anything else you'd like to tell us?"

Data analysis

Sample size calculations

We conservatively estimate a 6-month biochemically-confirmed 7-day point-prevalence tobacco abstinence rate of 15% in the SC group and 30% in the IC group [37-39, 79]. With a sample size of 268 participants, 134 in each arm, we will have 80% power to detect a difference of 15% with a two-sided significance level of 0.05. We conservatively estimate that 10% of participants will die within 6-months of enrollment [80], so an additional 10% (n=27) will be recruited. Thus, 295 participants will be needed to have a fully powered trial for the intention-to-treat analysis.

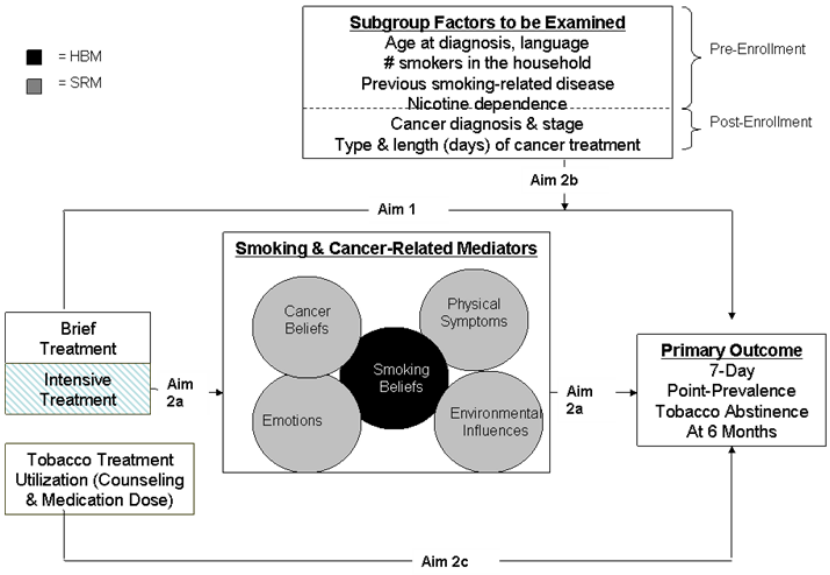
At the outset, we will examine the frequency distributions of all variables. We will compare the baseline characteristics of participants in the two groups. Data from both sites will be pooled for analysis, after confirming there is no significant heterogeneity between sites or adjusting as needed. Primary analyses will be intent-to-treat; we will classify participants who are lost to follow-up and those who do not provide a self-reported smoking status or saliva or air sample as current smokers [81]. In addition, we will determine whether there is differential dropout in the two groups and consider developing probability-of-completion weights [82] to obtain unbiased estimates of the effect of the treatment. We will assess whether the mechanism of missing data is missing at random [83]. The study results will be submitted for publication and thus available to the public and the medical community upon trial completion.

Aim 1

We will conduct univariate and multivariable analyses to examine the association of treatment group with the primary outcome (X→Y)(7-day cotinine confirmed abstinence) and secondary smoking outcomes. We will also explore associations between the primary and secondary smoking outcomes. For univariate analyses, we will compare the outcomes between the two treatment groups. For multivariable analyses, we will use logistic regression models to compare the two groups, adjusting for potential confounding factors. Then, to study the intervention effect over the entire follow-up period, we will likely use the Generalized Estimating Equations (GEE) approach to include data from both 3-month and 6-month follow-up.

Aim 2

Figure 2. Treatment Model



Aim 2a: We will explore the impact of potential mediators of the intervention effect (Figure 2: Treatment Model). We will test for 1) a significant association between treatment and the mediator (X→M) and 2) a significant association between the mediator and smoking outcome (M→Y) (controlling for treatment X) [84]. Supplemental to this approach, we will potentially use methods (e.g., difference in coefficients method or product of coefficients method) to estimate the

strength of the mediated effect (e.g. partial) [85]. We will likely use the latent-difference-score model, in which change in the mediator between the start and end of treatment influences abstinence at 3 months (acquisition of abstinence) and 6-months (maintenance of abstinence).

Aim 2b: We will also identify subgroups that experience a greater treatment effect. We will test the interaction terms between these variables and treatment assignment in the logistic regression models. Those with significant interactions ($p<.15$) will be considered as candidates for identifying subpopulations.

Aim 2c. We will conduct univariate and multivariable analyses to explore the association of treatment utilization on the primary smoking outcome. We will examine the "dose" (medication use and counseling use). Medication use and counseling use will potentially be considered as continuous variables and dichotomized variables. We will dichotomize medication and counseling use into two levels: low vs. high. A medication regimen completion of $\geq$10 weeks would likely be considered as high medication use [86]. From our pilot data, an equivalence of ≥8 counseling sessions would likely be considered as high counseling use for IC participants and $\geq$3 as high for SC participants. For univariate analysis, we will use chi-square tests to compare the primary smoking outcome between medication use and counseling use groups. For multivariable analysis, we will use logistic regression models.

Aim 3

Among eligible smokers, we will conduct univariate analyses and a multivariable logistic regression model to examine the associations of patient characteristics with enrollment (Y/N). Then, within each treatment group, we will determine the association between participant characteristics and treatment utilization. For multivariable analysis, we will use linear regression models to determine the effect of participant characteristics, adjusting for confounding factors, on treatment utilization.

Data management

The master database is located at MGH and was built and tested during Year 1. Each site has a secure, access-restricted MS Access database application for recording recruitment and enrollment data, tracking enrolled participants, and entering follow-up survey data. The database is designed to trap data entry errors.

MSKCC sends its database to MGH on a biweekly basis via an MGH mechanism for securely transferring files. The site databases are reviewed following each transfer, and questionable entries are flagged and reported back to the site PI and RA.

The trial is being monitored by a Data Safety and Monitoring Board (DSMB) comprised of five independent scientists not otherwise affiliated with the trial. They are experts in the field of oncology, psychiatric oncology, smoking cessation and biostatistics. The DSMB meets biannually to review ongoing patient safety, important protocol modifications, adverse events and protocol deviations, study progress, and data integrity.

Discussion

Continuing to smoke following a cancer diagnosis may result in poor clinical outcomes. Indeed, the 2014 Surgeon General's Report [2] concluded that there is sufficient evidence linking smoking to adverse health outcomes in cancer patients. Accordingly, several national organizations, including ASCO and the American Association for Cancer Research (AACR), promote incorporating tobacco treatment into the delivery of cancer care. However, existing PHS guidelines have yet to be integrated into oncology settings. Thus, we built on previous research to compare the effectiveness of integrating two evidence-based tobacco treatments into cancer care delivered at two NCI-designated Comprehensive Cancer Centers. This tobacco treatment effectiveness data could provide valuable guidance for the advancement and integration of tobacco treatment into cancer care settings.

This paper describes the study design and systems that were created to identify, approach and engage cancer patients who smoke in evidence-based tobacco treatment consisting of smoking cessation counseling and medication. Moreover, this paper provides detailed information of our treatment integration process and, specifically, it outlines methods for accomodating two existing care delivery systems; we provide essential information about variations in how patients are identified (e.g., automated versus created system) and approached (automated referral versus clinician approval), and we outline different strategies for medication dispensing (tobacco treatment specialist with prescription privileges versus treatment specialist without). This illustrates potential treatment program modifications that must be considered for broad program implementation.

This trial assesses the effectiveness of a combination tobacco treatment, consisting of extended counseling (11 sessions) plus in-hand FDA-approved medication choice versus standard care (standard counseling [4 sessions]) plus advice on FDA-approved medication choice. Our focus on assessing the impact of

an intervention that includes the provision of in-hand medications is noteworthy given that considerable treatment access and cost barriers may pose an obstacle to tobacco treatment. In 2014, the Affordable Care Act extended cessation coverage benefits [87], yet many patients remain unable to obtain, and receive coverage for, smoking cessation medications. If our IC treatment is effective, we will explore the relative contribution of the counseling and medication components; we intentionally did not select a factorial design, which would have allowed us to assess the independent effects of the counseling and medication, as previous work supported the use of combined treatment as the strongest intervention.

There are many design innovations of this work that will facilitate its implementation. Firstly is our ability to overcome system, provider, and patient barriers to intervene with smokers during the critical time period of cancer diagnosis. Correspondingly, our collaborative care approach links tobacco and oncology providers in a way that is sustainable and minimizes oncology provider burden. In the spirit of integration, our flexible inclusion criteria and telehealth counseling delivery modality maximizes patient inclusivity and accessibility; specifically, treating patients regardless of their level of quit motivation, cancer stage, or smoking cessation medication uptake. Our evidence-based treatment, guided by behavior change models that address the interplay of emotions and cognitions, is continued throughout the patients' cancer diagnosis, treatment determinations, and course; it is flexible in that it accommodates real world cancer treatment schedules among patients with a variety of tobacco-related and non-tobacco-related cancers.

At trial conclusion, we will investigate several unanswered questions about the provision of tobacco treatment as part of comprehensive cancer care. Specifically, we will assess why and how the proposed tobacco treatments work, for whom, and which patients may be reached. These answers will ensure the maximal impact of the disseminated results. To inform future implementation efforts for uptake of this treatment for cancer centers, we will assess the cost of each treatment. This information will help guide future research on the long-term impact of tobacco treatment on cancer care outcomes.

Declarations

Abbreviations

AACR: American Association for Cancer Research; ASCO: American Society for Clinical Oncology; BCC: Behavioral Change Consortium; CanCORS: Cancer Care Outcomes Research and Surveillance; CO: Air carbon monoxide; ECOG: Eastern Cooperative Oncology Group; EHR: Electronic health record; EQ-5D-5L: EuroQol 5-Dimensional 5-Level Quality of Life survey; FDA: Food and Drug Administration; GAD-7: Generalized Anxiety Disorder-7; GEE: Generalized Estimating Equations; GI: Gastrointestinal; GU: Genito-urinary; HBM: Health Belief Model; HCAHPS: Hospital Consumer Assessment of Healthcare Providers and Systems; IC: Intensive Counseling; MGH: Massachusetts General Hospital; MI: Motivational interviewing; MOS: Medical Outcomes Study; MSKCC: Memorial Sloan Kettering Cancer Center; NCCN: National Comprehensive Cancer Network; NCI: National Cancer Institute; NIH: National Institutes of Health; NRT: Nicotine replacement therapy; PHS: Public Health Service; PHQ-9: Patient Health Questionnaire-9; PI: Principal investigator; PIQ: Partner Interaction Questionnaire; PSS-4: Perceived Stress Scale-4; QOPI: Quality Oncology Practice Initiative; RA: Research Assistant; REDCap: Research Electronic Data Capture; SC: Standard of Care; SHSe: Second hand smoke exposure; SRM: Self-Regulation Model; SR: [Buproprion] sustained release; TTS: Tobacco treatment specialist; TTP: Tobacco treatment program

Ethics approval and consent to participate

The study is approved by the MGH/Partners Health System Institutional Review Board and the Memorial Sloan Kettering Cancer Center Institutional Review Board. Informed consent was obtained from all participants prior to participation in study activities.

Consent for publication

Not applicable.

Availability of data and material

Data requests can be directed to the corresponding author.

Conflicts of interest

Dr. Nancy Rigotti has a research grant and has been a consultant (without honorarium) for Pfizer. Drs. Rigotti

and Park receive royalties from UpToDate

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Author's contributions

All authors contributed to the design of the study. EP, JO, GP, SB, KH and EF contributed to the drafting of the manuscript. **All authors read and approved of the final manuscript.**

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Trial Registration

Integrating Tobacco Treatment into Cancer Care: A Randomized Controlled Comparative Effectiveness Trial (# NCT01871506). Registered June 4, 2013.

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