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Feasibility of Delivering a Quitline Based Smoking Cessation Intervention in Cancer Patients Receiving Outpatient Treatment: A Pilot Study

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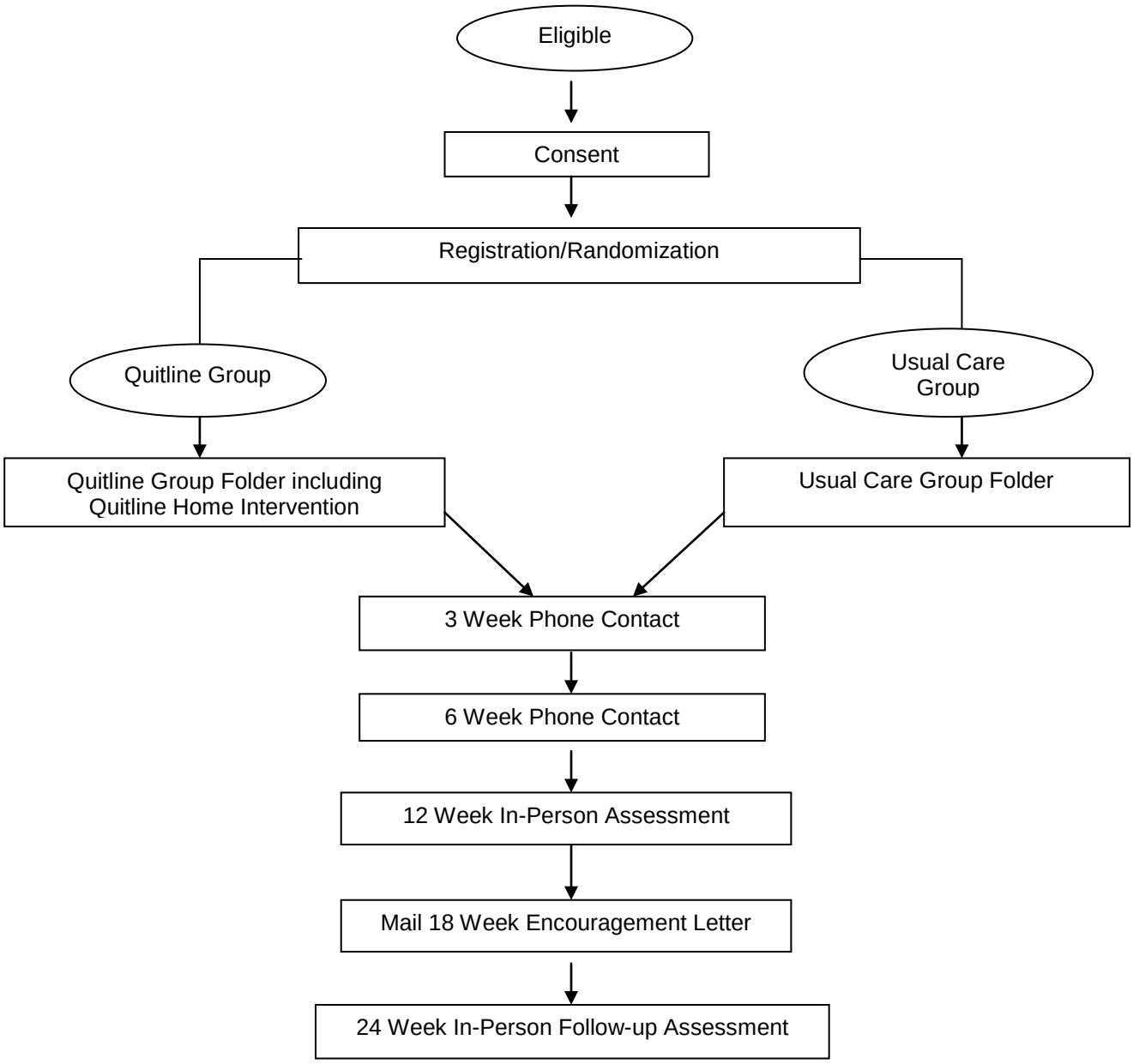
SCHEMA



Stratification: stratified by time since diagnosis (<3 months, ≥ 3 months) and number of cigarettes smoked per day (≤ 10, ≥ 11)

Sample Size: 146 total (2:1 randomization) 97 Intervention 49 Usual Care

Brief Inclusion Criteria:

- AJCC Stages 0, I, II, & III lung, breast, prostate, colorectal, bladder, head & neck, and cervical (all histologies).
- Reports smoking any amount in the last 7 days
- Scheduled to receive or currently receiving surgery, chemotherapy or radiation OR have received one or more of the following within the last 6 months surgery, last radiation treatment, or last chemotherapy treatment,

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1. OBJECTIVES

The goal of this study is to evaluate a smoking cessation intervention among cancer patients who are scheduled to receive or currently receiving surgery, radiation or chemotherapy OR have received one or more of the following within the last 6 months surgery, last radiation treatment, or last chemotherapy treatment in a community outpatient setting.

1.1 Primary Objective

To assess the feasibility of delivering a Quitline based smoking cessation intervention to cancer patients in an outpatient setting. To achieve this, we will deliver the intervention to cancer patients in the surgery, radiation and medical oncology departments of participating Community Clinical Oncology Program (CCOP) sites. Following the intervention, we will assess participant, CRA (Clinical Research Associate) Counselor and Quitline staff ratings of acceptability, resources required to deliver the intervention, protocol fidelity, and participant recruitment, retention and adherence.

1.2 Secondary Objectives

1. To obtain a preliminary estimate of the quit rate (as defined by 7 day point prevalence abstinence) in intervention and control groups. To accomplish this aim, following the intervention we will collect confirmed smoking status data for intervention and control subjects. We will also obtain a preliminary estimate of the treatment effect (difference in quit rates between the two groups) and the standard deviation to better determine the sample size for a future trial.
2. To evaluate primary patient reported outcomes, including quality of life (quantified by the FACT-G and for lung cancer patients only the FACT-L other concerns questions and the EORTC QLQ LC13), perceived life stress (quantified by the Perceived Stress Scale), and depression (quantified by the CESD-10), in cancer patients in the intervention and control groups.
3. To refine the recruitment and intervention protocols using data collected from participants, CRA Counselor and Quitline staff to increase acceptability and improve retention in future trials.

2. BACKGROUND

2.1 Study Disease

Risks of Cigarette Smoking after Cancer Diagnosis. Cigarette smoking accounts for approximately one in five deaths among US adults and is the leading cause of preventable death in the United States(1-5). Continued smoking after a cancer diagnosis has been linked with several adverse outcomes for cancer patients, including reduced treatment efficacy treatment complications, cancer recurrence, and second primary tumors(6, 7). In one study, head and neck cancer patients who continued to smoke during treatment had a reduction in complete treatment response (74% vs. 45%)(8). Cigarette smoke has been shown to interact with drug metabolizing enzymes and to effect plasma concentrations of certain chemotherapeutic agents, including erlotinib and irinotecan(9, 10). This may place smoking patients at increased risk for treatment failure. Smoking also places patients at higher risk for adverse outcomes associated with surgical, radiation, and chemotherapy

cancer treatments(6, 9). Smoking has been associated with severe pulmonary and wound-healing complications following surgery(11-13) and complications associated with radiation(14, 15). Continued smoking may also cause difficulties with chemotherapy, including exacerbated toxicity and side effects, further immune system impairment, and elevated incidence of infection(6, 16-19). Smoking among cancer patients may increase risk for and extend the duration of oral and gastrointestinal mucositis(20-22), which is associated with delayed and discontinued cancer treatment, a two-fold increase in hospital stay, and substantial financial burden(23). In one study of stage III non-small cell lung cancer patients receiving combined thoracic radiation therapy and chemotherapy, severe esophagitis was reported less frequently in those patients who stopped smoking more than 6 months prior to treatment compared to those who were smoking(24). Smoking has also been identified as a risk factor for cancer recurrence in several patient populations, including head and neck, bladder and prostate cancer survivors (15, 25, 26). One study found that bladder cancer patients who stopped smoking after their diagnosis had a significantly lower risk of disease recurrence or progression compared to patients who continued smoking(27). Cancer patients who smoke also have increased risk of second primary tumors (SPT), whether or not the first primary tumor is smoking-related (6, 28-31). Smoking may also interact with treatment to increase risk of SPTs. Women with breast cancer treated with chest irradiation who smoke had a significantly elevated risk of a subsequent lung cancer compared both to women who did not receive chest irradiation and with non-smoking women who received chest irradiation(32). Cigarette smoking also appears to amplify risk of subsequent lung cancers among patients treated for Hodgkin's lymphoma(33). Further, smoking after cancer diagnosis is associated with increased symptoms, poorer performance status, and poorer quality of life during and after cancer treatment (34-40).

Cigarette Smoking and Cancer Survival. Increasing evidence links cigarette smoking with poorer survival after cancer. In a study of over 25,000 cancer patients, every smokers had a significantly lower 5-year survival rate than nonsmokers, with significant effects observed for oral, pancreatic, breast, and prostate cancers in subgroup analyses(41). In a study of non-small cell lung cancer patients receiving radiation therapy, median survival for current/recent smokers was 13.7 months, compared to 27.9 months for non-smokers(42). Smoking has also been identified as a risk factor for poorer survival after lung, colorectal, cervical, ovarian, bladder, prostate, and head and neck cancers (3, 15, 25, 26, 43-48).The evidence linking smoking and poorer survival after breast cancer is mixed, with some studies finding no effect(49), but others finding increased risk of death, primarily due to lung cancer and respiratory disease(50).Few studies have been able to assess the specific survival impact of quitting smoking after a cancer diagnosis. However,in a meta-analysis of the effect of continued smoking after an early stage lung cancer diagnosis, continued smoking was shown to substantially increase the risk of death (Hazard Ratio 2.94, 95% confidence interval 1.15 to 7.54)(41). The majority of the increased risk was due to cancer progression rather than cardio respiratory disease.

Prevalence of Cigarette Smoking after Cancer Diagnosis. Unfortunately, a substantial number of patients with cancer continue to smoke after their cancer diagnosis, with estimates ranging from 15-25% for the overall population of survivors(2, 51-53). The highest rates of current smoking have been observed among patients with tobacco-related cancers, typically defined as lung, bladder, esophagus, and head and neck malignancies, with smoking prevalence around diagnosis estimated to be 20-40%(4, 51).High rates are also observed among cervical cancer survivors, with prevalence estimated at 48%(2, 3). Among recent studies of lung cancer patients, the rate of smoking at the time of diagnosis is estimated to be 24-40%(24, 37, 54, 55), with 10-20% smoking at some point after diagnosis(24, 42, 55, 56). Even among lung cancer patients who quit smoking to receive surgical treatment, nearly half return to smoking within the first year after treatment, and

most of this relapse occurs within the first two months after surgery(57). Lower risk perceptions, lower quitting self-efficacy, and more intense cravings have been linked with persistent smoking or relapse to smoking following lung cancer treatment(54, 57).

Previous Smoking Cessation Interventions in Adult Cancer Survivors. While smoking cessation intervention research is quite extensive, few empirical research studies have investigated the effectiveness of smoking cessation interventions among cancer patients. A systematic review of all quasi-experimental smoking cessation interventions on cancer patients conducted between 1976-2006 showed that of eight eligible interventions, only two showed an effect on smoking in adult cancer patients close to diagnosis(39). The most common limitations of the non-significant intervention studies included small sample size (three included less than 30 patients(58-60)), receipt of intervention components by the control group (approximately 50% of control participants received intervention components in two of the larger unsuccessful trials(61, 62)), and relatively high attrition (30-40%(62, 63)). Quit rates in intervention groups varied dramatically depending on sample characteristics (proximity to diagnosis, site) and duration. Six month quit rates ranged from 14-71%, with most in the 20-40% range. Control group quit rates were similarly variable, ranging from 12-55%. In general, higher quit rates were observed among head and neck cancer patients, those enrolled in more intensive intervention trials, and newly diagnosed cancer patients.

In the largest of the successful trials(64), 184 head and neck cancer patients reporting current smoking, an alcohol problem, and/or depression were randomized to one of two conditions: (a) usual care, which included a referral to smoking cessation, alcohol treatment, and/or psychiatric evaluation, or (b) a nurse- administered intervention including a cognitive behavioral therapy-based smoking cessation workbook with exercises coordinated by a nurse over the telephone, as well as nicotine replacement and bupropion. Smoking cessation rates were significantly higher in the intervention group compared to the control group at 6 months post-intervention (47% vs. 31%, $p<0.05$). Our intervention will share several characteristics with this successful intervention, including a high intensity cessation intervention delivered primarily by phone and provision of pharmacotherapy.

Smoking Cessation Quitlines. Telephone-based programs for facilitating cessation among tobacco users, or Quitlines, have been recognized as one of the most successful behavioral public health interventions(65). Their convenience and wide availability through state and national programs mean that Quitline interventions may have the ability to reach a large proportion of smokers in the United States, including underserved populations. Quitline based interventions have proven to be efficacious in trials including more than 24,000 participants. A large meta-analysis concluded that participants in Quitline interventions were almost 40% more likely to have quit at follow-up compared to control participants(66). To date, there have been no clinical trials examining the appropriateness or effectiveness of Quitline interventions for adults with cancer.

The Quit For Life Program. The Quit For Life program is a scientifically validated tobacco cessation program providing comprehensive cognitive-behavioral counseling and ongoing support through individualized telephone counseling, nicotine replacement therapy, mailed written materials, and an interactive online program designed to complement the phone-based treatment sessions. The program, currently delivered by the company Free and Clear, Inc., has been commercially available for over 20 years and its effectiveness has been demonstrated in six large randomized trials (67-71) and several program evaluations. The counseling approach is grounded in social cognitive theory(72) and incorporates the strategies for effective tobacco dependence treatment outlined in the U.S. Public Health Service Clinical Practice Guideline(73). Medication support, including the

recommendation of and provision of nicotine replacement medications, is commonly included in the Quit for Life Program.

Although the effectiveness of this program for adults with cancer has not been tested, results of the Quit for Life program have been examined for adults with diabetes and other chronic medical conditions (internal data provided by Free and Clear). Among quit line callers with diabetes, the 30-day quit rate was 24.3%, compared to 22.5% for adults without diabetes. Another analysis of 195,057 tobacco users from 15 states enrolled in the Quit for Life program found that 32.3% reported having asthma, heart disease, chronic obstructive pulmonary disease, or diabetes. Although those callers with a chronic disease were less likely to quit smoking (22.3% compared to 29.7%), a substantial proportion were still able to achieve cessation. These data suggest the Quit for Life intervention is an appropriate intervention for patients with smoking–related medical conditions.

Quit Coaches undergo 240 hours of training in topics such as nicotine dependence, clinical assessment, use of cessation medications, motivational interviewing and cognitive-behavioral counseling techniques, proven quitting strategies, privacy practices, crisis protocols, tobacco use among special populations, customer service, and software application skills. All Quit Coaches pass a skill assessment review before beginning a three week transition period during which they complete a minimum of 320 hours of experience and receive ongoing supervision. The Quit for Life Program has a rigorous ongoing call quality monitoring program using Aspect software called Envision to randomly record and evaluate call and data collection quality. Calls are graded against a call monitoring tool to enable clinical and data accuracy. Staff performance issues are addressed promptly during supervisor feedback sessions. Results from call evaluations are recorded in a centralized database and used to improve training and assess ongoing performance.

2.2 Intervention

Delivering a Quitline Based Smoking Cessation Intervention to Cancer Patients in Outpatient Settings. We propose to enhance the Quit For Life intervention for implementation in the outpatient oncology setting by adding a brief health care provider component and then assessing its feasibility among cancer patients (hereafter referred to as the Quitline intervention). Nicotine replacement patches will be offered at no cost to all participants enrolling in the Quit for Life Program through the Quitline intervention group. Habitrol patches will be the product of choice to be provided by Alere Wellbeing Inc. Delivery of a smoking cessation intervention in this cancer population and environment may take advantage of a teachable moment, as a cancer diagnosis can motivate patients to make quit attempts (74, 75). Some healthcare providers believe that the diagnosis of a serious disease, such as l cancer, could make smoking cessation less of a priority for the patient or may be unaware of the benefits of quitting smoking for cancer patients (76). However, research has demonstrated that patients with a life-threatening illness are more open to hearing smoking cessation advice and more motivated to quit smoking (62, 77-80). While providers sometimes hesitate to burden their cancer patients with the responsibility of quitting smoking(81), it may be empowering for patients to hear that there is something that they can do to improve their treatment outcomes and reduce complications. In addition, concerns about increasing psychological distress in a vulnerable population may be misplaced. Evidence in cancer patients suggests that quitting smoking can decrease anxiety and improve psychological adaptation to cancer diagnosis and treatment (82, 83). Cancer is a teachable moment for smoking cessation, and yet, this opportunity often goes underutilized (74, 78).

Beyond its promise in cancer patients, the outpatient oncology setting is an optimal environment for delivery of a Quitline based smoking cessation intervention. Many smokers who wish to quit do not look for help. This approach brings the intervention to the patient, rather than relying on patients to seek it out. The telephone format is convenient for cancer patients receiving treatment and reduces the travel and scheduling burden. In addition, the regular, consecutive interactions with cancer treatment providers may provide opportunities for the patient to receive ongoing encouragement and support for smoking cessation. Further, while the cost-effectiveness of this intervention has not been studied in cancer patients, it is expected to be inexpensive to deliver and a reasonable use of clinic resources.

Little is known about the smoking cessation interventions provided by oncologists in the outpatient setting. Preliminary research conducted by the PI suggests that most oncologists report advising patients to quit smoking, but far fewer regularly provide other cessation services (help setting a quit date, self-help materials, or medications). The Treating Tobacco Use and Dependence Clinical Practice Guideline(73) recommends that health care providers deliver brief interventions including the "5 A's". We will provide all oncologists who enroll a participant with a cancer-specific practice guide that include strategies for delivering a brief cessation intervention. We will also provide all participants in the usual care condition with a self-help guide to quitting smoking. We recognize that there may be considerable variability in what cessation services occur as part of "usual care" and will specifically assess cessation services used in both groups.

2.3 Rationale and Feasibility

Continued smoking after a cancer diagnosis has important health consequences beyond the risks associated with smoking in the general population. Smoking reduces the efficacy of cancer treatments including surgery, radiation and chemotherapy (6, 8-13). Cancer patients who smoke are at increased risk for second primary tumors and severe treatment complications, including mucositis of the oral cavity and gastrointestinal tracts(6, 9, 20-24, 31, 84). Continued smoking after cancer diagnosis is associated with diminished quality of life and reductions in survival (8, 26, 34, 37-39, 41, 85). Despite the negative consequences, it is estimated that between 15-75% of patients with cancer continue to smoke after their cancer diagnosis (51, 52, 56, 57, 75). The proposed study seeks to evaluate a smoking cessation intervention among cancer patients currently receiving treatment in an outpatient setting. Lung, breast, prostate, colorectal, bladder, head & neck, and cervical cancer patients were chosen because there is evidence of potential clinical benefit associated with quitting smoking in all of these populations and they represent a mix of both smoking and non-smoking related cancers.

The Comprehensive Cancer Center of Wake Forest (CCCWFU) Community Clinical Oncology Program (CCOP) Research Base (hereafter referred to as the "Research Base") is comprised of 25 participating CCOPs, 3 prevention members (non-CCOP aligned regional cancer centers), and the CCCWFU. Since many CCOPs have multiple sites, the total number of cancer centers participating in Research Base studies is 116. For all concepts submitted to the NCI for review, a survey is sent to participants to assess their interest in the concept and estimate accrual. For the proposed concept, the survey asked the following questions: 1) How many patients do you see annually with newly diagnosed Stage I-III non-small cell lung cancer? Small cell lung cancer? 2) What percent of these lung cancer patients are smokers?; and 3) How many patients do you think you can enter on study? Caucasian? Minority?. Sixteen of 25 CCOPs (64%) plus CCCWFU responded to the survey expressing their interest in participating on the study. The participants estimated that over two years

they would see 4407 patients with non-small cell lung cancer and 591 with small cell. Seventy percent of these patients (range, 15-100%) were thought to be smokers. The estimated number of patients who could be put on study over two years was 791, 606 with nonmetastatic non-small cell lung cancer and 185 with nonmetastatic small cell. This represents 18% of newly diagnosed lung cancer patients seen by respondents. The 791 estimated patients translate into 395 patients per year, or roughly 33 per month. The anticipated minority accrual was 23% of patients, about double the average minority accrual to Research Base studies over the last 5 years. The sample size for the present protocol is 146. In general, we estimate that actual accrual will be about one-quarter of that projected, or for the proposed study, 8 patients monthly. Thus, accrual for the proposed protocol should be completed in 18 months or less.

3. SUMMARY OF STUDY PLAN

3.1 Study Design

For the Primary Objective, we will deliver the enhanced Quitline intervention to lung, breast, prostate, colorectal, bladder, head & neck, and cervical cancer patients who are scheduled to receive or currently receiving surgery, chemotherapy or radiation OR have received one or more of the following within the last 6 months surgery, last radiation treatment, or last chemotherapy treatment at a participating Community Clinical Oncology Program (CCOP) sites. Following the intervention, we will assess participant, CRA Counselor and Quitline staff ratings of acceptability, resources required to deliver the intervention, protocol fidelity, and participant recruitment and retention. To achieve the Secondary Objectives, we will collect confirmed smoking status and participant reported outcomes data for intervention and control subjects for a follow-up period of 6 months.

3.2 Number of Participants

Number of participants to be enrolled (total number and number per arm): Total 146; 97 in intervention and 49 in usual care.

3.3 Study Population

All lung, breast, prostate, colorectal, bladder, head & neck, and cervical cancer patients with appointments in medical, radiation, or surgical oncology departments of participating CCOPs will be screened for this research study. Eligible patients include those who are scheduled to receive, receiving, or completed a first course of treatment (surgery, radiation, or chemotherapy) within the past 6 months whichever is most recent.

Consecutive patients with a diagnosis of AJCC Stages 0, I, II, & III lung, breast, prostate, colorectal, bladder, head & neck, and cervical cancers (all histologies), who are at least 18 years of age, speak English, report smoking within the past 7 days, and are willing to consider quitting smoking, will be asked to participate in the study. Patients will be excluded if they are unable to comprehend study documents and provide informed consent. (86). Patients with drug and alcohol abuse, assessed using screening questions for each, will also be excluded (87, 88)

3.4 Intervention Plan Overview

Study participants will receive a baseline assessment after they consent to participate and before randomization (see Table 1). The intervention period will last 12 weeks (approximately 1

week for the in-office intervention and 12 weeks for all components of the Quitline intervention-telephone counseling and nicotine patches). Follow-up assessments will be administered at 3, 6, 12, & 24 weeks after the date of the in-person intervention (for Quitline Intervention group) or the provision of the physician letter (for the Usual Care Plus group). (See Sections 7.1 for detailed plan and Section 7.9 for Study Parameters.)

3.5 Study Assessment Overview

Assessments of smoking status and primary patient reported outcomes at baseline, 3, 6, 12, & 24 weeks post-intervention. (See Section 7.2 for detail description of assessment tools and use.)

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

4.1.1 AJCC Stages 0, I, II, & III lung, breast, prostate, colorectal, bladder, head & neck, and cervical cancers (all histologies).

4.1.2 Reports smoking any amount in the last 7 days

4.1.3 Scheduled to receive or currently receiving surgery, radiation or chemotherapy OR have received one or more of the following in the last 6 months surgery, last radiation treatment or last chemotherapy treatment.

4.1.4 18 years of age or older

4.1.5 KPS of 70-100

4.1.6 Ability to understand and the willingness to sign a written informed consent document

4.1.7 Willing to consider quitting smoking

Note: Patients who decline to enroll in the study should be asked to complete the Decline Form (Appendix 16). No identifying information should be included on this form.

4.2 Exclusion Criteria

4.2.1 Unstable cardiac disease - defined as congestive heart failure, unstable angina, serious arrhythmias, or Myocardial Infarction in the past month

4.2.2 Current use or planned use of varenicline (Chantix), Zyban, Buproprion or any other nicotinic receptor agonist (Patients that discontinue use of these type drugs within 7 days are eligible.)

4.2.3 Current probable alcohol abuse as defined by more than 5 drinks per day for men and 4 drinks per day for women **and** a Alcohol Use Disorders Identification Test (AUDIT) score $\geq$ 8.

If patient answers “no” to 5 drinks per day for men and 4 drinks per day for women the patient is eligible. AUDIT assessment does not need to be administered.

If patient answers “yes “ to 5 drinks per day for men and 4 drinks per day for women the AUDIT assessment must be administered. If AUDIT score is ≥ 8 patient is not eligible..

4.2.4 Use of illegal drugs or use of prescription medications for non-medical reasons in the past month.

4.2.5 Current use of chewing, dipping and pipe tobacco, or cigars.

4.2.6 Patient does not have regular access to a telephone to receive Quitline calls lasting 15-30 minutes.

4.2.7 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nicotine replacement therapy.

4.2.8 Active Peptic Ulcer Disease

4.2.9 Uncontrolled intercurrent illness including, but not limited to, ongoing, psychiatric illness/social situations that would limit compliance with study requirements.

4.2.10 Due to unknown risks and potential harm to the unborn fetus, sexually active women of childbearing potential must use a reliable method of birth control while participating in this study. Reliable methods of birth control are: abstinence (not having sex), oral contraceptives, intrauterine device (IUD), DepoProvera, tubal ligation, or vasectomy of the partner (with confirmed negative sperm counts) in a monogamous relationship (same partner). An acceptable, although less reliable, method involves the careful use of condoms and spermicidal foam or gel and/or a cervical cap or sponge. We encourage you to discuss this issue further with your doctors if you have any questions.

4.2.11 If you are pregnant, should become pregnant or suspect you are pregnant prior to or while participating in this study, you should inform your study physician immediately. *Nicotine replacement therapy has* the potential for teratogenic or abortifacient effects and is classified as a FDA Pregnancy category D drug. The U.S. Clinical Practice Guideline states that pregnant smokers should be encouraged to quit without medication based on insufficient evidence of effectiveness and hypothetical concerns with safety. Pregnant women enrolled in the study and randomized to the Quitline group intervention should participate in the Quitline intervention but not receive the *nicotine replacement therapy.*

4.2.12 Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with *nicotine replacement therapy,* breastfeeding women are excluded from the study.

4.3 Inclusion of Women and Minorities

	Race/Ethnicity					
Gender	White, not of Hispanic Origin	Black, not of Hispanic Origin	Hispanic	Asian or Pacific Islander	Unknown	Total
Male	60	11	2	0	0	73
Female	60	11	2	0	0	73
Total	120	22	4	0	0	146

Note that sites anticipated they could recruit 23% minorities. Historically, our minority recruitment has been closer to 13%. For this study, we will aim for 18% minority representation, and recruitment of nonminority patients will be suspended after 120 accruals.

4.4 Recruitment and Retention Plan

We anticipate that recruitment will be done in the clinical setting by the physician or physician designee. Patients who are deemed ineligible because they have not smoked in the past 7 days may be rescreened at a later date and enrolled in the study if they meet all eligibility criteria.

To maximize participants' retention in the trial, we will employ several strategies. At enrollment, we will request several different contact methods for each participant, including current address, home and mobile phone numbers, and e-mail addresses. We will ask patients to identify their preferred method of contact. Site coordinators will call all participants' who do not attend scheduled appointments in an attempt to reschedule assessments. In addition, site coordinators will call all participants three weeks after randomization to insure that they received the appropriate intervention materials (self-help materials for the usual care group and a Quitline call and nicotine patches, for the Quitline intervention group).

The feasibility of retaining participants from both study arms will be assessed by tracking participant rates of withdrawal from the study, loss to follow-up, and reasons for withdrawal. In one large smoking cessation clinical trial conducted within the Eastern Cooperative Oncology Group(89), participant retention in the trial was 83.9% at 6 months (12.9% lost/refused & 3.2% deceased). Medium size, single site smoking cessation trials with cancer participants have reported similar or somewhat lower retention (61%(62), 64%(63), 84%(64)). We consider retention rates of >70% for the six month assessment in the proposed trial to indicate adequate feasibility to conduct a future larger trial.

Participants randomized to the enhanced Quitline Intervention group who do not complete their initial telephone call will be identified by the Research Base data manager from the monthly report provided by Alere Wellbeing, Inc. The Research Base data manager will notify the site coordinators and request them to contact these participants and provide encouragement to complete the initial intake call. All participants will be sent a letter at 18 weeks reminding them of their upcoming interview appointment at 24 weeks and offering them tips to maintain their new smoke free habit.

4.5 Planning for a Future Trial

We will examine the number and proportion of screened patients who were deemed ineligible to assess the adequacy of our inclusion and exclusion criterion. In addition, to the extent possible, we will categorize reasons for non-enrollment provided by eligible patients. We also plan to survey staff at each participating CCOP site to obtain data regarding barriers to enrollment. These activities will assist us in defining eligibility criteria and recruitment protocols for a future trial. In addition we will use the open-ended data provided by participants, interventionists, and physicians to identify strengths and weaknesses of the current intervention protocol. Participants who drop out of the study will be asked to complete a very brief survey providing their reasons for dropping out and querying whether potential changes in study design might have influenced their decision (e.g., adding a participant incentive, providing nicotine replacement to the control group). Examination of this data will allow us to refine the study intervention to improve acceptability and retention in future trials.

5. AGENT ADMINISTRATION

Intervention will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6.1.

5.1 Dose Regimen and Dose Groups

See Section 7.1 for details.

5.2 Study Intervention Administration

See Section 7.1 for details.

5.3 Contraindications

Participants should not smoke while using the nicotine replacement patch.
The Nicotine Replacement Patch should not be used in participants with the following:

- Pregnancy
- Congestive heart failure, unstable Angina, serious arrhythmias, or recent Myocardial Infarction
- Nicotine Replacement appears to be safe in stable CAD
- Active Peptic Ulcer Disease

5.4 Concomitant Medications

Participants should not use Varenicline (Chantix), Zyban, Buproprion or any other nicotinic receptor agonist while using the nicotine replacement patch.

5.5 Adherence/Compliance

- Analyses will be based on an intent-to-treat model.

- Participants in the Quitline Intervention group will record their daily use of nicotine replacement products on a medication calendar.

5.6 Dose Modification

If participant experiences itching, rash, or burning sensation at the patch site, they can rotate the patch and apply to a different site.

If participant experiences a minor skin rash or itchy skin at the patch site, they can apply hydrocortisone cream to the spot.

If participant has vivid dreams, they can remove the patch before going to sleep.

If skin irritation and/or vivid dreams occur, notify the participant's physician.

6. PHARMACEUTICAL INFORMATION

6.1 Reported Adverse Events and Potential Risks

Most common side effects for the nicotine replacement therapy include:

- Erythema,
- Pruritus,
- Localized burning sensation
- Insomnia
- Vivid dreams
- Dyspepsia
- Headache

Less Common side effects include:

- Anxiety
- Constipation
- Depression
- Diarrhea
- Dry Mouth
- Pain in muscles
- Nausea
- Nervousness

Serious but Less Common side effects include:

- Severe Dyspnea
- Severe Chest pain
- Swelling of the throat

6.2 Nicotine Patch: Ordering and Distribution

Receiving NRT is not required for study participants. However, with approval from the participant's physician and an Alere Wellbeing, Inc contractor, participants randomize to the Quitline Intervention Group may use NRT.

An Alere Wellbeing, Inc contractor will mail an 8 week supply of Habitrol nicotine replacement patches to all participants randomized to the Quitline Intervention Group. Alere Wellbeing, Inc will also ask the participant a series of questions to assess medical exclusions and will require additional physician consent, if indicated. If participant does not qualify to receive nicotine replacement therapy, the participant will continue in the Quitline group but nicotine patches will not be provided. Instructions for using the patch will be reviewed with the participant during the coaching call and will be sent with the nicotine patch shipment.

In accordance with clinical practice guidelines, the patch is placed directly on the skin and the following step-down approach, tailored to level of cigarette use, will be used:

- Daily Smoking > 10 cigarettes:
  Step 1: 4 weeks of 21 mg
  Step 2: 2 weeks 14 mg
  Step 3: 2 weeks of 7 mg

- Daily Smoking 5-10 cigarettes:
  Step 1: 4 weeks 14 mg
  Step 2: 4 weeks of 7 mg

- Daily Smoking 1-4 cigarettes or Non-daily Smoking:
  Step 1: 8 weeks of 7 mg

Participants receiving the patch will be asked to record patch usage and adverse events on the nicotine replacement diary.

6.3 Nicotine Patch Accountability N/A

6.4 Packaging and Labels

Eight weeks of Habitrol patches manufactured by Novartis Pharmaceuticals (56 total) will be sent to each participant. Written instructions will be included in the shipment reminding participants to apply one patch per day each morning, rotate the location where they apply the patch, and remove the old patch before putting the new one on.

6.5 Registration/Randomization

A form 310 or IRB letter of approval and an IRB approved consent form must be received by the Research Base Protocol Information Office – Attn: Site Coordinator prior to participant registration. Fax: (336)716-6275

Fill out Appendix 2, “Eligibility Checklist / Registration Form’. Use this to complete the on-line registration.

Online Registration

Log on to the CCCWFU Research Base registration web site at <http://ccrbis.phs.wfubmc.edu>. Enter your user name and password (which may be obtained by contacting June Fletcher-Steede at jsteede@wakehealth.edu.) *In the ‘Patient Registration and Protocol Information*’ *table, click the ‘Register Patient/Patient Info’, with the corresponding protocol number found in the drop down box to the right. Fill in the eligibility*

criteria forms using the drop down boxes. If further information is needed by Biologics or Data Management, they will contact you. Once the patient information has been entered online print a copy of the eligibility checklist/registration form for your records. Press the submit button, a confirmation page will appear. Print this confirmation sheet for your records. The CCCWFU On-line Protocol Registration/Eligibility form, initial flow sheet, signed consent, histology reports, scan reports and lab reports (as required in protocol) should be faxed to (336) 713-6476 or mailed to Data Management:

Research Base Data Management Center
Department of Radiation Oncology
1st Floor Cancer Center
WFBMC
Medical Center Boulevard
Winston-Salem, NC 27157

These forms should be retained in the participant's study file. These forms will be evaluated during an institutional NCI/CCCWFU CCOP Research Base site member audit.

If you have questions related to the registration process or require assistance with registration, please contact the CCCWFU CCOP Research Base DMC between 8:30am and 4:00pm EST, Monday through Friday at (336) 713-3172 or 713-6507.

Permuted variable block randomization with strata defined by time since diagnosis and number of cigarettes smoked will be used to assign patients to a treatment.

6.6 Intervention Destruction/Disposal

Unused nicotine replacement patches should be disposed of per Alere Wellbeing, Inc guidelines.

7. CLINICAL EVALUATIONS AND PROCEDURES

7.1 Overview

Patients who agree to participate in the study will be consented and administered the baseline questionnaire, and then randomized to one of two conditions:

1) Usual Care Plus Group
or
2) Quitline Intervention Group (counseling + nicotine replacement patch)

Participants on both arms will be assessed by their physician or intervention nurses for appropriateness for nicotine replacement patches.

Declined Form

Patients who are offered participation in this clinical trial and are eligible but decline will be asked to complete a Declined Form. The participant' should not sign the form or add any identifying information. These are to be submitted to the RB Data Management Center on a monthly basis.

Usual Care Group

The Usual Care group will receive the following:

1) A Tobacco Cessation Counseling Guide Sheet designed for health care providers interacting with cancer patients' will be provided to the participant's physician. Advice to quit smoking through a standardized form letter, signed by their physician, that includes information on the importance of quitting for cancer patients and a copy of the National Cancer Institute's "Clearing the Air" smoking cessation booklet will be given to the participant. Whenever possible, the physician will be encouraged to hand this letter directly to the participant.

   Prior to enrolling participant's it is suggested each site log on to the following website and place an order for "Clearing the Air" smoking cessation booklets at no cost.

   https://cissecure.nci.nih.gov/ncipubs/home.aspx?js=1

   Copy and paste this link in your web browser
   Page will be entitled: NCI Publications Locator
   Enter: Clearing the Air - in the search box and click
   Beside title: Clearing the Air: Quit Smoking Today - click the green order tab, enter quantity, add to cart and enter mailing information.

   If needed the option to print the PDF is available.

2) This group will continue to receive usual care from their oncology and other treatment providers which may or may not include nicotine replacement therapy.

Quitline Intervention Group

The Quitline Intervention group will receive a 3 component intervention: the physician intervention; the CRA counseling session (Motivational Talk); and the Quit for Life Program.

1) **Physician intervention**: Participant's will receive a letter advising them to quit smoking signed by their physician. Whenever possible, the physician will be encouraged to hand this letter directly to the participant'.

2) **CRA Counseling Session** (Motivational Talk); A trained research staff member will provide a 15-30 minute smoking cessation counseling session which educates the participant on the importance and benefits of quitting smoking for cancer patients, enhances motivation to quit, and addresses cancer-specific quitting issues such as managing the stressors associated with cancer diagnosis and treatment. The counseling session is intended to take place in person; however, in the event that the participant is unable to return to the hospital for an in-person meeting, the counseling session may take place by phone.

   The counseling session will be supplemented with a fact sheet about benefits of smoking cessation for cancer patients. At the end of this session, participants will complete and sign the enrollment referral form that will be sent to Alere Wellbeing, and the participant will be told to expect a call from the Quitline in the next 2-3 days.

For all patients assigned to the **Quitline arm only**: Immediately after faxing the Quit for Life Program Enrollment Form to the Quitline staff, email the notification request to Mark Campbell, the Quitline contact person, who will confirm your patients enrollment and ensure that your patient receives a phone call from the Quitline staff. (See Quit for Life Program Enrollment Form for details.)

3) **Quit For Life Program**: The Quitline phase of the intervention will include up to five proactive telephone calls (see Figure 2) made by the Quit for Life program staff and 8 weeks of nicotine replacement patches.

The Quit for Life Program staff will call each participant over a 12 week period. Each call is designed to provide practical expert support to help participants develop problem-solving and coping skills, secure social support, and design a plan for successful cessation and long-term abstinence.

Calls are scheduled at times convenient for the participants and at relapse-sensitive intervals including:

- an initial planning and assessment call,
- a quit date call,
- a follow-up call 7 days after the participant's quit date, and
- two additional calls at 2-3 week intervals.

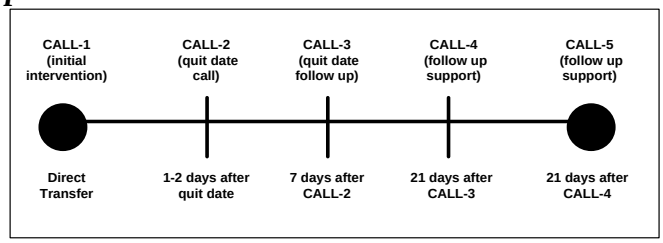
Participants can call the 1-800-QUIT-NOW (1-(800)-784-8669) number as needed for additional support between proactive calls.

During the initial planning call, Quit for Life staff fully assess each caller's tobacco use, nicotine dependence, quit history, motivation and self-efficacy. Information collected is used to develop a tailored treatment plan. Participants are then encouraged to set a quit date and follow-up calls are scheduled**.** Information on nicotine replacement patches will be provided, and an 8 week supply of Habitrol patches will be sent to all participants who agree to receive nicotine replacement. Each initial call is approximately 25-35 minutes in length and each additional follow-up call is approximately 15 minutes.

Follow-up calls focus on challenges that may have occurred on the quit date or with the use of medication. Quit for Life staff review and modify the participant's quit plan, and provide support as appropriate. If the participant does not quit on the planned quit date, the Quit for Life staff will work with the participant to plan a new quit date and/or resolve ambivalence.

For individuals who have successfully quit, the Quit for Life staff will focus on relapse prevention strategies. The call schedule is flexible and will be tailored to the participants' requests and needs.

Figure 2: Typical Five-Call Schedule



Alere Wellbeing, Inc will mail an 8 week supply of nicotine replacement patches to all participants randomized to the Quitline Intervention Group who have been cleared by their physician for nicotine replacement and request the patch. Quit for Life staff will provide medication education to all participants eligible and randomized to the intervention arm.

The Quitline Intervention participants are also encouraged to utilize the Quit for Life Web Coach, an interactive web application that combines evidence-based content with social forums. The online content and tools, based on the Stages of Change, support and assist tobacco users through the quit process. The site includes interactive self-assessment exercises and informational content on the health benefits of quitting, nicotine addiction and craving, strategies for coping with stress, and tips for managing weight and nutrition while quitting. The program guides participants to build online quit plans, set quit dates, and track their progress toward quitting.

Participants learn behavioral tips and coping skills by interacting with others in topic-based discussion forums. Participants have varied support needs and learning styles. To this end, the site offers planning, tracking, and informational tools as well as a supportive community. The content is organized around four areas: “My Quit Plan,” “Quit Trackers,” “My Resources,” and “Community.” This provides a consistent structure to the application and preserves a participant’s familiarity with the design.

Study participants will be randomized and will receive a baseline assessment after they sign consent. The intervention period will last 12 weeks (approximately 1 week for the in-office intervention and 8-12 weeks for all components of the Quitline intervention).

Follow-up assessments by site staff will be administered by telephone 3,and 6 weeks after Quitline intervention referral and clinic visits at 12, and 24 weeks. In the event that a follow-up assessment cannot be completed in person, study staff may administer the questionnaire by phone.

7.2 Schedule of Events

Registration and Baseline Testing

Most data will be captured through structured interviews and some additional information will be retrieved from subjects’ medical records. Demographics will be collected at registration and include age, education, race and ethnicity, marital status, employment status, income, medical history, height and weight.

The smoking history will be collected at baseline and will include number of years smoking, past quit attempts, degree of nicotine addiction, perceived ease of quitting, average number cigarettes smoked per day, alcohol consumption, smokers living in the household, current intention to quit, and perceived consequences of continued smoking.

Key participant reported outcomes will be collected at baseline, 3, 6, 12 and 24 weeks to assess the possible effects of smoking cessation on perceived life stress, depression, health-related quality of life, and symptoms. Cancer type, stage, date of diagnosis, and the presence of comorbid medical conditions at baseline will be ascertained from the participant’s medical record.

Perceived Stress Scale (10- item version) (90). This global measure of stress has been widely used in studies of cancer patients, has acceptable psychometric characteristics in patients undergoing treatment(91), is related both cross-sectionally and longitudinally to quality of life in cancer patients(92), and will be used to assess overall life stress (attributable to both cancer and potentially quitting smoking).

Center for Epidemiologic Studies Short Depression Scale [CES-D 10](93). This brief measure of depression symptoms has been validated(94) and widely used in studies of patients with lung and other cancers(95, 96) and will be used to asses changes in depression symptoms over the course of the study.

Functional Assessment of Cancer Therapy-General [FACT-G](97). The FACT-G is health-related quality of life (HRQoL) measure specifically designed for use in cancer patients. It assesses four domains of HRQoL: physical well-being, social/family well-being, emotional well-being, and functional well-being. This measure will be used to assess changes in HRQoL associated with smoking cessation.

For lung cancer patients only:

Functional Assessment of Cancer Therapy-Lung Cancer [FACT-L](97). The FACT-L is a 10-item supplement to the FACT-G that assesses symptoms and concerns specific to lung cancer. This measure will be used to assess changes in symptoms over the course of the trial among lung cancer patients only.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Lung Cancer (EORTC QLQ-LC13)(98). This measure assesses specific symptoms associated with lung cancer and side effects from chemotherapy and radiation, including dyspnea, mucositis, pain, and coughing. This measure will be used to assess changes in symptoms over the course of the trial in lung cancer patients only.

To assess active components of the smoking cessation intervention which is based on social cognitive theory, participants will complete measures of 1) smoking cessation self-efficacy and 2) smoking outcomes expectancies. The cessation self-efficacy scale assesses confidence in ability to refrain from smoking during emotional and social situations and confidence in ability to use various smoking cessation skills(99). Selected scales (negative affect reduction, stimulation, social facilitation, craving/addiction, negative physical feelings, boredom reduction, and negative social impression) from the Smoking Consequences Questionnaire (100) will also be used to assess perceived positive and negative consequences of smoking.

Baseline Assessment

Usual Care Group - *Intervention will begin when the participant is given the physician letter and educational materials.*

Quitline Intervention Group - *Intervention will begin when participant attends CRA counseling session (Motivational Talk).*

- KPS
- Medical Review for comorbidities
- Baseline Booklet includes:
  - Baseline Smoking Assessment Questionnaire
  - Smoking Cessation Self-Efficacy Questionnaire
  - Brief Smoking Consequences Questionnaire

- FACT-G Questionnaire
- FACT-L Questionnaire (lung cancer patients only)
- EORTC Quality of Life Questionnaire LC-13 (lung cancer patients only)
- Perceived Stress Scale Questionnaire
- CESD-10 for Depression Questionnaire

USUAL CARE GROUP FOLDER	QUITLINE INTERVENTION GROUP FOLDER
Tobacco Cessation Guide Sheet for Doctor **Mail the following forms to patient:** ➢ Letter to participant from Dr. ➢ "Clearing the Air" Booklet ➢ Study Visits and Procedures 6 Week Booklet	Motivational Talk - Quit for life program **Provide the following forms to participant:** ➢ Letter to patient from Dr. ➢ "Benefits of Quitting Smoking" Handout ➢ Quitline Enrollment Form ➢ "What Happens Next" Handout ➢ Study Visits and Procedures ➢ Nicotine Replacement Diary 6 Week Booklet

7.3 Week 3 Telephone Contact

- Telephone Contact Form

Week 6 Telephone Contact

6 Week Booklet Includes: (Request participant to return booklet by mail.)
- FACT-G Questionnaire
- FACT-L Questionnaire (lung cancer patients only)
- EORTC Quality of Life Questionnaire LC-13 (lung cancer patients only)
- Follow-up Smoking Assessment Questionnaire
- Telephone Contact Form

Quitline Group only
- Nicotine Replacement Diary **(Request participant to include diaries by mail.)**

7.4 Week 12 Assessment

- 12 Week Booklet Includes:
  - Smoking Cessation Self-Efficacy Questionnaire
  - Brief Smoking Consequences Questionnaire
  - FACT-G Questionnaire
  - FACT-L Questionnaire (lung cancer patients only)
  - EORTC Quality of Life Questionnaire LC-13 (lung cancer patients only)
  - Perceived Stress Scale Questionnaire
  - CESD-10 for Depression Questionnaire
  - Follow-up smoking assessment Questionnaire
  - Participant Feedback Questionnaire

Quitline Intervention Group only
- Nicotine Replacement Diary

- Urine Cotinine Level (*All participants who report* ***not smoking*** *and* ***have not used nicotine replacement therapy in the last 3 days)***

7.5 Week 18 Assessment

- Encouragement Letter

7.6 Week 24 Assessment

- 24 Week Booklet includes:
  - FACT-G Questionnaire
  - FACT-L Questionnaire (lung cancer patients only)
  - EORTC Quality of Life Questionnaire LC-13, (lung cancer patients only)
  - Perceived Stress Scale Questionnaire,
  - CESD-10 for Depression Questionnaire,
  - Follow-up Smoking Assessment Questionnaire

Urine Cotinine Level (*All participants who report* ***not smoking*** *and* ***have not used nicotine replacement therapy in the last 3 days)***

7.7 Completion of Study

- Study Completion Form: To be completed by each site staff member participating in protocol when sites final participant has completed the study.
- Quitline Staff Feedback Form: To be completed by each Quitline staff member participating in protocol when final participant has completed the study.
- Early Withdrawal From Treatment Form: Participants who withdraw from study prior to completion will be asked to complete an Early Withdrawal From Treatment Form.

7.8 Methods for Clinical Procedures

Assessment of Feasibility. To address the Primary Objective (to assess the feasibility of delivering a Quitline-based smoking cessation intervention to cancer patients in an outpatient setting), we will assess participants, CRA Counselors and Quitline staff ratings of acceptability, resources required to deliver the intervention, protocol fidelity, and participant retention in the study by using the feedback forms.

Quitline Intervention participants will be asked to rate the degree to which they:

1) liked the Quitline intervention
2) found the Quitline intervention helpful,
3) found the Quitline staff to be helpful,
4) found the Quitline staff to be sensitive to their concerns, and
5) assess the Quitline program

Both Quitline Intervention and Usual Care participants will be asked open-ended questions about what they liked the most and least about participating in the study and what suggestions they have to improve the program.

CRA counselors will be asked to rate the degree to which they found the intervention: 1) easy to deliver, 2) helpful to participants, and 3) disruptive to the clinic setting and 4) how much participants liked the intervention.

CRA counselors will also be asked to what degree they found the study training: 1) adequate to allow them to deliver the intervention with confidence and 2) helpful to them in their future clinical work. They will also be asked the same open-ended questions as participants.

The Quitline staff will be asked about 1) their comfort in delivering the intervention to cancer patients, 2) the degree to which they encountered cancer-related issues that they were not comfortable addressing, and 3) their perceived effectiveness of their counseling with cancer patients.

To further address feasibility, data will be obtained regarding training time for CRA counselor, intervention delivery time, and the cost of the Quitline intervention.

Protocol adherence data will be gathered to determine the degree of adherence to the intervention. CRA counselors will record the date and length of all interactions with intervention group participants. Alere Wellbeing, Inc will provide data on how many participants completed each of the planned calls, duration of each call, and cumulative duration of counseling contact. Data will also be provided about patient initiated calls for counseling, including number of calls to the support line and cumulative duration of counseling through the support line. Data regarding use of the web-based services, including number of logins, length of visits, and most frequently visited sections will also be recorded.

All participants will be asked if they received advice from their physician to quit smoking.

Participants in the Usual Care group will be further queried to determine what types of interactions they had with their physicians regarding smoking and use of pharmacotherapy and outside smoking cessation resources.

7.9 Study Parameters Table
Measures must be completed within +/- 14 days.

STUDY PARAMETERS TABLE	Screening	Baseline	3 Weeks after Intervention	6 Weeks after Intervention	12 Weeks after Intervention	18 Weeks after Intervention	24 Weeks after Intervention
Decline Form (Appendix 16)	X						
Consent		X					
Medical Review for co-morbidities		X					
Usual Care Group Folder (Appendix 10) Tobacco Cessation Guidesheet for Dr. **Mail the following forms to participant:** ➢ Letter to participant from Dr. ➢ "Clearing the Air" Booklet ➢ Study Visits and Procedures ➢ 6 Week Booklet (A)		X					
Quitline Group Folder (Appendix 11) Motivational Talk - Quit for life program (F) **Provide the following forms to participant:** ➢ Letter to patient from Dr. ➢ "Benefits of Quitting Smoking" Handout ➢ Quitline Enrollment Form ➢ "What Happens Next" Handout ➢ Study Visits and Procedures ➢ Nicotine Replacement Diary (B) ➢ 6 Week Booklet (A)		X		X (B)	X (B)		
Participant Contact Form **Every encounter is to be recorded by CRA** Appendix 17 (C)		X	X	X	X	X	X
Flow Sheet (Appendix 4)		X	X	X	X	X	X
Toxicity Assessment Sheet (Appendix 4)		X	X	X	X	X	X
Alcohol Use Form if indicated (Appendix 6)		X					
Urine Cotinine Level (Record on Flow Sheet)					X		X
Baseline Booklet (Appendix 7)		X					
Telephone Contact Form (Appendix 13) (D)			X	X			
12 Week Booklet (Appendix 8)					X		
18 Week Encouragement Letter (E) (Appendix14)						X	
24 Week Booklet (Appendix 9)							X
Study Completion Form (Appendix 12)		To be completed by each site staff member participating in protocol when sites **final participants has completed** the study.					
Declined Form (Appendix 16)		Request patients who are offered participation in this study, are eligible and decline, to complete form and submit to RB data management.					
Early Withdrawal From Treatment Form (Appendix 15)		Participants who withdraw from treatment or study prior to completion will be asked to complete the Early Withdrawal From Treatment Form.					

Usual Care Group - Intervention begins when the participant receives the physician letter and educational materials.

Quitline Intervention Group - Intervention begins when participant attends CRA Counseling Session (Motivational Talk).

(A) **6 Week Booklet:** Located in (App.10) or (App.11). It is suggested the booklet be provided and at 6 week telephone contact request participant to complete and return via mail. If needed, staff may complete forms during telephone contact.

(B) **Nicotine Replacement Diary** will be provided to the Quitline Group only. Participants using the patch are to be instructed in completing diary and to record time patch worn in hours per day.

(C) **Participant Contact Form** - every participant encounter (phone, in-person, e-mail) is to be recorded.

(D) **3 Week Telephone Contact**: **Usual Care Group** – Verify received reading material. **Quitline Intervention Group** – Verify received phone call and patches from Quitline.

(E) **18 Week**: **Encouragement Letter** to be mailed to patient.

(F) For all patients assigned to the **Quitline arm only**: Immediately after faxing the Quit for Life Program Enrollment Form to the Quitline staff, email the notification request to Mark Campbell, the Quitline contact person who will confirm your patients enrollment and ensure that your patient receives a phone call from the Quitline staff.

7.10 Off Treatment Criteria

Participants may stop taking study agent for the following reasons: completed the protocol-prescribed intervention, adverse event or serious adverse event, inadequate agent supply, noncompliance, concomitant medications, medical contraindication. Participants will continue to be followed, if possible, for safety reasons and in order to collect endpoint data according to the schedule of events. Early Withdrawal from Treatment Form should be completed.

7.11 Off Study Criteria

Participants may go 'off-study' for the following reasons: the protocol intervention and any protocol-required follow-up period is completed, adverse event/serious adverse event, lost to follow-up, non-compliance, concomitant medication, medical contraindication, withdraw consent, death, determination of ineligibility, pregnancy.

8. PROTOCOL SPECIFIC TRAINING REQUIREMENTS

8.1 Specific Training Procedures

At least one CRA at each site must undergo a one and a half-day training workshop on smoking cessation for cancer patients **prior to enrolling** the first participant. Training was provided at the CCCWFU Research Base Annual Meeting on October 20th and 21st, 2011. Training was provided by the study PI, a motivational interviewing trainer, and other facilitators. CEU credits were offered for this initial training activity. **Additional workshops or other training opportunities will be scheduled at the discretion of the study PI.**

During the training, site participants reviewed the protocol, learned about the scope of tobacco use after a cancer diagnosis and the benefits of quitting during and after cancer treatment. Physiological and social aspects of tobacco addiction were covered. Participants also learned about basic principles of motivational interviewing (MI) including: expressing empathy, developing discrepancy, rolling with resistance, and supporting self-efficacy. MI core skills taught included open-ended questions, affirmation, reflective listening, and summarizing. The smoking cessation study protocol was reviewed in detail. Workshop facilitators observed all CRA Counselors while they delivered the counseling session during a role play.

Any study personnel attending the training workshop but not certified may submit an audiotape of a practice session to the PI for review. If audiotape is acceptable study personnel will receive certification. If audiotape is not acceptable feedback will be provided and the study personnel will be encouraged to practice and submit a new audiotape.

In order to maintain continuity study personnel that do not actively participate in the smoking cessation counseling for more than 6 months will need to be recertified.

9. SPECIMEN MANAGEMENT

9.1 Collection and Handling Procedures

Urine Cotinine collecting specimen and testing at site

All participants who report **not smoking** at the 12 and 24 week follow-up assessments and **have not used nicotine replacement therapy in the last 3 days** will be confirmed using a Nicalert test kit, a point of contact drug testing device formulated for use with human urine specimens (available from Craig Medical). Nicalert detects the presence of cotinine, the principal metabolite of nicotine. A test result greater than two (indicating a cotinine content of at least 100-200 ng/ ml) will be considered positive for smoking. The study coordinator or research nurse will be responsible for conducting the test on study subjects.

No special training is necessary to perform the test procedures, which are as follows:

1. Collect the urine sample by using the urine specimen container provided. The test subject should provide approximately 25 mL of urine, collecting a mid-stream sample by collecting the sample a few seconds after the start of urination.
2. Visually check the urine sample for signs of contamination (foreign materials such as bathroom tissue or hair, particles, etc.). If sample is contaminated, request a new sample from the participant.
3. Remove the NicAlert test strip from pouch. Holding the strip by the handle, dip the sample end (the exposed cotton end of the strip) into the urine sample to a depth of ½ inch, holding the strip with gloves. Do not immerse the strip lower than the maximum sample line on the strip. Hold the strip in the urine for 20 seconds. Do not over-saturate.
4. Read the test strip after 10-15 minutes when the blue band at the end of the strip disappears or has faded substantially. During this period, you should see at least one reddish band appear in the numbered white zones on the strip.
5. Find the **lowest** numbered zone (Level 0 – 6) on the strip with a reddish color in it. This lowest level is the Nicalert test result. A result of 2 or higher indicates use of tobacco products.

6. Cotinine test results are to be recorded on the Flow Sheet. Sites should request cotinine test kits by using the NicAlert Request Form. NicAlert test kit instructions are located in the appendices section.

10. REPORTABLE ADVERSE EVENTS/SERIOUS ADVERSE EVENTS

A list of adverse events/serious adverse events that have occurred or might occur that are related to this study intervention can be found in Section 6.2.

Adverse Event/Serious Adverse Event reporting begins after the informed consent is signed Serious Adverse Events occurring within 30 days of study completion must be reported via FDA Form 3500 (MedWatch).

10.1 Protocol Specific Reporting for Adverse Events (AEs)

- DEFINITION: An adverse event (AE) is any untoward medical occurrence in a study participant.

- Grades 1, 2, and 3 expected (solicited) and unexpected (unsolicited) AEs that meet the above definition for an AE and are ONLY definitely related, possibly related or probably related to this study intervention should be reported to the RB DMC using the Toxicity Assessment Sheet.

10.2 Protocol Specific Reporting for Serious Adverse Events (SAEs)

DEFINITION: ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997 define serious adverse events as those events which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

Grades 3, 4, and 5 expected (solicited) and unexpected (unsolicited) SAEs that meet the above definition for SAEs and/or regardless of attribution (i.e. regardless of whether they are related to this study intervention or not) should be reported to the RB DMC using the FDA Form 3500 (MedWatch).

Site staff and/or Principal Investigators will report to the RB Data Management Staff within 24 hours of discovering the details of all unexpected severe, life-threatening (grade 4) and/or fatal adverse events (grade 5) if there is reasonable suspicion that the event was definitely, probably, or possibly related to the study intervention.

Otherwise, the MedWatch should be sent to the RB DMC by fax or email within 10 working days of discovering the details of the SAE.

- Data Elements to include on the MedWatch are:
- SAE reported date
- CTCAE Term (v4.03)
- Event onset date and event ended date
- Severity grade (use table provided in Section 10.3 below)
- Attribution to study intervention (relatedness)
- Action taken with the study participant and intervention
- Outcome of the event
- Comments

10.3 Guidelines to determine grade and severity of AEs and/or SAEs

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to the general guidelines for grading used in the CTCAE v4.03. as stated below.

Grade	Severity	Description
1	Mild	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	Moderate	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.
3	Severe	Severe or medically significant but not immediately life-threatening; Hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
4	Life threatening	Life-threatening consequences; urgent intervention indicated.
5	Fatal	Death related to AE.

Activities of Daily Living (ADL)

***** Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

****** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

The Research Base Grant PI, Safety and Toxicity Review Committee and/or Study Chair will take appropriate action to inform the membership and statistical personnel of any protocol modifications and/or precautionary measures, if this is warranted.

The RB DMC is responsible for communicating AEs/SAEs to the FDA, the drug sponsor, WF IRB, the WF Safety and Toxicity Review Committee (STRC) and/or other regulatory agencies as appropriate.

Institutions must comply with their individual Institutional Review Board (IRB) policy regarding submission of documentation of adverse events. All MedWatch reports should be sent to the local IRB in accordance with the local IRB policies.

10.4 Follow-up of SAEs

Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the MedWatch form in the appropriate format. Follow-up information should be sent to the RB Data Management Center as soon as available.

SAEs (Grade 4 and/or Grade 5) for this protocol should be followed for those related to the study intervention. Documentation should include:

- PID
- Date of SAE
- Description of the event
- Relationship of the SAE to the study intervention
- Severity
- Intervention/Resolution

11. STUDY MONITORING

11.1 Data Management Schedule

The Eligibility checklist/Registration Form should be completed on-line prior to placing the patient on study. Data forms will be submitted to the CCCWFU CCOP Research Base. See Section 10.2.2 for mailing address, or fax to (336) 713-6476 according to the timetable per Appendix 1, Data Submission Checklist.

11.2 Case Report Forms

Participant data will be collected using protocol-specific case report forms (CRF).

11.3 Source Documents

Source documents are the original signed and dated records of participant information (e.g., the medical record, shadow chart) which may include electronic documents containing all the information related to a participant's protocol participation. Source documents are used to verify the integrity of the study data, to verify participant eligibility, and to verify that mandatory protocol procedures were followed. An investigator and other designated staff are required to prepare and maintain adequate and accurate documentation that records all observations and other data pertinent to the investigation for each individual participating in the study. All data recorded in the research record (including data recorded on CRFs) must originate in the participant's medical record, study record, or other official document sources.

Source documents substantiate CRF information. All participant case records (e.g., flow sheets, clinical records, physician notes, correspondence) must adhere to the following standards:

- Clearly labeled in accordance with HIPAA practices so that they can be associated with a particular participant or PID;
- Legibly written in ink;
- Signed and dated in a real time basis by health care practitioner evaluating or treating the participant; and
- Correction liquid or tape must not be used in source documents or on CRFs.

- Corrections are made by drawing a single line through the error. Do not obliterate the original entry. Insert the correct information, initial, and date the entry.

11.4 Data and Safety Monitoring Board

The Data Safety Monitoring Board meets every six months to review all phase II and phase III protocols. The Board includes members demonstrating experience and expertise in oncology, biological sciences and ethics. The DSMB report is generated by the statistician. Areas of review may include the following: Date study Opened; Study Objectives; Participant Accrual; Participant Status and Retention; Study Status; Last Contact Status; Participant Compliance; Number of Biopsies/Labs as needed; Participant Characteristics; Summary of Observed Toxicities; Adverse Events; Date, Event briefly described, Relationship to Drug, Arm assigned; Summary of Secondary Measures.

11.5 Record retention

Clinical records for all participants, including CRFs, all source documentation (containing evidence to study eligibility, history and physical findings, laboratory data, results of consultations, etc.), as well as IRB records and other regulatory documentation will be retained by the Investigator in a secure storage facility in compliance with HIPAA, OHRP, FDA regulations and guidance, and NCI/DCP requirements unless the standard at the site is more stringent.

Record retention should be 2 years after the study is discontinued for studies without an IND (21 CFR 312.62).

11.6 CDUS Reporting

The CCCWFU CCOP Research Base Data Management Center will submit quarterly reports to DCP/CTEP by electronic means using the Clinical Data Update System (CDUS)

12. STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

This is a randomized, controlled, pilot study assessing the feasibility of a smoking cessation intervention in cancer survivors. The objectives for this trial are: 1) to assess feasibility (estimate accrual, retention, adherence, participation rates, and participant, interventionist, and provider acceptability), 2) to obtain a preliminary estimate of the treatment effect (difference in quit rates in the two groups), and 3) to assess quality of life, stress, and depression (estimates of variability and treatment effects). Estimates of treatment efficacy will be obtained using the ‘intent to treat’ approach. That is, all randomized participants will be used in the analyses, regardless of whether the participants were treated according to protocol.

12.2 Sample Size/Accrual Rate

While this is a pilot study and we will not be testing the effect of the intervention, we do want to be able to estimate the treatment effect with a fair degree of precision. Thus, the

sample size for this trial will be determined to provide a reasonably tight estimate of the treatment effect. Using 2:1 randomization, we will need a total of 102 participants to estimate the difference in quit rates to within ± 20% with 95% confidence. Even though retention will be stressed throughout the trial, and participants who refuse treatment will be encouraged to remain in the study to provide outcome data, some participants will drop out of the study. Assuming that 30% of the participants will drop out, we will need to accrue a total of 146 participants to this study.

12.3 Randomization and Stratification

Participants will be stratified by time since diagnosis (<3 months, ≥ 3 months) and number of cigarettes smoked per day (≤ 10, ≥ 11) and assigned within each stratum to the Quitline Intervention or Usual Care with 2:1 probability using variably sized random permuted block randomization. We are using a 2:1 allocation ratio to make the trial more attractive to the participants and because we want to learn more about the proposed intervention. Analyses will not be done separately by strata.

12.4 Primary Endpoint(s)

The primary endpoints for this study are measures of feasibility – accrual, retention, adherence, participation, and acceptability. Accrual will be estimated as the number of participants accrued divided by the number of months of accrual. A 95% confidence interval for the monthly accrual rate will be calculated based on the Poisson distribution. Retention will be primarily defined as the proportion of participants who provide 12 week and 24 week data. Participants who discontinue the intervention (refuse phone calls) but complete the outcome assessments will be counted in the numerator for calculating retention. Retention estimates will be calculated overall and by treatment arm. A Fisher exact test will be used to assess the difference in retention between the two arms. In addition, since participants drop out at varying times throughout the study, Kaplan-Meier methods will be used to estimate the time to drop-out, and a logrank test will be used to assess the difference in these distributions between treatment arms.

Adherence to the treatment protocol will be calculated as the number of planned calls completed in the treatment group. We will calculate and report the mean adherence across all individuals as well as the proportion of participants who completed three or more calls.

The participation rate will be estimated as the number of patients who are randomized divided by the number eligible. This estimate will be calculated separately by site to see if we can learn what does and does not work in getting patients to participate. An exact 95% CI will be calculated for this estimate at each site.

Several measures will be used to quantify acceptability, as described in Section 3.2.5. These include questions for both the participants and the providers. These questions will be asked on a 5-point Likert scale, and the proportion of participants/providers responding with each answer will be calculated. The highest two responses for each question will be combined and exact 95% CIs will be calculated for these estimates.

The quit rate (number quit divided by the number evaluable) will be measured at 6, 12 and 24 weeks following randomization. Exact 95% CIs will be calculated for the quit rate in each arm and an approximate 95% CI will be calculated for the difference in quit rates (providing a preliminary estimate of the treatment effect). Logistic regression will be used to assess the effect of treatment and participant characteristics on the quit rate. Pair-wise interactions between treatment and the participant characteristics will be assessed. The main effects and interactions will assist us in determining the need for

strata or possible changes in the eligibility criteria. A repeated measures logistic model fitted using estimating equations will be used to assess the change in quit rates over time and to assess the effect of participant characteristics on this change.

12.5 Secondary Endpoints(s)

Secondary study endpoints at 12 and 24 weeks include cotinine-confirmed smoking status (cotinine <10 or self-reported no smoking in past week for participants who are using NRT), perceived stress, symptoms, depression, and quality of life (QOL), as measured by validated assessment instruments. The QOL and symptom measures will also be assessed at 6 weeks. We expect that patients with greater baseline self-efficacy and less positive outcome expectancies will be more likely to report not smoking at 6, 12 & 24 weeks and that increases in self-efficacy and reductions in positive outcome expectancies from baseline to 12 weeks will be associated with greater likelihood of not smoking at 24 weeks. Repeated measures longitudinal models will be used to assess changes over time in QOL, stress, and depressive symptoms and to assess the effect of participant characteristics and self-efficacy on these changes. Regression diagnostics, residual plots, and exploratory analyses will be done to find appropriate transformations to satisfy the linearity, homogeneity of variances, and normality assumptions.

12.6 Reporting and Exclusions

Retention and adherence are two of the primary outcomes for this pilot study. The analyses done to estimate treatment efficacy will include all randomized participants, regardless of adherence. We will make a concerted effort to minimize the number of drop-outs, beginning with the participants that are accrued. If a patient seems unwilling to participate or indicates that he may not be able to be compliant, we will not press him to participate. In addition, participants who discontinue the treatment will be encouraged to stay in the study and provide outcome data.

12.7 Evaluation of Toxicity

While we do not expect many toxicities with the proposed intervention, participants receiving the nicotine patch may experience some side effects as described in Section 6.1. All participants will be evaluable for toxicity from the first day of treatment. Toxicities will be evaluated according to the CTCAE version 4 criteria and recorded on the Toxicity Assessment Forms. Psychological distress will be quantified using CESD-10, FACT-L, and Perceived Stress Scale. Fisher exact tests will be used to assess differences in toxicity between the two arms. Any severe adverse events or other unusual results will be reported to the IRB and to the Comprehensive Cancer Center Wake Forest Toxicity Assessment Committee for further action.

12.8 Evaluation of Response

All participants included in this study will have their outcomes assessed at baseline and at 6 (some outcomes), 12, and 24 weeks. Efforts will be made to collect these data even if participants refuse further treatment. Data should only be missing for those who expire or withdraw consent. As noted earlier, all randomized participants will be included in the analyses of treatment efficacy. The quit rates and estimates of treatment effect will be used in the design of a subsequent comparative trial.

12.9 Interim Analysis

There will be no interim analyses in this pilot study. However, all Research Base studies are monitored by the CCCWFU DSMB twice yearly for accrual (including minority recruitment), retention, adherence, data quality, and safety. Descriptive reports for the DSMB will consist of summary statistics (means, standard deviations, proportions, etc.) for participant characteristics and outcome measures, actual versus projected accrual, participation by the various sites, and quality control information (retention, adherence, missing data, etc.). Tables, graphs, and charts will be used to illustrate the data when appropriate.

REFERENCES

Reference List

(1) Danaei G, Ding EL, Mozaffarian D, Taylor B, Rehm J, Murray CJ, et al. The preventable causes of death in the United States: comparative risk assessment of dietary, lifestyle, and metabolic risk factors. PLoS Med 2009;6(4):e1000058.

(2) Mayer DK, Carlson J. Smoking Patterns in Cancer Survivors. Nicotine Tob Res 2011;13(1):34-40.

(3) Coker AL, DeSimone C, Eggleston KS, Hopenhayn C, Nee J, Tucker T. Smoking and survival among Kentucky women diagnosed with invasive cervical cancer: 1995-2005. Gynecol Oncol 2009;112(2):365-9.

(4) Underwood JM, Townsend JS, Tai E, White A, Davis SP, Fairley TL. Persistent cigarette smoking and other tobacco use after a tobacco-related cancer diagnosis. 2012.

(5) Samant RS, Tucker TL. Analysis of Cigarette Smoking Habits of Cancer Patients Referred to the Northeastern Ontario Regional Cancer Centre. 2003;18(3):157-60.

(6) Gritz ER, Dresler C, Sarna L. Smoking, the missing drug interaction in clinical trials: ignoring the obvious. Cancer Epidemiol Biomarkers Prev 2005;14(10):2287-93.

(7) Klosky JL, Tyc VL, Garces-Webb DM, Buscemi J, Klesges RC, Hudson MM. Emerging issues in smoking among adolescent and adult cancer survivors. 2007;110(11):2408-19.

(8) Browman GP, Wong G, Hodson I, Sathya J, Russell R, McAlpine L, et al. Influence of cigarette smoking on the efficacy of radiation therapy in head and neck cancer. N Engl J Med 1993;328(3):159-63.

(9) Waller LL, Miller AA, Petty WJ. Using erlotinib to treat patients with non-small cell lung cancer who continue to smoke. Lung Cancer 2009;67(1):12-6.

(10) van der Bol JM, Mathijssen RHJ, Loos WJ, Friberg LE, van Schaik RHN, de Jonge MJA, et al. Cigarette smoking and irinotecan treatment: pharmacokinetic interaction and effects on neutropenia. J Clin Oncol 2007;25(19):2719-26.

(11) Moller AM, Pedersen T, Villebro N, Schnaberich A, Haas M, Tonnesen R. A study of the impact of long-term tobacco smoking on postoperative intensive care admission. Anaesthesia 2003;58(1):55-9.

(12) Chang DW, Reece GP, Wang B, Robb GL, Miller MJ, Evans GR, et al. Effect of smoking on complications in patients undergoing free TRAM flap breast reconstruction. Plast Reconstr Surg 2000;105(7):2374-80.

(13) Goodwin SJ, McCarthy CM, Pusic AL, Bui D, Howard M, Disa JJ, et al. Complications in smokers after postmastectomy tissue expander/implant breast reconstruction. Ann Plast Surg 2005;55(1):16-9.

(14) Eifel PJ, Jhingran A, Bodurka DC, Levenback C, Thames H. Correlation of smoking history and other patient characteristics with major complications of pelvic radiation therapy for cervical cancer. J Clin Oncol 2002;20(17):3651-7.

(15) Chen AM, Chen LM, Vaughan A, Farwell DG, Luu Q, Purdy JA, et al. Head and neck cancer among lifelong never-smokers and ever-smokers: matched-pair analysis of outcomes after radiation therapy. Am J Clin Oncol 2011;34(3):270-5.

(16) Geng Y, Savage SM, Razani-Boroujerdi S, Sopori ML. Effects of nicotine on the immune response. II. Chronic nicotine treatment induces T cell anergy. J Immunol 1996;156(7):2384-90.

(17) Tollerud DJ, Clark JW, Brown LM, Neuland CY, Mann DL, Pankiw-Trost LK, et al. Association of cigarette smoking with decreased numbers of circulating natural killer cells. Am Rev Respir Dis 1989;139(1):194-8.

(18) Smith JB, Fenske NA. Cutaneous manifestations and consequences of smoking. J Am Acad Dermatol 1996;34(5 Pt 1):717-32.

(19) Arcavi L, Benowitz NL. Cigarette smoking and infection. Arch Intern Med 2004;164(20):2206-16.

(20) Cascinu S, Fedeli A, Fedeli SL, Catalano G. Oral cooling (cryotherapy), an effective treatment for the prevention of 5-fluorouracil-induced stomatitis. Eur J Cancer B Oral Oncol 1994;30B(4):234-6.

(21) Luo DH, Hong MH, Guo L, Cao KJ, Deng MQ, Mo HY. [Analysis of oral mucositis risk factors during radiotherapy for nasopharyngeal carcinoma patients and establishment of a discriminant model]. Ai Zheng 2005;24(7):850-4.

(22) Rugg T, Saunders MI, Dische S. Smoking and mucosal reactions to radiotherapy. Br J Radiol 1990;63(751):554-6.

(23) Sonis ST, Elting LS, Keefe D, Peterson DE, Schubert M, Hauer-Jensen M, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. Cancer 2004;100(9 Suppl):1995-2025.

(24) Sanderson CL, Sloan JA, Patten CA, Bonner JA, Geyer SM, McGinnis WL, et al. Smoking behavior of 226 patients with diagnosis of stage IIIA/IIIB non-small cell lung cancer. Psychooncology 2002;11(6):472-8.

(25) Rink M, Xylinas E, Margulis V, Cha EK, Ehdaie B, Raman JD, et al. Impact of Smoking on Oncologic Outcomes of Upper Tract Urothelial Carcinoma After Radical Nephroureterectomy. 2012.

(26) Kenfield SA SM. Smoking and prostate cancer survival and recurrence. Jama 2011;305(24):2548-55.

(27) Chen CH, Shun CT, Huang KH, Huang CY, Tsai YC, Yu HJ, et al. Stopping smoking might reduce tumour recurrence in nonmuscle-invasive bladder cancer. 2007;100(2):281-6.

(28) Day GL, Blot WJ, Shore RE, McLaughlin JK, Austin DF, Greenberg RS, et al. Second cancers following oral and pharyngeal cancers: role of tobacco and alcohol. J Natl Cancer Inst 1994;86(2):131-7.

(29) Li CI, Daling JR, Porter PL, Tang MT, Malone KE. Relationship Between Potentially Modifiable Lifestyle Factors and Risk of Second Primary Contralateral Breast Cancer Among Women Diagnosed With Estrogen Receptor-Positive Invasive Breast Cancer. J Clin Oncol 2009;27(32):5312-8.

(30) Underwood JM, Rim SH, Fairley TL, Tai E, Stewart SL. Cervical cancer survivors at increased risk of subsequent tobacco-related malignancies, United States 1992-2008. Cancer Causes Control 2012;23(7):1009-16.

(31) Kawahara M, Ushijima S, Kamimori T, Kodama N, Ogawara M, Matsui K, et al. Second primary tumours in more than 2-year disease-free survivors of small-cell lung cancer in Japan: the role of smoking cessation. Br J Cancer 1998;78(3):409-12.

(32) Kaufman EL, Jacobson JS, Hershman DL, Desai M, Neugut AI. Effect of Breast Cancer Radiotherapy and Cigarette Smoking on Risk of Second Primary Lung Cancer. JCO 2008;26(3):392-8.

(33) Lorigan P, Radford J, Howell A, Thatcher N. Lung cancer after treatment for Hodgkin's lymphoma: a systematic review. Lancet Oncol 2005;6(10):773-9.

(34) Schnoll RA, Malstrom M, James C, Rothman RL, Miller SM, Ridge JA, et al. Correlates of tobacco use among smokers and recent quitters diagnosed with cancer. Patient Educ Couns 2002;46(2):137-45.

(35) Baser S, Shannon VR, Eapen GA, Jimenez CA, Onn A, Lin E, et al. Smoking cessation after diagnosis of lung cancer is associated with a beneficial effect on performance status. Chest 2006;130(6):1784-90.

(36) Chen J, Qi Y, Wampfler JA, Jatoi A, Garces YI, Busta AJ, et al. Effect of cigarette smoking on quality of life in small cell lung cancer patients.

(37) Garces YI, Yang P, Parkinson J, Zhao X, Wampfler JA, Ebbert JO, et al. The relationship between cigarette smoking and quality of life after lung cancer diagnosis. Chest 2004;126(6):1733-41.

(38) National Cancer Institute. Smoking Cessation and Continued Risk in Cancer Patients (PDQ) Health Professional Version. 2008Available from: URL: http://www.cancer.gov/cancertopics/pdq/supportivecare/smokingcessation/healthprofessional

(39) de Moor JS, Elder K, Emmons KM. Smoking prevention and cessation interventions for cancer survivors. Semin Oncol 2008;24(3):180-92.

(40) Peppone LJ, Mustian KM, Morrow GR, Dozier AM, Ossip DJ, Janelsins MC, et al. The Effect of Cigarette Smoking on Cancer TreatmentGÇôRelated Side Effects. Oncologist 2011;16(12):1784-92.

(41) Parsons A, Daley A, Begh R, Aveyard P. Influence of smoking cessation after diagnosis of early stage lung cancer on prognosis: systematic review of observational studies with meta-analysis. Br Med J 2010;340(jan21_1):b5569.

(42) Fox JL, Rosenzweig KE, Ostroff JS. The effect of smoking status on survival following radiation therapy for non-small cell lung cancer. Lung Cancer 2004;44(3):287-93.

(43) Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. Chest 2004;125(1):27-37.

(44) Phipps AI, Baron J, Newcomb PA. Prediagnostic smoking history, alcohol consumption, and colorectal cancer survival: the Seattle Colon Cancer Family Registry. Cancer 2011;117(21):4948-57.

(45) Pytynia KB, Grant JR, Etzel CJ, Roberts DB, Wei Q, Sturgis EM. Matched-pair analysis of survival of never smokers and ever smokers with squamous cell carcinoma of the head and neck. J Clin Oncol 2004;22(19):3981-8.

(46) Nagle CM, Bain CJ, Webb PM. Cigarette Smoking and Survival after Ovarian Cancer Diagnosis. Cancer Epidemiol Biomarkers Prev 2006;15(12):2557-60.

(47) Duffy SA, Ronis DL, McLean S, Fowler KE, Gruber SB, Wolf GT, et al. Pretreatment health behaviors predict survival among patients with head and neck squamous cell carcinoma. J Clin Oncol 2009;27(12):1969-75.

(48) Wright JD, Li J, Gerhard DS, Zhang Z, Huettner PC, Powell MA, et al. Human papillomavirus type and tobacco use as predictors of survival in early stage cervical carcinoma. Gynecol Oncol 2005;98(1):84-91.

(49) Barnett GC, Shah M, Redman K, Easton DF, Ponder BAJ, Pharoah PDP. Risk Factors for the Incidence of Breast Cancer: Do They Affect Survival From the Disease? JCO 2008;26(20):3310-6.

(50) Holmes MD, Murin S, Chen WY, Kroenke CH, Spiegelman D, Colditz GA. Smoking and survival after breast cancer diagnosis. Int J Cancer 2007;120(12):2672-7.

(51) Samant RS, Tucker TL. Analysis of cigarette smoking habits of cancer patients referred to the Northeastern Ontario Regional Cancer Centre. J Cancer Educ 2003;18(3):157-60.

(52) Tseng TS, Lin HY, Martin M, Chen T, Partridge E. Disparities in smoking and cessation status among cancer survivors and non-cancer individuals: a population-based study from National Health and Nutrition Examination Survey. 2010;4(4):313-21.

(53) Bellizzi KM, Rowland JH, Jeffery DD, McNeel T. Health behaviors of cancer survivors: examining opportunities for cancer control intervention. J Clin Oncol 2005;23(34):8884-93.

(54) Schnoll RA, James C, Malstrom M, Rothman RL, Wang H, Babb J, et al. Longitudinal predictors of continued tobacco use among patients diagnosed with cancer. Ann Behav Med 2003;25(3):214-22.

(55) Cooley ME, Sarna L, Brown JK, Williams RD, Chernecky C, Padilla G, et al. Tobacco use in women with lung cancer. Ann Behav Med 2007;33(3):242-50.

(56) Cooley ME, Sarna L, Kotlerman J, Lukanich JM, Jaklitsch M, Green SB, et al. Smoking cessation is challenging even for patients recovering from lung cancer surgery with curative intent. Lung CancerIn Press, Corrected Proof.

(57) Walker MS, Vidrine DJ, Gritz ER, Larsen RJ, Yan Y, Govindan R, et al. Smoking relapse during the first year after treatment for early-stage non-small-cell lung cancer. Cancer Epidemiol Biomarkers Prev 2006;15(12):2370-7.

(58) Wewers ME, Bowen JM, Stanislaw AE, Desimone VB. A nurse-delivered smoking cessation intervention among hospitalized postoperative patients--influence of a smoking-related diagnosis: a pilot study. Heart Lung 1994;23(2):151-6.

(59) Browning KK, Ahijevych KL, Ross P, Jr., Wewers ME. Implementing the Agency for Health Care Policy and Research's Smoking Cessation Guideline in a lung cancer surgery clinic. Oncol Nurs Forum 2000;27(8):1248-54.

(60) Griebel B, Wewers ME, Baker CA. The effectiveness of a nurse-managed minimal smoking-cessation intervention among hospitalized patients with cancer. Oncol Nurs Forum 1998;25(5):897-902.

(61) Schnoll RA, Zhang B, Rue M, Krook JE, Spears WT, Marcus AC, et al. Brief physician-initiated quit-smoking strategies for clinical oncology settings: a trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2003;21(2):355-65.

(62) Gritz ER, Carr CR, Rapkin D, Abemayor E, Chang LJ, Wong WK, et al. Predictors of long-term smoking cessation in head and neck cancer patients. Cancer Epidemiol Biomarkers Prev 1993;2(3):261-70.

(63) Wakefield M, Olver I, Whitford H, Rosenfeld E. Motivational interviewing as a smoking cessation intervention for patients with cancer: randomized controlled trial. Nurs Res 2004;53(6):396-405.

(64) Duffy SA, Ronis DL, Valenstein M, Lambert MT, Fowler KE, Gregory L, et al. A tailored smoking, alcohol, and depression intervention for head and neck cancer patients. Cancer Epidemiol Biomarkers Prev 2006;15(11):2203-8.

(65) Lichtenstein E, Zhu SH, Tedeschi GJ. Smoking cessation quitlines: an underrecognized intervention success story. Am Psychol 2010;65(4):252-61.

(66) Stead LF, Perera R, Lancaster T. Telephone counselling for smoking cessation. Cochrane Database of Systematic Reviews 2006;3:CD002850.

(67) Orleans CT, Schoenbach VJ, Wagner EH, Quade D, Salmon MA, Pearson DC, et al. Self-help quit smoking interventions: effects of self-help materials, social support instructions, and telephone counseling. J Consult Clin Psychol 1991;59(3):439-48.

(68) Curry SJ, Grothaus LC, McAfee T, Pabiniak C. Use and cost effectiveness of smoking-cessation services under four insurance plans in a health maintenance organization. N Engl J Med 1998;339(10):673-9.

(69) Swan GE, McAfee T, Curry SJ, Jack LM, Javitz H, Dacey S, et al. Effectiveness of bupropion sustained release for smoking cessation in a health care setting: a randomized trial. Arch Intern Med 2003;163(19):2337-44.

(70) Hollis JF, McAfee TA, Fellows JL, Zbikowski SM, Stark M, Riedlinger K. The effectiveness and cost effectiveness of telephone counselling and the nicotine patch in a state tobacco quitline. Tob Control 2007;16 Suppl 1:i53-i59.

(71) McAfee TA, Bush T, Deprey TM, Mahoney LD, Zbikowski SM, Fellows JL, et al. Nicotine patches and uninsured quitline callers. A randomized trial of two versus eight weeks. Am J Prev Med 2008;35(2):103-10.

(72) Bandura A. Social foundations of thought and action: a social cognitive theory. Englewood Cliffs, N.J.: Prentice-Hall, 1986.

(73) Fiore MC, Jaen CR, Baker TB, Bailey WC, Benowitz NL, Curry SJ, et al. Treating tobacco use and dependence: 2008 update US Public Health Service Clinical Practice Guideline executive summary. Respir Care 2008;53(9):1217-22.

(74) Gritz ER, Fingeret MC, Vidrine DJ, Lazev AB, Mehta NV, Reece GP. Successes and failures of the teachable moment: smoking cessation in cancer patients. Cancer 2006;106(1):17-27.

(75) McBride CM, Ostroff JS. Teachable moments for promoting smoking cessation: The context of cancer care and survivorship. Cancer Control 2003;10(4):325-33.

(76) Sarna LP, Brown JK, Lillington L, Rose M, Wewers ME, Brecht ML. Tobacco interventions by oncology nurses in clinical practice: report from a national survey. Cancer 2000;89(4):881-9.

(77) Cox LS, Africano NL, Tercyak KP, Taylor KL. Nicotine dependence treatment for patients with cancer. Cancer 2003;98(3):632-44.

(78) Sharp L, Johansson H, Fagerstrom K, Rutqvist LE. Smoking cessation among patients with head and neck cancer: cancer as a 'teachable moment'. Eur J Cancer Care (Engl) 2008;17(2):114-9.

(79) Gritz ER, Nisenbaum R, Elashoff RE, Holmes EC. Smoking behavior following diagnosis in patients with stage I non-small cell lung cancer. Cancer Causes Control 1991;2(2):105-12.

(80) Ostroff JS, Jacobsen PB, Moadel AB, Spiro RH, Shah JP, Strong EW, et al. Prevalence and predictors of continued tobacco use after treatment of patients with head and neck cancer. Cancer 1995;75(2):569-76.

(81) Davison AG, Duffy M. Smoking habits of long-term survivors of surgery for lung cancer. Thorax 1982;37(5):331-3.

(82) Moadel AB, Lederberg MS, Ostroff JS. Nicotine dependence and withdrawal in an oncology setting: a risk factor for psychiatric comorbidity and treatment non-adherence. Psychooncology 1999;8(3):264-7.

(83) Gritz ER, Schacherer C, Koehly L, Nielsen IR, Abemayor E. Smoking withdrawal and relapse in head and neck cancer patients. Head Neck 1999;21(5):420-7.

(84) Gritz ER, Demark-Wahnefried W. Health behaviors influence cancer survival. J Clin Oncol 2009;27(12):1930-2.

(85) Yu GP, Ostroff JS, Zhang ZF, Tang J, Schantz SP. Smoking history and cancer patient survival: a hospital cancer registry study. Cancer Detect Prev 1997;21(6):497-509.

(86) Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-55.

(87) Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. Primary care validation of a single-question alcohol screening test. J Gen Intern Med 2009;24(7):783-8.

(88) Smith PC, Schmidt SM, Allensworth-Davies D. A single-question screening test for drug use in primary care. Arch Intern Med 2010;170(13):1155-60.

(89) Schnoll RA, Zhang B, Rue M, Krook JE, Spears WT, Marcus AC, et al. Brief Physician-Initiated Quit-Smoking Strategies for Clinical Oncology Settings: A Trial Coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol 2003;21(2):355-65.

(90) Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health Soc Behav 1983;24(4):385-96.

(91) Golden-Kreutz DM, Browne MW, Frierson GM, Andersen BL. Assessing Stress in Cancer Patients. Assessment 2004;11(3):216-23.

(92) Golden-Kreutz DM, Thornton LM, Wells-Di Gregorio S, Frierson GM, Jim HS, Carpenter KM, et al. Traumatic Stress, Perceived Global Stress, and Life Events: Prospectively Predicting Quality of Life in Breast Cancer Patients. Health Psychol 2005;24(3):288-96.

(93) Radloff LS. The CES-D scale: A self-report depression scale for research in the general population. Appl Psychol Meas 1977;1:385-401.

(94) Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: Evaluation of the center for epidemiological studies depression scale (Ces-d). J Psychosom Res 1999;46(5):437-43.

(95) Sarna L, Cooley ME, Brown JK, Williams RD, Chernecky C, Padilla G, et al. Quality of life and health status of dyads of women with lung cancer and family members. Oncol Nurs Forum 2006;33(6):1109-16.

(96) Sarna L, Padilla G, Holmes C, Tashkin D, Brecht ML, Evangelista L. Quality of Life of Long-Term Survivors of Non-ûSmall-Cell Lung Cancer. J Clin Oncol 2002;20(13):2920-9.

(97) Cella DF, Bonomi AE, Lloyd SR, Tulsky DS, Kaplan E, Bonomi P. Reliability and validity of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality of life instrument. Lung Cancer 1995;12(3):199-220.

(98) Bergman B, Aaronson NK, Ahmedzai S, Kaasa S, Sullivan M. The EORTC QLQ-LC13: a modular supplement to the EORTC core quality of life questionnaire (QLQ-C30) for use in lung cancer clinical trials. Eur J Cancer 1994;30(5):635-42.

(99) Dijkstra A, De Vries H. Self-efficacy expectations with regard to different tasks in smoking cessation. Psychology & Health 2000;15(4):501-11.

(100) Rash CJ, Copeland AL. The Brief Smoking Consequences Questionnaire-Adult (BSCQ-A): development of a short form of the SCQ-A. Nicotine Tob Res 2008;10(11):1633-43.