STUDY PROTOCOL

Version Date: 09/30/2025.

UW HS-IRB # 2023-1025

NCT 06218823

"Tobacco Treatment Comparison for Cancer Care"

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Funding Sponsor: DHHS, PHS, National Institutes of Health (NIH)

PROTOCOL TITLE:

Comparative Effectiveness Trial of Tobacco Cessation Treatments among Cancer Patients who Smoke

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VERSION NUMBER/DATE:

Version 6, September 12, 2025

REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	8/18/2023	Response to PRMC concerns regarding varenicline start date (noting there is a 1-week pre-quit run-in period), counseling end date (moved to 12 weeks post-quit in enhanced care), and adverse event monitoring schedule (the 8 week follow-up has now been moved to 12-weeks post-quit for both conditions).	Yes, regarding timing of counseling contacts and follow-up assessments
2	9/7/2023	Response to IRB Pre-review comments	Yes, to add a comprehensi

			on question and data sharing consent to the oral consent script and to update the study information sheet
#3	12/18/2023	Addition of a qualitative substudy that will inform tobacco treatment outreach and counseling in the parent study. Clarification of secondary endpoint/outcome and exploratory aims. Additional minor edits for consistency and accuracy regarding the following: • Biochemical sample collection occurs only at the 26-week follow-up (not at 12-weeks) • Target windows for counseling calls are the same for the first 3 counseling calls in both comparative effectiveness trial arms • Update section 11.2 to reflect a change in personnel who handle medication dispensing • Add a cover letter that will accompany materials mailed to participants who enroll in the comparative effectiveness trial • Updating the protocol to reflect the step-down nicotine patch dose schedule for people who receive 12 weeks of nicotine patches • Updating the protocol to note that randomization occurs after baseline assessment rather than immediately after consent	Yes, addition of a new oral consent script for a 1-time qualitative interview with up to 32 patients with a history of cancer.
#4	2/13/2024	Updated eligibility criteria to remove exclusion of participants of enrolled in another cancer clinical trial. Added recruitment flier for participating clinics.	No

#5	4/25/2024	Updated medication eligibility criteria to require daily smoking, to be consistent across medication conditions. Separate oral consent and screening materials into two separate documents for clarity. Minor editorial changes to these documents to improve flow. Added baseline assessment of current smoking cessation medications. Updated qualitative interview substudy recruitment to include participants enrolled in CET at 12- and 26-week follow up.	Yes
#6	5/1/2025	Revised descriptions of payment delivery method to account for the University's retirement of custodial checking account payments. After May 16th 2025 participants will be sent gift cards in lieu of checks.	Yes, all mentions of sending a check have been stricken.
#7	7/16/2025	Added exploratory aim regarding relations between treatment engagement and abstinence and health and healthcare utilization outcomes. Clarified electronic health record (EHR) and Cancer Registry data extraction among all patients identified as eligible who did not actively decline study participation to examine cancer care and outcomes, estimate cancer care costs, and capture information on environmental exposure. Waiver of consent and HIPAA waiver justification for EHR data extraction for patients who did not actively decline study participation. Added Jesse Kaye, PhD as Co-Investigator	No

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1.0 Study Summary

Study Title	
Brief Summary	This pilot comparative effectiveness trial will compare two active smoking cessation treatments in terms of effectiveness, equity across patient subpopulations, and efficiency among adult patients diagnosed with cancer within the past 3 years. An enhanced treatment comprising 12 weeks of varenicline treatment and 7 smoking cessation coaching calls with a cancer focus will be compared against an active comparator modeled after standard quitline treatments (2 weeks of nicotine patch therapy with 3 phone coaching calls). Approximately 50 participants will be recruited for this 7-month study to generate estimates of the effects, acceptability, costs, and equity of enhanced treatment (vs. standard treatment), with the primary outcome being abstinence from smoking 12 and 26 weeks after trying to quit. Qualitative interviews will be conducted with up to 32 adult patients with a history of cancer to inform study methods and smoking cessation counseling tailored to cancer care.
Number of study sites	1 health system (3-10 clinical departments)
Study Design	2-arm pilot comparative effectiveness trial of enhanced care (high-intensity, cancer-targeted smoking cessation treatment) versus low-intensity standard smoking cessation treatment.
Primary Objective	Generate an effect size estimate for enhanced care intensive smoking cessation treatment targeted to cancer patients (versus an active standard care control) effects on abstinence 3 to 6 months following a target quit date.
Secondary Objective(s)	Compare treatments in terms of patient acceptability, completion, adherence, costs, and cost-effectiveness. Estimate the extent to which intensive, cancer-specific treatment benefits (relative to control) differ across patient subpopulations based on demographics (age, race, sex, ethnicity, socioeconomic disadvantage); nicotine dependence; and cancer site, stage, and treatment phase. Explore relations between 1) engagement in tobacco treatment and 2) quitting smoking and health and healthcare utilization outcomes, including cancer outcomes overall (among identified patients who did not actively decline participation), and as a function of environmental exposures and, for those enrolled in the CET, randomly assigned treatment condition.

Research Intervention(s)/ Investigational Agent(s)	The two active treatments will be 1) standard treatment comprising 2 weeks of free nicotine patch therapy, 3 telephone counseling sessions, and information about quitline and National Cancer Institute text messaging support services (SmokefreeTXT); and 2) enhanced treatment comprising 12-weeks of varenicline therapy, 7 counseling sessions targeted to cancer patients, and information about quitline and SmokefreeTXT services. Comparative effects will be measured in terms of the proportion of patients randomized to treatment who achieve biochemically confirmed abstinence overall, and across patient subpopulations, acceptability and adherence (measured in terms of treatment completion, patient satisfaction), costs (including intervention delivery costs and patient burden and costs), and cost-effectiveness to identify which treatment is most effective, efficient, and equitable.
Drugs/devices used on study (including any IND/IDE #)	Transdermal nicotine patches (FDA approved for smoking cessation). Varenicline (FDA approved for smoking cessation).
Study Population	Adults who currently smoke cigarettes and who have been diagnosed with cancer in the past 3 years and received cancer care from a participating UW Health clinic in the past year will be recruited for the comparative effectiveness trial. Adult patients with a history of cancer will be eligible for qualitative interviews that will inform study procedures and interventions.
Sample Size	82
Study Duration for individual participants	Up to 8 months
Study Specific Abbreviations/ Definitions	ACS=American Cancer Society EC=Enhanced care (intensive, cancer-specific smoking cessation counseling and 12 weeks of varenicline) CO=carbon monoxide CET=Comparative effectiveness trial NCI=National Cancer Institute NRT=nicotine replacement therapy SC=Standard care (low-intensity general smoking cessation coaching and nicotine patch starter kit) USDHHS=United State Department of Health and Human Services UW-CCC=University of Wisconsin Carbone Cancer Center UW-CTRI=University of Wisconsin Center for Tobacco Research and Intervention

Note: Include only elements relevant to this study.

2.0 Background

2.1 Prior experience and gaps in current knowledge.

Smoking causes multiple types of cancer, including cancers of the oral cavity and pharynx, larynx, esophagus, lung, stomach, kidney, pancreas, liver, bladder, cervix, colon and rectum, and acute myeloid leukemia (American Cancer Society (ACS), 2021, US Department of Health and Human Services (USDHHS), 2014). Further, patients who smoke at the time of their cancer diagnosis have an increased risk of cancer recurrence, treatment complications, and mortality due to cancer-related and all-cause mortality (USDHHS 2014; National Cancer Institute (NCI), 2022). Moreover, evidence is accumulating that smoking cessation after diagnosis is associated with significantly reduced all-cause mortality (USDHHS, 2014; NCI, 2022).

While smoking is clearly related to increased risk negative health outcomes amongst cancer patients, it is also clear that patients with cancer far too rarely receive treatment for their smoking as part of their cancer care (Cooley et al., 2018; Croyle et al. 2019; Day et al., 2019; Peters et al. 2012). Research suggests that rates of undertreatment may be related to cancer care clinicians' beliefs that they are too busy to intervene with smoking or that they are not adequately prepared to treat their patients' smoking (Price et al. 2019).

Unfortunately, we currently know far too little about how to best help cancer patients quit smoking. This knowledge gap reflects a lack of rigorous trials of smoking cessation interventions for cancer patients (NCI, 2022). As such, at present the evidence is mixed as to whether smoking cessation pharmacotherapy and counseling significantly improve smoking cessation rates in cancer patients (NCI, 2022). There are reasons to suspect that treatments that effectively promote smoking cessation in general adult populations may be less effective in patients with cancer (e.g., those who continue smoking after a cancer diagnosis may be especially dependent on nicotine, the stress of cancer or its treatment may be a potent trigger to smoking lapses or relapses, patients may lack the energy or time to complete smoking cessation treatment in the midst of cancer treatment; fatalism may undermine motivation to quit). As such, it is important to identify treatments that are effective in promoting smoking cessation among cancer patients, and in the context of cancer care.

In addition, evidence regarding the comparative effectiveness of smoking treatments that differ in burden and costs is also lacking, particularly in cancer care. An intensive treatment that yields slightly better abstinence rates, but at greatly increased costs in terms of money or burden, may not be efficient or sustainable. Likewise, an intensive treatment that benefits only a small subset of patients with cancer who smoke may exacerbate health disparities, while also being inefficient. For these reasons, it is

important to evaluate smoking cessation treatments along all three of these dimensions: effectiveness, efficiency, and equity when determining which treatment approaches to disseminate in cancer care settings.

The proposed small comparative effectiveness trial will be informed by qualitative interviews with adult patients who have had cancer, and will generate pilot data that will be used to estimate effect sizes regarding the comparative effectiveness, acceptability, efficiency, and equity of intensive and cancer-specific smoking cessation treatment versus a generic, recommended-care, active, control condition. These pilot data will serve as preliminary data that will inform the design of a future full-scale comparative effectiveness trial.

2.2 Primary Aim

The primary aims of the proposed pilot CET are:

1. To establish the feasibility of the CET protocol and procedures in preparation for a full-scale future trial.
2. To generate estimates of the size of the comparative effects of enhanced, cancer-specific smoking cessation treatment versus a generic standard care package similar to quitline care in terms of biochemically confirmed 7-day point prevalence abstinence (no smoking in the past 7 days) 26 weeks after a target quit date.

2.3 Exploratory Aims

Exploratory aims of the pilot CET are:

3. To estimate differences in CET arms in exploratory outcomes including patient acceptability, completion, adherence, costs, and cost-effectiveness.
4. To elicit input from patients who have experienced cancer to inform study methods and interventions.
5. To estimate the extent to which treatment effects on abstinence and exploratory outcomes differ across patient subpopulations based on demographics (age, race, sex, ethnicity, socioeconomic disadvantage); nicotine dependence; and cancer site, stage, and treatment phase.
6. To explore relations between 1) engagement in tobacco treatment and 2) quitting smoking and health and healthcare utilization outcomes, including cancer outcomes overall, and as a function of environmental exposures and, for those enrolled in the CET, randomly assigned treatment condition.

2.4 Preliminary data.

The opt-out referral model to be adapted in this project has increased the reach of smoking cessation treatment in primary care and inpatient contexts (Creswell et al., 2022; McCarthy et al., 2022). In this approach, referral to or connection with treatment is the default for all adults whose EHR records suggest they currently smoke, unless a patient actively opts out of such referral. We are currently employing a similar opt-out referral

approach in 22 clinics in 2 health systems (UW IRB Protocol #: 2019-0054, 2019-0939, 2022-0124, and especially 2022-0973) with great success. Over the past 2.75 years, this referral strategy has led to the enrollment of more than 1300 adult patients who smoke in smoking treatment trials. All of these protocols involve mailing patients who meet initial eligibility prerequisites based on information in their EHR a study launch letter that offers them an opportunity to opt out of study recruitment, and then proactive telephone outreach to patients who have not opted out of such contact to offer both standard tobacco treatment and the opportunity to enroll in a tobacco treatment trial.

The design of the proposed CET is similar to a CET that we recently completed with primary care patients (Piper et al., 2018, UW HS IRB Protocol # 2014-1041). This 2-arm CET compared an even more intensive treatment (26 weeks of varenicline with 11 counseling contacts) with a recommended usual treatment comparator that comprised 8 weeks of nicotine patch therapy, a single 10-minute counseling call, and referral to the Wisconsin Tobacco Quitline and a smoking cessation app. Participants were 623 adult primary care patients whose EHR indicated they currently smoked cigarettes and who either contacted the research team after receiving an outreach letter alerting them to the study opportunity or agreed to be referred to the treatment team when they presented for primary care. Results indicated that optimized care nearly tripled rates of biochemically verified 7-day point-prevalence abstinence 26 weeks after participants' target quit dates (Odds ratio=2.94, 95% Confidence Interval=1.69, 5.14; Piper et al., 2018).

The proposed project seeks to conduct a similar CET of an enhanced treatment targeted to cancer-related challenges and concerns and offering 12 weeks of varenicline treatment with an active comparator representing standard care (2 weeks of nicotine patch, 3 counseling sessions, and information about digital and quitline cessation support, not targeted to cancer).

2.5 **Scientific background, rationale, and significance.**

Combustible cigarette smoking is a leading preventable cause of cancer (USDHHS, 2014; NCI, 2022), and continued smoking after diagnosis is associated with poor clinical outcomes. Evidence synthesized from the 2014 and 2020 Surgeon General's Reports shows a causal relationship in patients with cancer between smoking and adverse health outcomes, increased all-cause mortality, increased cancer-specific mortality, and increased risk of second primary smoking-related tumors (USDHHS, 2014, 2022). Evidence also suggests that smoking in cancer patients is associated with risk of cancer recurrence, reduced efficacy of cancer treatment, and increased cancer treatment-related toxicity (NCI, 2022).

Despite compelling evidence that smoking increases risks for negative outcomes, many patients with cancer continue to smoke after diagnosis, and cessation treatment is not consistently integrated into cancer care, particularly for minoritized groups (Cooley et al., 2018; Croyle et al., 2019; Ramaswamy et al., 2016; D'Angelo et al., 2021). Research suggests that while many patients with cancer are advised to stop smoking, fewer than half of cancer patients receive treatment to help them do so (Borger et al., 2022; Price et al., 2019). Importantly, evidence shows that many cancer patients are interested in trying to quit and the majority of cancer patients try to quit following their diagnosis (Gritz et al., 2020). However, such quit attempts are very often unsuccessful with at least half of patients with cancer continuing to smoke after diagnosis (Gritz et al., 2020; Sharp et al., 2014). Even with strong motivation to quit, only half of head and neck cancer patients in a recent study abstained from smoking for at least 24 hours, and only 10% were able to quit for at least 30 days (Borger et al., 2022).

Given the known risks of smoking in cancer patients, it is imperative that accessible, evidence-based smoking cessation treatment be offered consistently to patients receiving cancer care. Opt-out approaches to referring patients to treatment have shown promise in broader populations (Creswell et al., 2022; McCarthy et al., 2022), including patients receiving cancer care (D'Angelo et al., 2022). In an opt-out referral system, patients are automatically referred to a proactive smoking treatment service that offers quitting assistance, unless the patient has specifically requested that they not receive such offers. This opt-out referral process does not burden front-line cancer care teams. Instead, tobacco treatment offers are extended by tobacco treatment specialty teams directly to patients identified based on reports extracted from EHR data who do not opt out of such outreach. Importantly, this approach seems to enhance the equity of smoking treatment reach among historically underserved populations that have been disproportionately affected by tobacco use (e.g., minoritized individuals; Creswell et al., 2022; McCarthy et al., 2022). As such, an opt-out referral to a centralized smoking treatment outreach program may be a promising way to equitably engage more people with cancer in effective smoking cessation interventions while imposing little to no burden on clinic staff or providers.

Important unanswered questions in the literature include which cessation interventions are effective in patients with cancer and whether more intensive intervention improves abstinence outcomes relative to less intensive treatment in this population. There are few rigorous controlled clinical trials of smoking cessation treatments in patients with cancer (NCI, 2022). Some studies of patients with cancer have shown that relatively intensive counseling and pharmacotherapy can improve cessation rates more than less-intensive treatment (Duffy et al., 2006; Park et al., 2020; Rettig et al., 2018). However, other studies show little or no benefit of more intense treatment (Schnoll et al., 2010, 2019; NCI, 2022). A recent meta-analysis also failed to find consistent evidence that cessation intervention improves smoking abstinence rates amongst cancer patients (Sheeren

et al., 2019). One reason for the uncertainty in this area is that too few randomized controlled trials have been done with cancer patients; most of the available evidence comes from studies that are small and underpowered (NCI, 2022).

Currently, clinicians must rely on more general treatment research and guidelines (e.g., NCCN, 2022) when offering cessation care to people with cancer. The general cessation intervention literature and guidelines support 2 first line pharmacotherapies: varenicline, a selective nicotine acetylcholine receptor partial agonist; and the combination of nicotine patches with fast-acting nicotine replacement therapies (NRT) such as nicotine gum or lozenges (Cahill et al., 2013). Research suggests that varenicline is well tolerated in patients with cancer (Crawford et al., 2019; Schnoll et al., 2019). Some recent guidelines have also promoted varenicline as the preferred first line therapy for smoking cessation based on evidence of its superiority to NRT (Leone et al., 2020). The study will generate much needed evidence on the effectiveness of varenicline treatment in patients with cancer.

Importantly, the proposed study will also evaluate an opt-out referral mechanism for people receiving cancer care to address the critical undertreatment of smoking in cancer care. Patients receiving cancer care at UW-CCC will be referred to smoking cessation treatments facilitated or delivered by centralized staff at UW-CTRI. Patients will be automatically referred via quarterly UW Institute for Clinical and Translational Research (ICTR) Clinical Research Data Service (CRDS) reports to the UW-CTRI cessation study coordinators who will first send patients letters to inform them of the proactive outreach program and give them a chance to opt out. Then, UW-CTRI study coordinators will call patients who have not opted out to invite them to enroll in either the current standard of care at UW Health (connection with the Wisconsin Tobacco Quitline (WTQL) and/or referral to their primary care provider) or to randomized smoking treatment delivered in a comparative effectiveness trial of 2 smoking cessation interventions:

1) Standard treatment comprising a 2-week supply of transdermal nicotine patches; 3 brief telephone smoking cessation counseling sessions; and mailed information about standard care resources (NCI-sponsored resources including the 8-week SmokefreeTXT program, WTQL services, and primary care or oncology support).

2) Enhanced treatment comprising 12 weeks of varenicline, 7 remote counseling sessions adapted for cancer patients from the Park et al., 2020 counseling protocol, and information about SmokefreeTXT and WTQL services.

These 2 treatments will be compared in terms of smoking abstinence rates, but also in terms of costs, patient burden, adherence, and side effects to gauge the value of intensive smoking treatment in terms of patient acceptability, engagement, effectiveness, and cost-effectiveness and efficiency. Equity in treatment effects across patient subpopulations will

also be examined. As such, the project will evaluate both an opt-out referral method designed to make offering smoking treatment the default rather than the exception for patients with cancer and the effects of 2 highly distinct smoking treatment packages in cancer care.

An opt-out treatment referral mechanism that has shown promise in primary care (McCarthy et al., 2022) will be adapted to the cancer care context. This is innovative and important, given the elevated risks of continued smoking and critical benefits of smoking cessation in patients with cancer, and current low rates of evidence-based treatment use among cancer patients (Borger et al., 2022; NCI, 2022). In addition, the proposed project will compare an intensive, tailored smoking cessation intervention with a less intensive treatment similar to quitline services. This comparison will demonstrate to cancer care programs the extent to which their patients would benefit from enhanced smoking cessation treatment that has cancer focused content versus a treatment that is similar to a quitline intervention. Such evidence does not currently exist.

The cancer-focused smoking cessation counseling protocol that will be used in the intensive treatment will be based on the counseling used in the recent randomized controlled trial conducted by Park and colleagues (Park et al., 2020), and informed by the qualitative interviews completed with patients in the qualitative substudy. The Park et al. study was conducted in patients with a variety of cancer diagnoses and showed that such intensive treatment produced higher smoking abstinence rates at 6 months post-treatment than did a less intense treatment (34.5% vs. 21.5%). However, few studies of smoking treatment in cancer patients have manipulated pharmacotherapy intensity, and results to date have been inconclusive (Schnoll et al., 2010, 2019). In addition, the Park et al., (2020) did not systematically vary pharmacotherapy treatment across the two experimental conditions; thus, it may underestimate the effectiveness of more intensive treatment.

In addition to addressing a novel research question, the research methods for the CET are also innovative in their integration of patient self-report data on treatment utilization, acceptability, burden, tolerability, adherence, and success (in terms of abstinence rates) with treatment cost data and EHR-extracted data on healthcare utilization, complications, and clinical outcomes to facilitate a multi-dimensional comparison of the 2 treatment conditions (i.e., a comparison of treatment not just in terms of abstinence, but also in terms of likely population impact and efficiency). This work is much needed given the dearth of rigorous trials of smoking treatments in this high-priority population.

We anticipate that the proposed feasibility pilot test will demonstrate that automatic, opt-out referral of cancer patients who smoke to centralized, low-barrier smoking cessation treatment resources is feasible. We anticipate that at least 12% of patients eligible for referral will enter evidence-based smoking treatment, the rate we observe in primary care settings. We also anticipate that

reach may be stronger in historically underserved populations most adversely affected by tobacco use, including African-American patients and those who are uninsured or eligible for Medicaid. If recruitment of minoritized individuals is slow, we will reach out to partners at Wisconsin Oncology Network to enhance sample diversity. We will elicit patient input through qualitative interviews to enhance the design of outreach materials and counseling protocols in an effort to enhance acceptability for patients, as well.

The study will accelerate progress in an important but neglected facet of cancer care. Identifying ways to connect more patients with cancer to evidence-based treatments that show particular promise in this population is critically important and can lead to significant improvement in the lives of people with cancer.

3.0 Study Objectives and Endpoints

3.1 Study objectives.

The objectives of the proposed study are:

1) To evaluate the feasibility and acceptability of a proactive tobacco treatment referral model for patients who use tobacco after diagnosis with cancer.
2) To generate estimates of the reach, effectiveness (in terms of abstinence up to 6 months after a target quit day), efficiency (i.e., cost-effectiveness), and equity of enhanced smoking treatment relative to a lower-intensity standard care comparator.

The primary endpoints in this feasibility pilot will be the reach of smoking treatment among adult patients diagnosed with cancer who continue smoking after diagnosis and 7-day point-prevalence abstinence from smoking 26 weeks after a target day to quit smoking (as a measure of effectiveness). Additional important endpoints include: patient perspectives on smoking treatment outreach and counseling (elicited in qualitative interviews), retention in and completion of treatment activities (as additional measures of feasibility and acceptability), costs and cost-effectiveness (to assess relative efficiency of the two active treatments), and differences in comparative treatment effects across patient subpopulations (to assess equity in treatment outcomes). Given the limited sample size in this pilot CET, these endpoints will be used to generate estimates of effects and sample size needs for a future full-scale CET.

3.2 Primary & Exploratory Aims

Primary Aims

Aim 1: To establish the feasibility of the CET protocol and procedures in preparation for a full-scale future trial.

Aim 2: To generate estimates of the size of the comparative effects of intensive, cancer-specific smoking cessation treatment versus a generic, lower-

intensity recommended smoking cessation treatment in terms of biochemically confirmed 7-day point prevalence abstinence (no smoking in the past 7 days) 26 weeks after a target quit date.

Exploratory Aims

Aim 3: To estimate differences in CET arms in exploratory outcomes including patient acceptability, completion, adherence, costs, and cost-effectiveness.

Aim 4. To elicit input from patients who have experienced cancer to inform study methods and interventions.

Aim 5. To estimate the extent to which treatment effects on abstinence and exploratory outcomes differ across patient subpopulations based on demographics (age, race, sex, ethnicity, socioeconomic disadvantage); nicotine dependence; and cancer site, stage, and treatment phase.

Aim 4. To explore relations between 1) engagement in tobacco treatment and 2) quitting smoking and health and healthcare utilization outcomes, including cancer outcomes overall, and as a function of environmental exposures and, for those enrolled in the CET, randomly assigned treatment condition.

3.3 **Study hypotheses.**

The primary hypothesis to be tested for Aim 1 is that at least 12% of eligible adult patients who have cancer and smoke cigarettes and are referred to the tobacco treatment outreach team will initiate an evidence-based form of smoking treatment (either Wisconsin Tobacco Quit Line care or treatment offered in the CET).

The primary hypothesis to be tested for Aim 2 is that more-intensive, cancer-specific smoking cessation treatment will increase the log odds of achieving 7-day abstinence 26 weeks after a target quit date by at least 50% over the comparator condition (predicted odds ratio >=1.50).

Exploratory hypotheses include the following:

For Aim 3, we hypothesize that the majority of patients assigned to each condition will initiate treatment and will receive at least some counseling and use at least some of the provided medication. We also hypothesize that patient ratings of acceptability and satisfaction will be favorable. We also expect retention, adherence, and satisfaction with treatment to be higher in enhanced care relative to the standard care control condition. We anticipate that the more-intensive treatment, although more costly, will be cost-effective in terms of the incremental cost effectiveness ratio per additional

patient who quits smoking, relative to the comparator condition and to other preventive health interventions.

For Aim 4, we are not testing a specific hypothesis. Instead, we are seeking patient input to enhance the acceptability of tobacco treatment outreach and the relevance of smoking cessation counseling for participants in the CET.

For Aim 5, we expect treatment reach to be especially high among historically undertreated populations (including African-American, Medicaid-eligible patients, and those from disadvantaged neighborhoods), and for the effects of enhanced care (vs. the standard care comparator) to be similar across patient subgroups.

3.4 **Study endpoints.**

Primary endpoints:

1. Reach of smoking treatment, defined as the proportion of eligible patients who initiate evidence-based smoking treatment through the opt-out referral program. (Aim 1)
2. Biochemically verified 7-day point-prevalence abstinence 26 weeks after a target quit date (confirmed by expired carbon monoxide and/or a cotinine urine or saliva sample test). (Aim 2)

Secondary endpoint:

1. Self-reported 7-day point-prevalence abstinence 12 weeks after a target quit date. (Aim 2).

Exploratory endpoints:

1. Treatment acceptability and feasibility indicators including treatment retention (at each treatment contact/milestone) and completion, medication adherence, patient satisfaction, and patient ratings of burden. (Aim 3).
2. Treatment costs from payer and patient perspectives. (Aim 3).
3. Incremental cost-effectiveness ratios for each additional patient who quits smoking with higher-intensity treatment versus lower-intensity treatment. (Aim 4).
4. Differences in rates of treatment reach, retention, and completion by patient factors (demographics, nicotine dependence, smoking history). (Aim 5).
5. Moderation of treatment effects (high- vs. low-intensity) by patient factors. (Aim 5).

6. Health outcomes (e.g., cancer mortality, cancer progression, new cancer diagnoses, treatment side effects).

3.5 **Primary safety endpoints.**

1. Adverse events, by treatment condition.
2. Serious adverse events, by treatment condition.

4.0 Number of Participants

4.1 **Total number of participants to be accrued.** Up to 82 adult participants will be enrolled in the clinical trial by UW-CTRI staff from UW Carbon Cancer Center clinic referrals over 12-30 months. We will continue enrolling within each clinic until we reach saturation in qualitative data analysis of patient interviews (maximum N=32) and until we reach our target enrollment for the CET (N=50).

4.2 **Number of participants needed to complete the research procedures.** We anticipate that we will engage 12% of participants in some form of evidence-based treatment, and that 50 will enroll in the proposed comparative effectiveness study while another 50 will opt for the Wisconsin Tobacco Quit Line. As such, we anticipate that we will need to reach out to approximately 833 patients who meet criteria to be included on the quarterly CRDS reports that will guide proactive outreach letters and calls. We anticipate that the remaining 733 participants will either opt-out of smoking treatment outreach, will not be reached by the outreach team, will decline tobacco treatment, will elect to pursue treatment via their primary care provider or other means (e.g., over-the-counter) rather than to use formal treatment, or will not complete the treatment enrollment process for other reasons.

Among the 50 participants who enroll in the CET, we will use an intent-to-treat approach to data analyses so that all randomized participants will be included in key analyses of feasibility, acceptability, and abstinence rates, even if lost to follow-up. In primary analyses of abstinence outcomes, missing cases will be treated as still smoking. This will be supplemented by sensitivity analyses under varying assumptions regarding censored data (i.e., that 5%, 10%, or 20% of missing data are abstinent).

For the qualitative interviews, even 2-5 interviews could inform and enhance study methods. We anticipate that we could reach thematic saturation in qualitative data coding with fewer than 32 interviews, and have set 32 as an upper limit for recruitment.

4.3 **Criteria for considering participants "enrolled."** Individuals will be considered enrolled in the study at the point of randomization to a study arm in the CET. Randomization will occur after oral consent to participate and completion of baseline assessments. People who do not complete oral consent and randomization will not be considered fully enrolled and will be replaced until 50 people are randomized in the CET (25 in each arm).

5.0 Inclusion and Exclusion Criteria

5.1 **Eligibility screening and retention.** Adult, living patients potentially eligible for the CET based on their current tobacco use status (as recorded in Health Link), a diagnosis of cancer within the past 3 years, receipt of care in a participating cancer clinic in the past year, and not having a preferred language other than English recorded in the EHR, will be identified by UW Health CRDS reports sent securely to UW-CTRI on a quarterly basis through ICTR REDCap.

This list of potentially eligible patients will guide UW-CTRI study coordinators who will first send letters notifying patients that they have been identified as potentially eligible for the CET and Wisconsin Tobacco Quit Line treatment.

The study letters sent to participants will include all required elements of such recruitment tools, and will inform patients that they will receive phone calls inviting them to learn more about smoking treatment options, unless they elect to opt-out of such outreach. The letter will direct patients who wish to opt out of such calls and future mailings to call UW-CTRI to request that they be removed from future outreach efforts. Patients will also have the opportunity to opt out of future outreach at any outreach calls, as well (if they have not already opted out after receiving the letter).

All opt-out requests will be respected throughout the duration of the project. In order to ensure that such opt-outs are respected, we will need to maintain a list of people who opted out until the project ends, as they may appear on future quarterly reports that will guide outreach, and we will need to maintain a cumulative list of patients who opted out to ensure we do not contact them against their stated wishes. This list will need to contain enough information to identify patients (name, phone numbers, date of birth, and MRN), along with their study status (i.e., opted out of all contact). These identifiers will be stripped from the data after the close of recruitment/outreach activities. Basic demographics (age, sex, gender, race, ethnicity) and insurance type will also be collected, and this will be maintained after the close of recruitment/outreach in de-identified manner (i.e., age will be truncated at 90 and recoded into 5-year bins) for analyses

of the representativeness of tobacco treatment reach of both Wisconsin Tobacco Quit Line standard care and comparative effectiveness trial treatment.

Recruitment fliers will also be placed in participating clinics and/or distributed by cancer care teams so that patients may proactively contact the study team to learn about tobacco treatment options.

For patients who do not opt-out of tobacco treatment outreach, UW-CTRI study coordinators will make up to 5 phone call attempts to the patient telephone numbers in the EHR over 12 weeks. When a study coordinator reaches a patient, s/he will explain that UW-CTRI is reaching out to patients who smoke and receive cancer care at UW Health/Carbone to offer support and resources, including both standard care (e.g., Wisconsin Tobacco Quit Line referral) and the opportunity to screen for eligibility for a UW-CTRI study.

Patients who are interested in treatment from their care teams or the Wisconsin Tobacco Quit Line (WTQL) (or the quit line in their home state, if outside of Wisconsin) will be given the appropriate referrals. Patients who are interested in the UW-CTRI study will be given a brief description of this study and invited to complete a brief screening for the study (See uploaded Recruitment Call Script) to determine study eligibility.

Please note that being medically eligible to use study medication is not required for study entry. Participants will be screened for medication eligibility if they elect to enter treatment, but participants who are medically ineligible to use study medications will still receive smoking cessation counseling as part of study treatment.

For the one-time qualitative interviews, eligibility criteria are minimal. Participants will be adults with a history of cancer. Past tobacco use is not a criterion for interview eligibility.

Actively declining study participation by notifying the study team that patients would like to be removed from the list of potentially eligible patients will be exclusionary in EHR data extraction. As such, deidentified EHR data will not be gathered from patients who stated they did not want to be included in the study.

5.2 **Inclusion criteria.** The following criteria will be used to identify patients eligible for initial outreach based on data recorded in Health Link.

- Alive.
- Age 18 years or older.
- Diagnosed with cancer in the past 3 years.

- Received care from a participating oncology clinic in the past year.
- Has a current tobacco use status.
- Does not have a preferred language other than English (missing language preference will be included).
- Valid address that is not a correctional facility or residential treatment/care facility.
- No flag for patient cognitive impairment, activated health care power of attorney, or other health care agent (e.g., legally authorized representative) in the EHR.

The following additional inclusion criteria must be met for inclusion in the CET

- Smoked combustible cigarettes in the past month.
- Able to speak and understand English.
- Willing to set a date to quit smoking in the next 60 days.
- Willing to receive smoking treatment information.
- Willing to complete study activities.

For qualitative interviews, the only inclusion criteria are:

- At least 18 years of age.
- Have a history of cancer.
- Willing to participate in an audio-recorded interview about their experiences and perspectives.

5.3 **Exclusion criteria.** The following exclusion criteria apply to the CET:

- Current suicidal ideation.
- Suicide attempt in the past year.
- Currently receiving treatment for bipolar disorder, schizophrenia, schizoaffective disorder, or psychotic disorder.
- Incarceration.
- Unable to provide informed consent to treatment (i.e., cannot answer questions about study procedures or risks after hearing about the study).

Those who decline the screening invitation or do not meet eligibility criteria will be advised to quit smoking and offered standard smoking cessation treatment (referral to their primary care provider

and/or to the Wisconsin Tobacco Quit Line or other tobacco quit line, as appropriate given state of residence).

The only exclusion criterion for qualitative interviews is not being able to provide informed consent due to difficulty understanding the consent information.

5.4 **Target populations.** We will not target specific subpopulations in the proposed study, but hope instead to enroll a broad and representative sample by reaching out to all adult patients who smoke and meet the prerequisites listed above. The proactive outreach approach to be adapted in this project has increased the reach and equity of smoking cessation treatment in primary care and inpatient contexts (Creswell et al., 2022; McCarthy et al., 2022). In this approach, proactive outreach regarding smoking treatment options is the default for all adults whose EHR records suggest they currently smoke, unless they opt out of such outreach. Such proactive outreach processes have especially strong reach in historically underserved populations (e.g., African-American, Hispanic, and/or Medicaid-eligible patients; Creswell et al., 2022; McCarthy et al., 2022) and we anticipate this will hold in population of patients with cancer that will be the focus of this project.

6.0 Special Populations

6.1 **Special population inclusion, justification, and safeguards.**

☐ Children/Minors (HRP-416 - CHECKLIST - Children)
☒ Pregnant persons / fetuses (HRP-412 - CHECKLIST - Pregnant Persons; HRP-413 - CHECKLIST - Non-Viable Neonates; HRP-414 - CHECKLIST - Neonates of Uncertain Viability)
☐ Prisoners (HRP-415 - CHECKLIST - Prisoners)
☐ Participants with impaired decision-making capacity (HRP-417 - CHECKLIST - Adults with Impaired Decision-Making Capacity)

Although pregnant persons will be eligible for CET inclusion and smoking cessation counseling, they will not be eligible for any study medication while pregnant or breastfeeding. Quitting smoking has important health benefits for both pregnant persons and their fetuses, so we will not withhold smoking cessation counseling for pregnant persons. We will not dispense study medications during pregnancy or breastfeeding, however, to prevent any adverse effects of medication on fetuses.

We will not target special populations for qualitative interviews. Adult patients with a history of cancer will be referred to the study team if interested in participating in an interview by their cancer care team, without targeting to special populations.

6.2 **Vulnerable population inclusion, justification, and safeguards.**

☒ Individuals who are receiving inpatient or outpatient services for mental illness, developmental disability, or alcohol and other drug abuse (AODA)
☐ Individuals who are protectively placed by a court in a treatment facility
☒ Veterans/Military Personnel
☐ Emancipated minors
☒ Anyone especially vulnerable to manipulation or inducements for participation as a result of their illness or socioeconomic condition

We will not target any vulnerable populations in the proposed recruitment strategy, but we anticipate that our broad approach in which proactive outreach regarding smoking treatment is the default will reach members of some special populations, as these populations have especially high smoking rates (e.g., veterans, socioeconomically disadvantaged people, and people with mental health and substance use smoke at higher rates than the general population). We will not assess all special population status (i.e., we will not ask if participants are veterans or ask about current mental health or substance use treatment).

Special and vulnerable populations are disproportionately affected by tobacco use and its devastating effects. As such, we will not exclude them from participation in the study if they meet all other eligibility criteria. We seek to evaluate interventions that will promote abstinence from smoking from the full range of adult smokers receiving oncology care.

Study coordinators will reach out to the PCP (if at UW Health) and UW Health oncologist of patients who consented to the CET to ask them to review the randomly assigned medication regiment, and to disapprove the medication within 5 business days if they have any concerns about study medications for their patients. Study medications will be sent to participants who have provided informed consent for CET participation only after providers have had this opportunity to review and disapprove study medications. Patients whose providers disapprove varenicline, but not patch, will receive nicotine patches (for 2 weeks in the recommended usual care control condition or for 12 weeks in the intensive treatment condition). Patients whose providers disapprove nicotine patches will receive psychosocial treatments, but no study medications.

We will not reach out to patients flagged in quarterly CRDS reports as having cognitive impairment, an active power of attorney for health care, or other active health care agent.

Vulnerable populations will not be targeted for qualitative interviews.

6.3 **Consent considerations in particular populations.** We anticipate recruiting at least some participants from the groups checked below:

☐ Non-English speaking participants

☐ Illiterate or Low Literacy participants

☒ Participants with visual or hearing impairments

☐ Status Relationship: Individuals with a status relationship with the PI or other study team members (e.g., employees, students, family members)

To avoid enrolling people incapable of consent we will not reach out to patients flagged in quarterly CRDS reports as having cognitive impairment, an active power of attorney for health care, or other active health care agent. Second, an audio version of the letter sent to patients will be available via QR code for patients who would prefer to hear the information about proactive outreach rather than read it. This accommodation is offered to address concerns about low literacy among some patients. In addition, in the CET, we will only include people who speak and understand English so we can obtain informed consent and administer study treatments and surveys orally over the phone. We will use oral means of communication as our primary modality in CET consent, treatment, and assessment procedures. This will be supplemented by a written study information sheet and medication instructions, but all information will be presented orally to eliminate literacy-related barriers to participant understanding. These accommodations will also reduce barriers to understanding or participation among patients with visual impairments. Patients with hearing impairments who have TTY technology will still be able to communicate by phone with study coordinators and smoking cessation counselors, as well.

7.0 Recruitment Methods

7.1 **Source(s) of participants.**

Prospective participants in the tobacco treatment outreach and CET will be patients identified via health records at UW Health. We will adapt the process that we have used in primary care (IRB protocols 2019-0054, 2019-0939, 2022-0973) that similarly identifies UW Health patients eligible to receive smoking treatment outreach based on health records. As in those studies, patients identified in CRDS reports will receive study recruitment letters and tobacco treatment outreach offering both standard treatment and research participation opportunities unless they opt out of such outreach. This study will focus on adult patients receiving oncology care rather than primary care, however. Fliers will also be placed in participating clinics or cancer care team members may share the flier with patients.

Participants in qualitative interviews will be referred by cancer care team members to the research team, if interested in sharing their perspectives and experiences related to cancer. Participants in the CET will be offered the chance to participate in the qualitative interviews following their 12- and 26-week follow up contacts.

7.2 **Identification of potential participants.** Potential participants in tobacco treatment outreach and the CET will be identified based on private/protected records (medical records) at UW Health. Records will be accessed by requesting CRDS reports regarding eligible patients on a quarterly basis. These reports will be transferred from UW Health to UW CTRI securely via ICTR REDCap to a secure UW-CTRI REDCap database that will guide study coordinator outreach to patients, and track all patients who opt out of future outreach. Patients may also proactively call the UW-CTRI study team to learn more about their treatment options if they see or receive a recruitment flier in their cancer care clinic.

Participants in qualitative interviews will be identified by cancer care providers who will refer interested patients to the study team. The study team will offer all participants who are enrolled in the CET the opportunity to complete the qualitative interview substudy following their 12- and 26-week follow up contacts.

7.3 **Recruitment process.** Potential tobacco treatment outreach and CET participants will first receive a mailed letter. This letter will inform patients that they have been identified based on their health records for tobacco treatment outreach from UW-CTRI, and will tell them how to opt out of such outreach by calling study coordinators at UW-CTRI. Letters will be sent no more frequently than once per quarter.

Patients who do not opt out of outreach in response to letters will receive up to 5 phone calls per quarter from UW-CTRI study coordinators who will offer tobacco treatment options including both standard care and the CET as available options. Patients can opt out of future outreach at all such phone calls, as well.

Recruitment fliers will also be placed in participating cancer care clinics and/or cancer care providers may give these study invitation fliers to patients interested in participating. These patients may call the study team to learn more about their tobacco treatment options.

Recruitment for qualitative interviews will be conducted by cancer care providers who will have study invitation fliers to give to patients interested in participating. Cancer care providers may also send Health Link InBasket messages to study lead McCarthy to indicate that the patient is interested and has agreed to receive a call about participating in interviews. In addition, people who are not

interested in or eligible for the CET will be asked if they would be interested in participating in the one-time qualitative interview. Participants in the CET will be offered the chance to participate in the qualitative interviews following their 12- and 26-week follow up contacts.

7.4 **Recruitment materials.** The tobacco treatment outreach and CET recruitment letter and an audio version of the recruitment letter is uploaded with the application. These letters will be sent no more frequently than once per quarter during the recruitment period (anticipated to last 2.5 years). The clinic recruitment flier is uploaded with the application.

The script for outreach calls from UW-CTRI study coordinators is also uploaded with the application. Although study coordinators may make up to 5 attempts to reach participants over 12 weeks, this script will be completed only once per quarter with participants. Participants may be eligible for a new round of call attempts in future quarters if they appear on a subsequent quarterly CRDS report (and have not already opted out of such calls).

The patient flier and template for Health Link InBasket messages to be used in recruitment for qualitative interviews are uploaded with the application. The script that will be used during interview recruitment calls for referred patients and those who decline or do not meet criteria for the CET is also uploaded with the application.

7.5 **Compensation.** Participants who enroll in the CET will receive pharmacotherapy at no cost (if medically eligible) and will be compensated for completing study assessments according to the following schedule: Baseline phone survey ($50), 8-week phone follow-up ($50), 26-week phone follow-up ($50), biochemical verification of abstinence ($75 via visit to UW-CTRI for carbon monoxide breath test or urinary cotinine test, or mailed saliva sample kit for cotinine testing). As such, the maximum compensation available to participants will be $225.

Participants in qualitative interviews will be paid $40 for completing the interview.

8.0 Consent/Assent Process

8.1 **Informed consent process.**

Those who assent to and pass the phone screening for CET participation will be asked to complete an oral consent and HIPAA authorization process in accordance with UW-Madison HRP-090-SOP. This will be completed by phone at the screening call, or at a subsequent call, if necessary. During the phone consent process, a

UW-CTRI study coordinator will follow the phone screen and consent script uploaded with the application. These study coordinators will not be involved in patients' ongoing care at UW Health (i.e., this is consent for research and occurs outside of clinical care at UW Health). The consent process will be facilitated by a REDCap database that will conduct automatic validation checks regarding eligibility and will both prompt and document completion of the informed consent process. Participants will have the opportunity to ask questions and to request more information before, during, or after the informed consent process, and they can take time to consider their decision after hearing about the study. They can also elect to receive a written copy of the study information sheet that contains the information covered in the oral consent script before making a decision about participation. Even if they decide to consent without receiving this information in writing, it will be sent to them after the consent is completed by phone. As such, all participants will receive a written study information sheet covering all required elements of informed consent after hearing this information over the phone.

After presenting oral informed consent information, study coordinators will ask a comprehension question to ensure participants understand key components and risks of the study (see uploaded Screening and Consent Script). If participants are still unable to answer these questions correctly after the study coordinator reviews key aspects of the study with them over the phone, the participant will be considered unable to consent. In addition, study coordinators will be trained to monitor for participant understanding during phone contacts and to stop the informed consent process if they have concerns about the participant's mental status or level of comprehension.

If we learn of new risks or alternative treatments that participants need to know (as determined by the study team, DSMC, and/or IRB), we will re-consent participants at the next scheduled study contact, or as needed. We do not anticipate that such changes will occur, however.

Participants in the one-time qualitative interviews will also complete an oral consent process before completing the interviews.

We are proposing an alteration of informed consent to omit certain required elements of consent so we can use an oral consent process for the comparative effectiveness trial and for the qualitative interviews, and a waiver of informed consent for the initial outreach

activities so we can reach out to patients identified based on medical record review without their prior affirmative consent for such contact. We request these alternatives due to the following considerations (as outlined in CHECKLISTS HRP-410 and 411):

8.2 Alteration of consent justification.

We are requesting an alteration of consent to abbreviate certain elements of informed consent. The oral consent script includes most required elements of consent but does not include all the recommended template language to streamline and shorten the oral consent script. These abbreviated elements are included in the written information sheet that all participants in the CET will receive. Omitting these elements from the oral script allows us to focus the script on information most important to deciding whether to participate in the study activities.

- Participation in qualitative interviews or the CET poses **no more than minimal risk** to subjects. Study procedures involve answering phone survey questions; completing smoking cessation treatments that are known to be safe and effective in adult patients who smoke combustible cigarettes; and possibly providing a breath, urine, or saliva sample for biochemical verification of smoking status at the end of the study. The study medications to be administered to participants are FDA approved for smoking cessation and are recommended as first-line medications to help patients quit smoking (Fiore et al., 2008), including patients with cancer (NCCN, 2022). In addition, risks of adverse effects from these medications will be reduced by screening participants for medication eligibility and giving their primary care providers (if at UW Health) and oncologists at UW-CCC the opportunity to review and disapprove study medications for participants before study medication is dispensed. These strategies will ensure that the proposed study procedures pose minimal risk to participants, particularly compared to the known risks of continued smoking.
- Altering informed consent for study participation **will not adversely affect the rights and welfare of subjects** because subjects will be informed of the risks, benefits, and alternatives prior to providing oral consent to join the CET or participate in interviews. Participants will receive this information over the phone and will have the option to request a written study information sheet about the CET prior to consent, or to view this CET information online, if they would like additional time to review this material before making a consent decision.

- The clinical investigation **could not practicably be carried out without this alteration** of consent because including all required elements of informed consent in the oral consent script in greater detail would increase participant burden and may bias the sample toward those with the greatest motivation to join a smoking treatment study and/or the greatest tolerance for receiving lengthy and detailed information over the phone. Because the proposed research seeks to identify strategies that cancer treatment programs can use to equitably increase the rates at which their patients who smoke use evidence-based smoking treatment and achieve lasting abstinence from tobacco, it is vital that we not impose barriers to participation that would restrict representativeness of the sample in these ways.
- **Subjects will be provided with additional pertinent information before, during, or after participation**. All those who provide oral consent for the CET will be mailed a detailed study information sheet containing all required elements of consent and HIPAA authorization.

8.3 Waiver of informed consent

We are requesting a waiver of informed consent for the proactive outreach calls and outreach mailings that will occur up to once per quarter for patients identified as eligible based on record review. We are requesting a full waiver of informed consent for the creation of a de-identified data set from health records and cancer registry data to examine cancer care outcomes, estimate cancer care costs, and capture information on environmental exposure, among the patients initially identified as eligible for outreach who did not actively decline study participation. The justification for this waiver of informed consent for this FDA-regulated study is as follows (using criteria outlined in CHECKLIST HRP-410):

- The proposed outreach involves **no more than minimal risk** to subjects as the primary study activities include receiving written and oral information about readily available standard treatments for quitting smoking, in addition to information about the comparative effectiveness trial. The risk is minimal due to the informational nature of the outreach and the fact that only standard care and FDA-approved over-the-counter medications and publicly sponsored psychosocial treatments for smoking (e.g., through the Wisconsin Tobacco Quit Line and Smokfree.gov) will be promoted in the study.

- Waiving informed consent for proactive outreach **will not adversely affect the rights and welfare of subjects** because subjects will be informed in writing of their right to opt out of proactive outreach at study initiation; any and all requests to opt out of proactive outreach mailings and letters will be honored; subjects may choose to decline or dispose of letters or decline to take calls, without any penalty, punishment, or alteration in their treatment in their host health system.
- The clinical investigation **could not practicably be carried out without this waiver** of consent because only including patients who proactively volunteer or agree to receive information about their smoking treatment options would bias the sample toward patients with the greatest interest in smoking treatment. Results of such a study would not address the critical gaps in the research literature on ways to better engage patients with cancer who smoke in EBST, and would not provide clear guidance to health systems about how best to reach or treat the cancer patients who are not initially or intrinsically interested in smoking treatment.
- **Subjects will be provided with additional pertinent information during or after outreach**. In the initial launch letter, patients will be provided basic information about the study (e.g., who is leading the study, why the patient was included, why the study is being done and what it entails), and what smoking treatments are available through either standard care or the comparative effectiveness trial. In addition, the launch letter will direct patients to research staff who can provide additional information, answer any questions patients may have, address any concerns raised by patients (in consultation with the study team and/or DSMC or IRB, as needed), and can honor any patient requests to cease smoking treatment outreach activities. Oral versions of the same information will be available to all letter recipients, either via the web or via phone call to a research team member.
- A full waiver of consent is necessary for the **creation of a de-identified data** set from health records and cancer registry data to examine cancer care outcomes, estimate cancer care costs, and capture information on environmental exposure among identified patients who did not actively decline study participation. The medical record is the best source of the PHI and critical data source to examine study outcomes. If consent was required for this retrospective data analysis it could significantly bias the results and reduce value of the research as a goal is to examine how tobacco treatment relates to clinical outcomes captured in the medical record. For example, the

sociodemographic and cancer diagnosis elements are needed to assess the representativeness of the recruited clinical trial sample and equity in the reach of smoking treatment among eligible patients (relative to all patients who were initially identified as potentially eligible per EHR eligibility criteria). For this reason, it is critical to the representativeness and generalizability of these study aims that de-identified health record data is included from all patients who were initially eligible for proactive outreach (excluding those who actively declined to participate in further outreach or the comparative effectiveness clinical trial).

We also seek a waiver of HIPAA authorization for the medical record review and proactive (mailed and telephone) outreach for recruitment and conduct of the CET, and an alteration of HIPAA authorization for the CET (as signatures will not be required and not all elements of HIPAA authorization will be covered during the oral consent process). We seek a waiver of HIPAA authorization for the creation of a de-identified data set from health records and cancer registry data to examine cancer care outcomes, estimate cancer care costs, and capture information on environmental exposure, among the patients initially identified as eligible for outreach (excluding those who actively declined study participation). All required HIPAA authorization information will be included in mailed information sheets that will be sent to participants who consent to the CET, and this will be available online or in writing by request prior to consent, as well. The justification for this request is as follows (using CHECKLIST HRP-441 as a guide):

- The PHI needed for **recruitment and for study conduct** is described in the protocol and is **limited to information needed** to mail outreach letters and to make outreach calls to adult patients who smoke and meet eligibility requirements for both standard treatment options and study recruitment. Data collected about patients prior to consent will include: MRN, name, DOB, date visited a participating clinic, care team members who treat the patient (at the most recent clinic and for primary care), address, phone numbers, preferred language, preferred communication modality, tobacco use status, insurance, and demographics).
- The use or disclosure of PHI involves **no more than minimal risk** to privacy because there are thorough plans in place to: protect identifiers from improper use and disclosure (e.g., secure data transfer and storage practices; tight access controls, with access limited to study coordinators and those who maintain the databases or oversee their outreach;

logging of record access); destroy identifiers at the earliest opportunity after achievement of the study aims; prevent reuse or disclosure of PHI (except as required by law or authorized oversight bodies).

- The **research is not practicable without a waiver and alteration** of HIPAA authorization due to the sampling bias and reduced generalizability that would result.
- The research **could not practicably be conducted without access to PHI** because outreach letters must be mailed to eligible patients, and study coordinators must have access to phone numbers to call patients to offer them smoking treatment (both standard treatment and the CET) to assess the reach and equity in reach of such proactive outreach in cancer care at UW Health.
- A full waiver of HIPAA authorization is necessary for the **creation of a de-identified data** set from health records and cancer registry data to examine cancer care outcomes, estimate cancer care costs, and capture information on environmental exposure. The medical record is the best source of the PHI and critical data source to examine study outcomes. If consent was required for this retrospective data analysis it could significantly bias the results and reduce value of the research as a goal is to examine how tobacco treatment relates to clinical outcomes captured in the medical record. For example, the sociodemographic and cancer diagnosis elements are needed to assess the representativeness of the recruited clinical trial sample and equity in the reach of smoking treatment among eligible patients (relative to all patients who were initially identified as potentially eligible per EHR eligibility criteria). For this reason, it is critical to the representativeness and generalizability of these study aims that de-identified health record data is included from all patients who were initially eligible for proactive outreach (excluding those who declined to participate in further outreach or the comparative effectiveness clinical trial).

Non-English Speaking Participants

We do not plan to enroll participants who do not speak or understand English. We will reach out only to patients who have not designated a language other than English as their preferred language in the EHR, and we will only enroll participants who speak and understand English in the CET.

Participants who are not yet adults (infants, children, teenagers)

Individuals under the age of 18 will not be included in tobacco treatment outreach efforts and will not be eligible for the CET or qualitative interviews. Being an adult is a criterion for inclusion on the CRDS reports that will guide tobacco treatment outreach and study recruitment efforts, and for participation in qualitative interviews.

Adults with Impaired Decision-Making Capacity

Process to determine whether an individual is capable of consent. We will first filter out patients with evidence of impaired decision-making capacity in their EHR by excluding patients with an EHR flag for cognitive impairment, an active power of attorney for health care, or another active health agent (e.g., legally authorized representative). Patients meeting these exclusion criteria will not be on the CRDS reports that will guide tobacco treatment outreach calls and CET recruitment efforts.

Next, study coordinators will be trained to monitor for comprehension problems during the consent process and will not accept consent from participants who are unable to correctly answer questions about the study after hearing the consent script.

Process for individuals with impaired decision-making capacity who are capable of consent. We will not enroll participants who we know to have impaired decision-making capacity.

Adults Unable to Consent

We will not attempt to secure consent from designated representatives of participants with impaired decision-making capacity due to the level of engagement and decision-making that would be required of participants during the treatment selection (pre-CET) and smoking cessation counseling processes (in the CET), or in qualitative interviews.

9.0 Process to Document Consent in Writing

9.1 **Waiver of written documentation of consent.** Consent for participation in the opt-out tobacco treatment outreach component of the study will not be documented in writing, as this will occur on an opt-out basis (patients who are sent notices of such outreach who do

not opt out will be enrolled in proactive outreach without documented consent).

For the CET, study participation will not be documented in writing by the participant, but the study coordinator will document that oral informed consent was obtained using a time-stamped field in the CET REDCap database. This consent will be obtained using an IRB-approved script and will be followed with a mailed version of the IRB-approved study information sheet (which will also be available online before and during the consent process).

For the qualitative interviews, interviewers will obtain oral consent prior to beginning the interview, as guided by the oral consent script, and will document this in a securely stored interview tracking sheet.

Documentation of informed consent via other means (wet signature or e-consent) would be impracticable due to the bias that would result in the study samples if in-person contact or access to e-consent computing resources were required to opt into tobacco outreach or to consent to smoking cessation treatment in the CET or to participation in qualitative interviews. The consent scripts and written study information sheet are uploaded with the application.

The proposed research will use an oral consent process, as it presents no more than minimal risk of harm to participants and involves no procedures for which written documentation of consent is normally required outside of the research context, as health systems routinely accept oral consent for smoking cessation treatment initiation. Although we will not collect participant signatures to demonstrate consent, we will document consent obtained orally or online using scripts uploaded with the application.

10.0 Setting

10.1 **Research sites.**

All research procedures will be performed at UW-CTRI, including telephone qualitative interviews, telephone outreach regarding tobacco treatment and CET recruitment, screening, enrollment, treatment, and follow-up activities. Participants will be recruited from oncology clinics of the UW Carbone Cancer Center (UW-CCC) that treat diverse populations of patients with cancer. The UW-CCC treats more than 30,000 people annually for diagnosis, therapy, follow-up care or consultations.

11.0 Study Intervention

11.1 **Description.**

The outreach strategy that is being evaluated in terms of reach and reach equity comprises mailings (no more than quarterly) and proactive telephone calls offering smoking treatment information and access.

The smoking cessation treatment strategies being evaluated in terms of comparative effectiveness, efficiency, and equity are 2 treatment packages that vary in terms of intensity, cancer-specificity, costs, and burden on patients. These interventions are described below.

- Standard treatment
    - 3 counseling calls (each 10-15 minutes in length) on the following schedule (an outline of the counseling protocol is uploaded with the application):
        - Pre-quit call (1 week before the target quit date they selected at enrollment)
        - Post-quit call 1 (target quit date or next day)
        - Post-quit call 2 (1 week after the target quit date).
    - Nicotine patch starter kit (1 14-count box of transdermal nicotine patches) for use starting on the target quit date, at the following dosing schedule (medication instructions to be mailed to participants are uploaded with the application):
        - For those who smoke 10 or more cigarettes per day at enrollment, 21-mg patches.
        - For those who smoke 5-9 cigarettes per day, 14-mg patches.
        - For those who smoke 1-4 cigarettes per day, 7-mg patches.
        - Those who smoke less frequently than daily will not be eligible for patches.
        - Those whose clinicians disapprove of nicotine patch therapy for their patients will not receive patches.
    - Mailed information about smoking cessation treatments available from the Wisconsin Tobacco Quit Line (or state quit line in patient's state of residence) and SmokefreeTXT, two publicly funded, remotely delivered treatment services available to the general public.
- Enhanced treatment
    - 7 counseling calls (each 10-15 minutes in length) on the following schedule (an outline of the intensive counseling protocol is uploaded with the application):
        - Pre-quit call (1 week before the target quit date they selected at enrollment).
        - Post-quit call 1 (target quit date or next day).
        - Post-quit call 2 (1 week after the target quit date).

        - Post-quit call 3 (2 weeks after the target quit date).
        - Post-quit call 4 (4 weeks after the target quit date).
        - Post-quit call 5 (8 weeks after the target quit date).
        - Post-quit call 6 (12 weeks after the target quit date).
    - Varenicline starting 7 days before the target quit date (0.5 mg once per day for 3 days, 0.5 mg twice per day for 4 days, 1 mg twice per day for 11 weeks), as per the package insert (medication instructions for patients are uploaded with the application). Those who smoke less frequently than daily will not be eligible for varenicline.
        - If patients in high-intensity treatment are ineligible for varenicline (due to contraindications reported at initial medication screening or clinician disapproval of varenicline for the patient), patients will instead be offered 12 weeks of nicotine patch therapy for use starting on the target quit date, at the following dosing schedule:
            - For those who smoke 10 or more cigarettes per day at enrollment, 21-mg patches (week 1-8), 14-mg patches (week 9-10), 7-mg patches (week 11-12).
            - For those who smoke 5-9 cigarettes per day, 14-mg patches (week 1-10), 7-mg patches (week 11-12).
            - For those who smoke 1-4 cigarettes per day, 7-mg patches.
            - Those who smoke less frequently than daily will not be eligible for patches.
            - Those whose clinicians disapprove of nicotine patch therapy for their patients will not receive patches.
    - Mailed information about smoking cessation treatments available from the Wisconsin Tobacco Quit Line (or state quit line in patient's state of residence) and SmokefreeTXT, two publicly funded, remotely delivered treatment services available to the general public. These information sheets are uploaded with the application.

11.2 **Drug/Device Handling.**

- Study medications (nicotine patches, varenicline) will be received at the Center for Tobacco Research and Intervention by the Study Coordinator or designees in the Madison office.
- Nicotine patches will arrive in commercially packaged boxes of 14 patches each (two weeks of 21mg, 14mg, or 7 mg patches).

- Varenicline will arrive in commercially packaged 28-day starter packs that clearly designate when and how to start the medication run-in period (beginning 1 week before the target quit day), or 28-day continuation packs (standard commercial packaging sizes).
- Study medications will be stored in designated locked drug cabinets in Madison until processed for dispensing.
- Dissemination mailings containing processed study medication will be labeled with Study ID and subject initials and stored in secure, locked cabinets, closets, or rooms in Madison.
- Medication will be mailed to participants. Due to the need to match nicotine patch dose to smoking heaviness at enrollment and potential changes in medication based on clinician disapproval of varenicline, medication mailings will be assembled to order rather than preassembled.
- Medications returned by mail will NOT be recirculated.

11.3 IND status.

No investigational drugs will be used. Both varenicline and transdermal nicotine patches are currently FDA approved for use to treat smoking and are broadly available. Both medications will be used as directed in the package inserts. This use of varenicline and nicotine patches in this study is considered IND exempt under category 1 (21 CFR 312.2(b)(1)).

12.0 Study Timelines

12.1 CET Timeline.

1. **The duration of an individual participant's participation in the study.** Participants will be in the outreach component of the study in which they may receive mailings and calls regarding tobacco treatment options up to once per quarter for up to 30 months if they continue to meet inclusion criteria for the reports that guide such outreach**.**

   Participants who consent to the CET will be in the study for up to 8 months (up to 2 months before a target quit date and to 6 months post-quit-date.

   Participants in qualitative interviews will participate in one hour-long interview (with the option to break this interview up over multiple calls if they prefer not to do it all at one call). The total duration of the interview will be about one hour.

2. **The duration anticipated to enroll all study participants.** We anticipate completing recruitment in 30 months.

3. **The estimated date for the researchers to complete this study (complete primary analyses).** We will need 1 year after completion of recruitment to complete the study (8 months to complete follow-up data collection and 4 months to complete primary analyses), and thus anticipate completing this study by mid 2027).

13.0 Procedures Involved

13.1 Study Procedures.

Tobacco treatment outreach. Patients who meet criteria for inclusion on quarterly CRDS reports will first receive a mailed letter informing them that tobacco treatments are available and that quitting smoking has important benefits during cancer care. Patients will also be informed in the letter that they will receive phone outreach from UW-CTRI regarding their tobacco treatment options over the next 12 weeks unless they prefer to opt out of such outreach by calling UW-CTRI to ask that they not receive future tobacco treatment outreach. UW-CTRI study coordinators will make up to 5 attempts to reach patients who do not opt of such calls over 12 weeks. The outreach letter and phone outreach script are uploaded with the application.

Tobacco treatment facilitation. When they reach patients on the phone, UW-CTRI study coordinators will talk with patients about the benefits and challenges of quitting smoking during cancer care and will describe available treatment options (enrolling in Wisconsin Tobacco Quit Line (or other applicable quit line) services; working with their primary or oncology care team; enrolling in the CET) and ask which, if any, treatments the patient would prefer. Patients who decline any treatment will be offered the number of the WTQL/national quit line number. A script for these treatment offers is uploaded with the application.

CET screening. Patients who express interest in the CET will be given information about screening and enrollment procedures and then asked if they assent to eligibility screening. Those who do will complete a brief eligibility screen during the same phone call. Those who do not meet eligibility criteria to continue will be offered quit line services and reminded that their care teams may be able to help them quit smoking, as well. Ineligible participants will also be asked if they would like to participate in a sub-study that involves one phone interview. Those who pass the screening will move on to the oral informed consent process.

Interviews. Up to 32 people, including those who are not eligible or do not enroll in the CET, will be offered an additional $40 to complete a one-hour telephone interview to gather information that will help improve the way tobacco treatment is offered to people who have had cancer. Participants will first complete an oral consent procedure (uploaded with

the application). The interview will address the participants' cancer experiences, tobacco use history, smoking and supportive care outreach, and smoking treatment. The interview outline is uploaded with the application. These interviews will be recorded and transcribed without participant identifying information.

Oral consent. In the oral consent process, UW-CTRI study coordinators will read the oral informed consent script to participants and will then ask if they have any questions. The study coordinator will answer questions during the call, or will schedule a follow-up call if the patient needs more time to make a decision about the study or if the study coordinator needs to consult with the PI or other team member to address the patient's concerns or questions. Once the patient's questions have been fully addressed, the patient will be asked questions to assess their comprehension of key CET study features. People who are unable to answer these questions correctly, even after review of key points by the study coordinator, will be considered unable to consent and will be referred to their care team and given information about WTQL services. Those who pass the comprehension screening will be asked if they consent to participate in the CET study.

Baseline assessment. Next, participants will complete a baseline assessment (see uploaded survey) of their tobacco use history, nicotine dependence, quitting motivation, quitting confidence, stress, mood, wellbeing, quality of life, support system, symptom burden, and demographics. Participants will also select a target date to quit smoking within the next 60 days at this call. These activities will occur during the enrollment phone call if participants are willing and able to stay on the call. If they are not, the UW-CTRI study coordinator will schedule this assessment call within the following 1-2 weeks.

Randomization. Participants will next be randomized to treatment. Participants will be considered fully enrolled once consented, baseline assessment is complete, and randomized. Study coordinators and participants will be informed of the randomly assigned condition after the baseline assessment is completed.

Treatment procedures. These are described in section 13.1 above.

Follow-up assessments. UW-CTRI follow-up assessors will call CET participants 12 and 26 weeks after their target quit dates to collect outcome data (see uploaded follow-up surveys) including: tobacco use; quitting motivation and confidence; stress, mood, wellbeing, quality of life, support, and symptom burden; and treatment utilization, satisfaction, and adverse events. In addition to these self-report measures, counseling utilization and medication refill data will be used to track smoking treatment adherence; EHR data on healthcare utilization and diagnoses will be extracted (with patient consent provided at enrollment); and biochemical verification of abstinence claims at the 6-months post-quit follow-up

will be obtained via carbon monoxide breath samples and urinary cotinine samples, or mailed saliva samples (as participants are able to provide them).

13.2 **CET procedure schedule.**

Study Phase	Enroll-ment	Treatment/Intervention Calls							Follow Up Calls		FU Visit
Study Contact	1	2	3	4	5	6	7	8	9	10	11
Week relative to target quit day (tqd, day 0)	-8 to -3	-1	0 tqd	1	2	4	8	12	12	26	26-29
Eligibility screening	✓										
Oral informed consent & HIPAA Authorization	✓										
Clinician(s) given 5 business days to disapprove study medication; medications dispensed if not disapproved	✓										
Tobacco, alcohol, and cannabis history	✓										
Nicotine dependence	✓										
Motivation to quit	✓	✓	✓	✓					✓	✓	
Quitting confidence	✓	✓	✓	✓					✓	✓	
Stress, mood, and withdrawal		✓	✓	✓					✓	✓	
Wellbeing and quality of life	✓								✓	✓	
Social support	✓								✓	✓	
Demographics	✓										
Randomization	✓										
Welcome mailing packet with study information sheet sent	✓										
Standard care (SC) counseling (10-15 minutes)		SC	SC	SC							
Standard care nicotine patch treatment (2 weeks)			SC	SC							
Enhanced care (EC), cancer-specific counseling		EC	EC	EC	EC	EC	EC	EC			
Enhanced care varenicline treatment (12 weeks		EC	EC	EC	EC	EC	EC	EC			

beginning with run-in period 1 week pre-quit followed by 11 weeks at full dose post-quit, as per package insert)											
Recent tobacco, alcohol, and cannabis use									✓	✓	✓
Treatment use									✓	✓	✓
Treatment satisfaction									✓	✓	
Adverse Event Assessment (all participants will be assessed through 26 weeks post-target-quit date; those in enhanced care will have additional assessments at counseling contacts specific to that arm)		✓	✓	✓	EC	EC	EC	EC	✓	✓	✓
Biochemical verification via CO and urine cotinine (or mailed saliva cotinine)											✓

✓ = applies to both treatment arms
SC = applies only to standard care arm
EC = applies only to enhanced care arm

13.3 **Research procedures:**

1. Safety monitoring and risk prevention.

To reduce risks to CET participants, we will first screen them for eligibility prior to enrollment, will ask their clinicians to review and disapprove study medications that raise safety concerns for them, and then we will monitor for adverse events at all study contacts following the initiation of smoking cessation treatments in the trial. The schedule for these activities is presented above. Please note that follow-up contacts will occur for all study participants 12 and 26 weeks after their target quit date (i.e., after the end of pharmacotherapy in both conditions, which will end 2 weeks after a target quit date in the control condition and 11 weeks after the target quit date in the enhanced care condition for varenicline). The final counseling contact in the enhanced care condition will also occur at the 12-week post-quit time point.

For qualitative interviews, interviewers will monitor for distress or confusion during the interview and will stop the interview and address the distress or confusion, as needed.

2. **Biospecimens.**

The only biospecimens to be collected in the study will be collected directly from CET participants at the follow-up visit 6 months after a participant's target quit date, if the participant reported no use of tobacco products at the 26-week post-quit-date follow-up call. These participants reporting abstinence from tobacco will be asked to provide a breath sample for CO testing and a single urine sample for cotinine testing at either the UW-CTRI Madison office or at their oncology clinic (if willing to schedule this so it coincides with a clinic visit). Breath samples cannot be stored and urine samples will be tested immediately after collection and then discarded the same day. If patients are unable to travel to Madison for biochemical verification of abstinence, they will be given the option of providing a saliva sample in the mail using a kit supplied by the research team. These kits would be retained only until testing by a lab is complete and would then be destroyed.

3. **Drugs.**

The medications to be used in this study include transdermal nicotine patches and varenicline. Both medications are approved by the FDA for use as smoking cessation aids. No other medications or devices will be used in the research.

13.4 Data Collection.

- **List of data elements.**

The following data elements will be extracted from EHR data via CRDS reports. These data elements are needed to enable preparation of initial study recruitment mailings that will let patients know they have been identified for the study and that they can opt out of recruitment calls and letters.

- MRN
- Name
- Phone numbers (with preferred number flagged)
- Address
- City
- State
- ZIP code
- Communication preferences (MyChart, mail, phone)
- Tobacco use status (must be smoking currently)

  - Preferred language (must be English or missing)
  - Use of smokeless tobacco
  - Use of e-cigarettes
  - Date of birth (must be at least 18 years old)
  - Sex
  - Gender
  - Race
  - Ethnicity
  - Insurance type
  - Assigned primary care provider
  - Oncologist
  - Clinic department (where seen in the past year to achieve eligibility)
  - Cancer diagnosis (diagnosis in past 3 years that conferred eligibility)

- Additional de-identified data elements will be extracted from the EHR data and Cancer Registry for patients who were initially identified as potentially eligible for the study per EHR eligibility criteria, but excluding those who actively declined study participation. The sociodemographic and cancer diagnosis elements are needed to assess the representativeness of the recruited sample and equity in the reach of smoking treatment among eligible patients. The data regarding healthcare utilization, cancer care outcomes, and environmental exposures are needed to assess care outcomes and estimate cancer care costs (overall and between Standard and Enhanced care conditions) from participants in the CET. Specific data fields are listed in supplemental documents. These data will be extracted with identifiers only for participants who enrolled in the CET and provided informed consent for EHR data use.
- In addition, self-reported data regarding the constructs shown in the study schedule above will be collected directly from participants over the phone or at the final follow-up visit. Participant responses will be documented in REDCap.
- Completion of study counseling sessions and medication refill requests and dispensing will also be tracked in REDCap to assess treatment utilization and adherence.
- Fidelity to counseling protocols will be assessed by reviewing a subset of audio-recorded counseling sessions and coding for fidelity using a checklist.
- Qualitative interviews will be transcribed and thoroughly deidentified prior to review of transcripts for interviewer feedback and for thematic analysis.

- **Questionnaires.**
  Questionnaires to be administered as structured interviews to collect participant self-report data following the schedule shown above are uploaded with the application.

- **Source records:**
  - ☑ UW Health medical or billing records via ICTR's Clinical Research Data Service (CRDS)
  - ☑ UW Health HealthLink Records (study team will directly access) Study team members will access HealthLink directly to communicate with providers about patient medication eligibility and to document study medication dispensing in patient records for care teams).
  - ☐ Data from departmental QA or QI database
  - ☐ Data from UW Health Enterprise Data Warehouse (EDW)
  - ☐ Data from PACS (Picture Archiving and Communication System); *specify whether study will use the clinical or research instance in the Radiology Department's warehouse*: _____
  - ☐ Data from Center for Medicare/Medicaid Services
  - ☐ Data from publicly available datasets (e.g., U.S. census data)
  - ☐ Data from outside institutions or organizations (specify: _____)
  - ☐ Other (specify: _____)

13.5 Long-term follow-up.

There are no plans for long-term follow-up.

13.6 Regulatory status of study drugs.

Both varenicline and transdermal nicotine patches are currently FDA approved for use to treat smoking and are broadly available. This use of varenicline and nicotine patches in this study is considered IND exempt under category 1 (21 CFH 312.2(b)(1)).

14.0 Comparison of usual care and study procedures

14.1 Alternatives to participation.

The current standard of care for treating tobacco use at UW Health is to electronically refer patients to the Wisconsin Tobacco Quit Line if patients consent to such referral. Clinicians are also able to prescribe smoking cessation pharmacotherapies, including nicotine patches, varenicline, other

forms of nicotine replacement therapy, and/or bupropion and to provide smoking cessation counseling to patients.

The proposed study will proactively offer patients both these standard forms of care available at UW Health and will present the option to screen for and possibly enroll in the proposed CET. These alternatives will be presented on an even footing to prospective participants, with all options presented before asking patients to choose among them.

Proactive outreach will occur because evidence suggests that existing standard care options (Quit Line referral, UW Health clinician intervention) are delivered rarely to patients. The proactive model of treatment offers seeks to address this issue that limits the reach of evidence-based smoking treatment by making outreach regarding tobacco treatment options the default, unless the patient opts out of such contacts.

The CET recruitment and consent process will highlight differences between standard care and the treatments offered in the CET, and will clearly identify procedures that are just for research (e.g., assessments, biochemical verification). The CET has also been designed so that participants in both arms will receive treatment that meets the current standard of care available through the Wisconsin Tobacco QuitLine. In addition, participants in both CET arms will receive information about available QuitLine and NCI-sponsored text messaging program (SmokefreeTXT) resources available to them. As such, no patients will be assigned to a condition that offers less than standard care to address their smoking, and participating in the study will not inhibit participants' ability to take advantage of publicly funded smoking cessation treatment resources.

The alternative to participating in the qualitative interview is simply not to participate, and this will not affect the care the patients receive or any other aspect of their relationships with UW Health, UW CCC, or UW more broadly.

14.2 **Standard of care.**

The current standard of care for treating tobacco use at UW Health is to electronically refer patients to the Wisconsin Tobacco Quit Line if patients consent to such referral. Clinicians are also able to prescribe smoking cessation pharmacotherapies, including nicotine patches, varenicline, other forms of nicotine replacement therapy, and/or bupropion and to provide smoking cessation counseling to patients. Quitline reports and past projects suggest that this standard of care is not being applied consistently, and that relatively few patients are receiving such care.

14.3 **Research procedure overlap with standard practice.**

As noted above, the current standard of care for addressing tobacco use at UW Health is to refer patients to the Wisconsin Tobacco Quit Line, and there is an order set clinicians can use to place orders for pharmacotherapies to help patients stop smoking. These tools are rarely used, however. All patients contacted by UW-CTRI will hear about these standard care options, and will still have these options, and more (e.g., SmokefreeTXT, no-cost pharmacotherapies) available to them if they enroll in the CET. To ensure that study treatments do not interfere with standard care, UW Health primary care providers and oncologists of patient care teams will be able to review and disapprove study medications, and UW Health prescribers will be able to see which study medications were dispensed to patients in Health Link. No other research procedures (e.g., assessments, counseling calls) overlap with standard care activities, and none should interfere with standard care.

14.4 Research participation effects on standard clinical care.

Participation in this research will not affect standard clinical care. Patients will remain eligible for standard smoking cessation treatment, and standard cancer treatment, without delay or disruption.

15.0 Withdrawal of Participants

15.1 Withdrawal from the research without participant consent.

Participants will be withdrawn from the study without their consent if they are found to have diminished capacity to consent to ongoing participation, or if, in the judgment of the lead investigators, continued participation would not be in the best interest of the participant (i.e., if participation is causing distress or dysregulation in the participant). Participants may also be withdrawn from the study without consent if they are no longer willing or able to fulfill their responsibilities as study participants.

15.2 Orderly termination.

For patients in the medical records review portion of the study, termination will simply entail excluding records from withdrawn participants in CRDS reports and/or outreach efforts. For patients who consent to the CET, termination will be accomplished by cessation of all proactive outbound communications to the participant and by not fulfilling medication or treatment requests that are deemed not in the patient's best interests (e.g., if a patient has developed a contraindication to a study medication). For participants who consent to qualitative interviews, termination will mean ending

the interview early and may also involve referrals to supportive care resources, as needed.

15.3 Withdrawal procedures.

Participants who withdraw from the medical records portion of the study and opt out of tobacco treatment outreach will have this change of status noted in both the REDCap project that guides outreach activities and CET recruitment, and in OnCore (to prevent inclusion in future CRDS reports). Participants who withdraw from the CET will have this status change noted in the REDCap project that study team members use to guide communication, treatment, and assessment activities in the CET.

Previously collected data from people who consent to the CET and later request to withdraw will be retained in study datasets, in keeping with HRP-314 criteria for approval for FDA-regulated research. Removal will not be possible once deidentification has occurred; it will not be possible to identify and delete records for specific participants.

Participants who are incarcerated during the study or who request temporary suspensions of outreach, treatment, or communication will be given a temporary suspension status until they are able to resume participation because their incarceration or inability to participate has ended (e.g., they have been released or transitioned to parole or probation).

Patients withdrawn from the due to safety risk related to their health or wellbeing will be notified by the research team and advised if any safety procedures are recommended. This will be documented in study records, and adverse and serious adverse event reporting guidelines will be followed.

People who choose to withdraw during the qualitative interview will have the option to request that none of the information they shared will be used in the study. In that case, the interview recording will be destroyed and no transcript will be created.

16.0 Data Management and Confidentiality

16.1 Quality control.

Both an internal quality improvement team and an external Data Safety and Monitoring Committee will help to monitor and ensure data quality. The project will follow a thorough Data and Safety Monitoring Plan (DSMP). Under this DSMP, the Lead Researcher will develop and implement protocols for assuring UW-CTRI data collection accuracy and protocol compliance, with the support of the UW-CTRI staff including the Director of Information Technology (IT) and the Regulatory and Compliance Coordinator, among others

(e.g., our database and implementation teams and study coordinators). Study protocols will include data verification and protocol compliance checks. The Lead Researcher will also be responsible for ensuring that the data for the project are securely transferred from UW Health and securely stored at UW-CTRI, in compliance with University and federal regulations, and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. HIPAA regulations and guidelines are currently implemented at UW-CTRI, and all study staff must complete approved human subjects and HIPAA training programs. In addition, the Department of Medicine employs extensive data backup and server redundancy procedures and performs full backups weekly of all servers, along with incremental and daily backups to prevent loss of data.

16.2 **Data security.**

As specified in the DSMP, the Lead Researcher will be responsible for ensuring that the data for the project are securely transferred from UW Health and securely stored at UW-CTRI, in compliance with University and federal regulations, and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. HIPAA regulations and guidelines are currently implemented at UW-CTRI, and all study staff must complete approved human subjects and HIPAA training programs. Inter-site data transfers are accomplished via secure UW REDCap or file transfer protocols (SFTP) using an internet server maintained by the UW School of Medicine and Public Health (UWSMPH) Department of Medicine. To protect the privacy of database records and the integrity of the network, this server is firewall-protected and is stored in a locked server room with a numeric keypad to restrict entry. The server is continuously scanned for viruses. A complete virus scan of all workstations also takes place once a week. Server system log files are scanned for unusual activity, which is immediately investigated. Network and server administration staff members apply critical and non-critical patches as needed. In addition, UW-CTRI and UWSMPH Department of Medicine also have multiple mechanisms for preserving confidentiality of research participants and providing data security in the transfer of data from participant machines to the SFTP server. The Department of Medicine web servers use Secure Socket Layer (SSL or https) technology to encrypt data exchanged between the client and the server. In addition, all online and offline components of data systems will be accessible only through a login and password unique to each user. The security access levels for these login accounts are tiered and the features and privileges given to each staff member will be determined by the PI and UW-CTRI Director of Information Technology (IT). To further protect confidentiality, only the UW-CTRI Director of IT will be permitted to transmit data to the SFTP server. Additional measures include*:*

- ☑ Data will be coded, and the "key" linking identities to codes will be kept separately from the data.
- ☐ Data will be coded, and the "key" linking identities to codes will be kept on paper only. The study data will be stored electronically and labeled only with codes.
- ☐ Only those listed as key personnel will have access to the "key."
- ☑ Access to the "key" will be limited to the following people (e.g., Database Administrator): Database Administrators, Saliva Sample Collection Coordinator.
- ☑ This study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.
- ☐ This study is NOT funded by the National Institutes of Health but because it will collect sensitive information, the research team will apply for a Certificate of Confidentiality to protect data from being requested without the subject's consent as part of a legal proceeding.
- ☐ Other: _____

A unique study ID will be used to store all data on individual participants and information linking that study ID to participant identifying information will be accessible only to Database Administrators. Data being used for analysis will be identified with the study ID only. Participant contact information will only be available to study staff having direct contact with participants, and only when needed to complete such contacts, as per protocol.

For qualitative interview data, a random ID will be assigned to each transcript, and all transcripts will be thoroughly deidentified.

If a saliva sample is needed from a participant, a separate unique identifying code will be used to label the saliva collection kit. Only the person coordinating saliva sample data collection will have the key to that code.

Participant study data will be collected by UW-CTRI research personnel through REDCap and will be stored on secure, password protected servers. Data will be accessible only to assigned study staff for their study function; computer workstations will be password-protected, and thus secured from unauthorized use. Healthcare systems will transmit identifying information to UW-CTRI via secure, HIPAA compliant means. A Certificate of Confidentiality will be issued for the study.

16.3 **Data storage:**

- ☑ Online Collaborative Research Environment (OnCore) Biospecimen Management
- ☑ Research Electronic Data Capture (REDCap) *Specify which instance you will be using (e.g., ICTR's, Department of Medicine's)*: UW-CTRI Instance_____
- ☐ Other software option that will be stored on departmental server. *Specify the department*: _UW-CTRI_____
- ☐ Locked filing cabinet or drawer inside a locked room. Specify the building: _____
- ☑ Other (describe): _Saliva samples returned via mail by participants will be stored in a locked cabinet in a locked office until ready to be shipped to a lab for testing. Samples will be identified by a code number only.
- ☐ Data will not be stored or accessed on portable devices.
- ☑ Portable devices such as laptops will be used to access secure web-based data collection sites such as REDCap. No data will be stored locally on the devices.
- ☐ Data stored on portable devices will be coded with the key stored separately. No identifiers will be stored on portable devices.
- ☐ Data stored on portable devices and therefore only encrypted devices will be used.

16.4 Management of Identifiers:

- ☐ Identifiers will be destroyed after all data has been collected.
- ☑ Identifiers will be destroyed at study closure.
- ☐ Identifiers will be destroyed at study closure or at the time of publication.

16.5 **Data and specimen handling:**

1. **Data associated with specimens.**
   A subset of participants in the CET who report no smoking in the past 7 days 26 weeks after their target date to quit smoking and who are unable to come to Madison to provide a breath and urine sample for biochemical verification of abstinence will be sent saliva collection kits identified by a unique code number specific to saliva tests kits. These kits will include instructions for home collection of saliva using the passive drool method, collection materials, and a stamped, addressed return envelope to return samples to the study team. Only the team member

coordinating saliva sample collection will have the key to this code, and they will be responsible for entering results from the saliva testing in the REDCap database. This unique key will be destroyed on study closure. No other biospecimens (breath or urine samples) will be banked. These samples will instead be tested immediately and recorded in the REDCap database.

2. **Where and how data or specimens will be stored.**
   Saliva samples will be stored in a locked cabinet in a locked office until ready to ship to the lab that conducts the testing and returns results identified only by the unique sample identifier to the saliva collection coordinator for the study.
3. **How long will the data or specimens will be stored.**
   Saliva samples will be stored until ready to ship to the testing lab (within 3 weeks of sample collection). The samples will be destroyed by the testing lab after testing is complete and a study team member has received testing results via a secure portal maintained by the lab.
4. **Who will have access to the data or specimens.**
   The Lead Researcher will designate a Research Manager to serve as the Saliva Sample Collection Coordinator for this project. This person will be the only one to have access to the samples, and will be responsible for transcribing the results into the REDCap project. The Lead Researcher will serve as backup to this Coordinator if he/she is unable to fulfill these duties.
5. **Who is responsible for receipt and transmission of the data or specimens.**
   The Lead Researcher and the Research Manager designated to serve as the Saliva Sample Collection Coordinator will be responsible for receipt and transmission of data or specimens, and transcription of results in REDCap.
6. **How data or specimens will be transported.**
   The saliva sample collection kit is designed to collect and store samples at room temperature for up to 23 days. As such, regular mail or shipping methods (e.g., USPS, UPS, FedEx) will be used to transport specimens.

16.6 **Sharing of data or specimens.**

1. **What data and/or specimens will be shared.**
   No specimens will be shared with those outside the research team and testing laboratory. Self-report data, treatment utilization data, and biochemically confirmed abstinence data will be shared with other researchers in a fully deidentified manner via the BioLINCC repository (rather than directly to other researchers), under approved and fully executed data use

agreements (the BioLINCC RMDA), in accordance with the policy on resource sharing at NIH, the funder of this research.

2. **Identifiers.**
   Data shared will be stripped of all identifiers and assigned a random ID code rather than remaining linked to participant identifiers in any way.
3. **Transmission.** Data transfers will occur via secure means (e.g., SFTP, secure BOX) in accordance with University policy.
4. **The study will NOT share large-scale genomic data.**
5. **Repository.**
   The study will use the BioLINCC repository.
6. **Limitations on the sharing of data.**
   Data will be shared with controlled access in BioLINCC for general research use, as allowed by the participant's informed consent and Institutional Certification.. We will submit a future change of protocol to request Institutional Certification when we have draft materials (e.g., data dictonaries, explanation of coded variables) ready for submission to the BioLINCC repository.

17.0 Provisions to Protect the Privacy Interests of Participants

17.1 **Steps to protect participants' privacy interests.** If any of the following apply, check the box for convenience:

- ☑ Procedures will be performed in a private area where others cannot see the procedures being performed or overhear the conversation between subjects and researchers.
- ☑ All members of the study team are up to date on their institutional HIPAA training.
- ☑ The study is not collecting information that could pose legal or reputational risks to participants.

Almost all study activities (apart from biochemical verification visits) will occur by phone. To protect participant privacy, study coordinators will encourage participants to move to private spaces during recruitment and study calls, and will offer to reschedule calls if participants are unable to do so. Biochemical verification tests will happen in private spaces, as well (CO tests will be conducted in private rooms and urine samples will be self-collected by participants in private restrooms, without staff observation).

17.2 **Sensitive information.**

The only sensitive information to be collected in the study is self-reported use of cannabis. This information is needed to assess concurrent use of cannabis that may influence smoking cessation success and to interpret carbon monoxide and cotinine tests that

could be influenced by use of combustible cannabis (in the case of CO) and use of cannabis in tobacco leaf wrappers (in the case of CO and cotinine).

17.3 **Steps to make the participants feel at ease.**

Collection of sensitive information about subjects will be limited to the amount necessary to achieve the aims of the research and to interpret biochemically verified abstinence data correctly. Participants will be informed that they have the right to decline to answer any question they prefer not to answer, without penalty or punishment, and that the study has a Certificate of Confidentiality.

17.4 **Authorized access to UW Health records.**

UW Health records will be accessed to identify patients eligible for tobacco treatment outreach by the UW-CTRI team only with authorization from UW Health. UW Health EHR and Cancer Registry data of identified potentially eligible patients who did not actively decline study participation will be extracted and de-identified to examine the representativeness of the patients who enrolled in the CET. A list of the specific data elements is available in a protocol supplement document.

In the CET, participants will provide informed consent for UW-CTRI study coordinators to coordinate care with their care teams in Health Link (i.e., to give providers an opportunity to review and disapprove study medications prior to their dispensing, and to update patient medication lists to reflect study medications dispensed). This will be covered during the informed consent process. UW Health records of CET participants will be accessed and EHR data and Cancer Registry data will be extracted to examine preliminary treatment utilization, complications, clinical outcomes, and cost-effectiveness. A list of the specific data elements is available in a protocol supplement document.

18.0 Sharing of Results

18.1 **Result sharing with participants or others.**

The only results that will be shared with participants will be CO test results, as these results are available immediately upon testing. Study coordinators collecting CO samples will congratulate patients whose CO tests indicate abstinence from combustible products, and will explore sources of exposure to CO (e.g., passive smoke exposure, car exhaust, improperly vented or malfunctioning equipment) among those whose expired breath contains more than 5 parts per million CO. Urine cotinine and salivary cotinine testing results will not be

available immediately (urine testing takes at least 15 minutes, saliva samples need to be shipped for testing). These results will not be captured in participants' health records, as they capture abstinence at a particular time (in the past 1-2 days for CO, and in the past 1-2 weeks for cotinine), and should not be used to influence ongoing healthcare.

18.2 **Plans to share study results with the public.**

Aggregate results from this research will be shared with the scientific community and our research collaborators. The findings from this research will also be shared upon request with study participants.

19.0 Data and Specimen Banking

19.1 **Data and/or specimens banking for future use.** No study specimens will be banked for future uses outside of the currently described protocol. Study data and records will be de-identified and archived per record retention policy. Fully deidentified/anonymized data will be stored for 7 years in case replication, follow-up, or sensitivity analyses are necessary.

19.2 **Data to be stored.** Data to be stored for additional analyses consistent with the original study purpose described to participants will be fully deidentified and anonymized and will include EHR-derived data on smoking status, demographics (in broad categories), and REDCap data on smoking cessation treatment utilization, experiences, and abstinence. Data from qualitative interviews will be anonymized transcripts and thematic codes and sample quotes.

19.3 **Procedures to release data.** Data will only be shared under the auspices of an approved and executed Data Use Agreement, in accordance with university regulations.

19.4 **Participant withdrawal of banked data/specimens from future research use.** CET participants will not be able to withdraw data from the repository, as it will be fully anonymized and it will no longer be possible to withdraw data from a particular individual due to the lack of identifiers in the data.

20.0 Study Analysis

20.1 **Statistical Hypotheses.**

The primary hypothesis to be tested for Aim 1 is that at least 12% of eligible adult patients who have cancer and smoke cigarettes and are referred to the tobacco treatment outreach team will initiate an

evidence-based form of smoking treatment (either Wisconsin Tobacco Quit Line care or treatment offered in the CET).

The primary hypothesis to be tested for Aim 2 is that more-intensive, cancer-specific smoking cessation treatment will increase the log odds of achieving 7-day abstinence 6 months after a target quit date by at least 50% over the comparator condition (predicted odds ratio >=1.50 in this superiority comparison).

Secondary hypotheses include the following:

For Aim 3, we hypothesize that the majority (>=50%) of patients assigned to each condition will initiate treatment and will receive at least some counseling and use at least some of the provided medication. We expect retention, adherence, and satisfaction with treatment to be higher in the enhanced treatment relative to standard care. We anticipate that the more intensive, enhanced treatment, although more costly, will be cost-effective in terms of the incremental cost effectiveness ratio per additional patient who quits smoking, relative to the comparator condition and to other preventive health interventions. For these superiority hypotheses, the null hypotheses are that the two treatments are equally acceptable and efficient.

For Aim 4, we expect to elicit information that will help us better communicate with and support patients eligible for tobacco treatment outreach and CET counseling by learning more about the experiences and perspectives of people who have had cancer.

For Aim 5, we expect treatment reach to be especially high among historically undertreated populations (including African-American, Medicaid-eligible patients, and those from disadvantaged neighborhoods), and for the effects of enhanced treatment (vs. standard care) to be similar across patient subgroups. Thus, we are anticipating superior reach in historically underserved patient groups, and equivalent effectiveness across patient groups.

20.2 **Sample Size Justification.**

In this pilot study, we seek to demonstrate the feasibility and acceptability of the proactive outreach model as a way to enhance the reach of smoking treatment, and as a feasible way to recruit participants for a CET of enhanced vs. standard smoking cessation treatment. We also hope to generate estimates of enhanced vs. standard treatment effects on biochemically verified 7-day point-prevalence abstinence rates 6 months after a target quit date (primary outcome) and other abstinence measures (e.g., self-reported prolonged and point-prevalence abstinence 3 and 6 months post-quit). As such, we selected a sample size of 50 to generate stable estimates of the size of treatment effects on these outcomes and costs,

and to permit exploration of differences in treatment effects by sex, race, ethnicity, and disadvantage. A sample of 50, while too small to sensitively test for moderate treatment benefits, is sufficient to pilot test all study and treatment procedures and to yield informative effect estimates that will guide a future, full-scale CET of standard and enhanced care.

The primary outcome will be analyzed in an intent-to-treat analysis in which all randomized participants are included, and missing cases are assumed to be non-abstinent. This will be supplemented by sensitivity analyses that again use the full sample of randomized participants to examine robustness of results across different assumptions regarding missingness. Multiple imputation will not be used in this pilot project.

For the qualitative study, we will recruit as many participants as we can until we reach thematic saturation in qualitative data coding. We anticipate that this will occur with fewer than 32 participants.

20.3 **Participant Population(s) for Analysis.**

We will examine reach of the treatment by computing the proportion of all participants meeting inclusion criteria for proactive tobacco outreach who were referred to WTQL, referred to their PCP, and the proportion who were screened for, eligible for, and enrolled/randomized in the CET. As such, the pool of participants for Aim 1 includes everyone eligible for inclusion on at least 1 CRDS report that guides proactive tobacco treatment outreach. The pool of participants included in Aims 2, 3 and 5 will comprise all participants who were randomized to treatment in the CET. The pool for Aim 4 will include all participants who participated in a qualitative interview.

20.4 **Statistical Methods.**

Descriptive statistics will be used to characterize smoking treatment reach (the proportion of eligible patients who initiate any smoking cessation treatment, and the proportion who enroll in the CET. These rates will be computed overall, and by patient subpopulation.

Logistic regression will be used to estimate the effects of treatment condition on binary outcome data (e.g., abstinence, side effects), overall and by patient subgroups (i.e., moderation effects). Odds ratios and numbers needed to treat will be computed to estimate treatment effect sizes.

Analyses of variance will be used to examine condition effects on continuous variables such as ratings of treatment satisfaction, burden, and treatment effects on ratings of patient experiences and candidate treatment mediators (e.g., withdrawal). Treatment effect sizes will be computed. Cost-effectiveness will be calculated based on the incremental cost-effectiveness

ratio of enhanced treatment versus standard treatment per each additional case of abstinence.

Thematic analysis of qualitative interview will identify themes that emerge in patient interviews in the following areas: cancer experiences, supportive care outreach, tobacco history, and tobacco treatment.

20.5 **Planned Interim Analysis.**
No formal inferential interim analyses are planned for this pilot study, but safety data will be examined on an on-going basis to determine if individual participants are at risk or if any treatment element or condition is exerting an iatrogenic effect. If any meaningful evidence of this is detected the DSMC will be consulted along with the IRB to consider study discontinuation or changes. If any danger is deemed likely and significant the study will be immediately suspended.

20.6 **Handling of Missing Data.** The intent-to-treat principle will be applied to primary analyses. Patients who do not initiate smoking treatment via a UW-CTRI study coordinator will be assumed to not have initiated treatment. In analyses of abstinence, cases who do not report abstinence and provide biochemical evidence of abstinence will be coded as still smoking in primary analyses. This will be supplemented by sensitivity analyses to estimate treatment effects under different assumptions regarding missing data (e.g., if 10%, 20% or 30% of people without verified abstinence are abstinent).

21.0 Potential Benefits to Participants

21.1 **Potential benefits.**
Every participant who uses tobacco in the study will be given information about ways to access evidence-based treatment to help them stop smoking and will be given access to that treatment at no direct personal cost (apart from possible telephone charges for telephone-delivered care such as cessation counseling). UW-CTRI study coordinators will proactively offer smoking treatment options to patients, including tobacco quitline services (the Wisconsin Tobacco Quit Line for Wisconsin residents), referral back to their healthcare teams, or either standard or enhanced treatment in the CET (as randomly assigned). Given the known efficacy of brief smoking counseling and medication (offered by both tobacco quitlines and the CET) and the known benefits for quitting smoking for patients with cancer (NCI, 2022), offering to connect patients with cancer who smoke to evidence-based smoking treatment can benefit them. Patients who enter the CET will be offered, at minimum, 2 weeks of nicotine replacement therapy, 3 proactive individual counseling calls, information regarding the Wisconsin Tobacco Quit Line (which also offers individual counseling, 2 weeks of free pharmacotherapy, and digital and remote group support) and

the NCI-sponsored SmokefreeTXT program. This exceeds the current standard of care at UW Health (referral to the Wisconsin Tobacco Quit Line). Some participants will be randomly assigned to receive 7 individual sessions and 12 weeks of varenicline. As such, all patients will have access to both pharmacotherapy (if medically appropriate for them) and counseling, whether they enter the CET or elect standard treatment.

For patients who participate in the qualitative interviews and who do not use tobacco, there will be no benefits of participation.

22.0 Risks to Participants

22.1 **Risks.**

This project poses minimal risk to participants, as it provides only FDA-approved, evidence-based smoking cessation treatment to patients who continue to smoke after cancer diagnosis, and involves minimal risk assessments procedures (providing self-report data and possibly a breath, urine, or saliva sample for biochemical verification of abstinence).

The chief risks to participants include:

- Side effects from medications
    - Nicotine patches can cause skin irritation at the site of application, vivid dreams, and insomnia. Severe allergic reactions are also possible.
    - Common sides effects of varenicline include nausea and sleep disturbances. Some people taking varenicline may experience negative moods. Varenicline may also be associated with a small increase in the risk of heart problems in people with heart and blood vessel disease. Rare allergic reactions or skin reactions may occur.
- Psychological discomfort or nicotine withdrawal symptoms. This may occur if participants reduce or quit smoking, and could include negative moods, cigarette cravings, difficulty concentrating, hunger, and problems sleeping. Psychological distress may also be triggered by talking about cancer and cancer care experiences during qualitative interviews.
- Loss of privacy or breach of confidentiality. Although we will not collect sensitive information about participants (apart from cannabis, alcohol, and tobacco use), there is still a risk that participant information may become known to someone

not involved in the study, and that this could have negative social or economic consequences for participants.

22.2 **Risks associated with participants delaying, being withdrawn from, or being asked to forgo standard treatment to participate in the study.**

All patients will have access to evidence-based smoking cessation treatment at no cost (through their primary care provider, oncology care team, a state quit line that offers evidence-based cessation treatment at no cost to callers), or to no-cost treatment through the CET. Receiving treatment is not contingent on consenting to this study. To ensure that smoking treatment does not interfere with ongoing cancer care, oncology clinicians will have the opportunity to review and disapprove medications for patients in the CET. It is also important to note that all participants will have the ability to decline or withdraw from the study and any study activities at any time without jeopardizing access to standard treatment.

22.3 **Currently unforeseeable risks.** The minimal risk study procedures are unlikely to pose unforeseeable risks to participants.

22.4 **Risks to an embryo or fetus.** Medications will not be dispensed to people who are pregnant. Smoke cessation counseling poses no risks to embryos or fetuses, whereas continued smoking poses known risks to fetuses.

22.5 **Risks to others who are not participants.** Study procedures pose no risks to people in participants' lives.

22.6 **Strategies to minimize risks of harm or discomfort.** Study procedures are designed to protect patient choice and safety, and to ensure that people with impaired decision making will not receive proactive outreach or enrolled in the CET. Participants reached in proactive outreach attempts will be presented standard care options alongside the CET study invitation to protect patient autonomy and choice. Only those who understand and speak English will be eligible for the CET, to ensure they can ask questions and understand study information before and during study enrollment. To protect participant safety, screenings for the CET will exclude people with serious mental illness, recent suicidal behavior, and current suicidal ideation to reduce the risk of psychological distress among participants. Study medications will be dispensed only to people who pass inclusion/exclusion criteria screening and whose clinicians do not deny approval for the medications. Study procedures to monitor adverse events and safety and to protect participant privacy and confidentiality are described elsewhere in this protocol.

23.0 Provisions to Monitor the Data to Ensure the Safety of Participants

23.1 **Describe:**

1. Data review.

The Lead Researcher (McCarthy) will be responsible for routinely monitoring study progress and participant safety, and will report on this to the independent Data and Safetry Monitoring Committee (DSMC) at least twice per year. The existing UW-CTRI DSMC is chaired by Dr. James Cleary, Director of Supportive Oncology, Department of Medicine, Indiana University, and Simon Cancer Center, Indiana University School of Medicine. Dr. Cleary is an experienced physician and clinical trial researcher with no involvement in any of the proposed research activities. Dr. Cleary is joined on the DSMC by Dr. James Sosman and Dr. Burke Richmond. Dr. Sosman is an Associate Professor of Medicine and the Medical Director of the HIV/AIDS Comprehensive Care Program at UW Hospital and Clinics who previously collaborated on a clinical trial of smoking cessation with UW-CTRI, but has no role in the proposed research. Dr. Richmond is an otolaryngologist who served on independent DSMCs for Phase II and III trials involving a nicotine vaccine who also has no direct involvement in the proposed research. UW-CTRI has an adverse event monitoring protocol and team in place and will alert the study Lead Researcher to adverse events among study participants who receive smoking cessation treatment in the CET. Any data safety concerns will be reported to the Lead Researcher immediately and addressed. The Lead Researcher will meet with the study team no less often than monthly to discuss study procedure safety. We will report any unanticipated problems to the IRB promptly.

Study investigators will notify NIH and the University of Wisconsin IRB in a timely manner (consistent with IRB and NIH policies) of the occurrence of any SAE or any AE which is severe, unexpected, and possibly related to study medication or protocol. Any adverse, study-related events that emerge during the study will be assessed fully and reported. If an SAE might be related to study drug use, both the Food and Drug Administration (FDA) and the manufacturer will be notified within 5 days of investigators becoming aware of the event. Examples of SAEs would be untoward medical or intervention occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create

persistent or significant disability/incapacity, or involve congenital abnormality/birth defects. Unanticipated problems will be monitored and reported to the DSMC. The assessment of adverse events will occur via phone calls at all study contacts that occur after the initiation of treatment (study contacts 2 through 11). Adverse events are events that meet the following criteria: 1) suggest the research places subjects or others at increased risk of harm, 2) are unexpected (in terms of nature, severity or frequency) given the research procedures that are described in the study-related documents, and 3) possibly related to study participation. Any SAE will be queried and reported if it meets the definition of an unanticipated problem. All study-related adverse events will be assessed in a timely manner so that NIH, FDA, and the IRB may be notified, as needed. Adverse event assessment, recording, reporting, and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by the study team. Also, any adverse event that affects the patient's ability to receive cancer therapy will be reported to his or her oncologic care team as soon as possible. The Lead Researcher and PI has ultimate responsibility for ensuring that SAEs are reported in a timely manner. Additionally, the IRB will receive an annual report of all SAEs and AEs meeting the criteria listed above.

2. **Safety data, untoward events, and efficacy data review.** The study team will continuously monitor adverse event data collected using a standardized prompt in contacts 2-11 in the CET, and any adverse event data that come to light at other times (e.g., if a patient or oncologist reports a health event). The study team will review this information no less often than monthly and the DSMC will review these data at least twice per year.
3. **Safety data collection.** Adverse event data will be collected during phone contacts and the final biochemical verification visit.
4. **Frequency of data collection.** In the CET, safety data will be collected from study contact 2 (approximately 1 week prior to a participant's target quit date) through the final study visit (study contact 11, approximately 6 months after the participant's target quit date).
5. **Who will review the data.** Safety data will be reviewed by the Lead Researcher, study physician, and the DSMC.

6. **The frequency of review of cumulative data.** The Lead Researcher and study team will review all adverse event data as they are collected. The study physician will review any adverse events that are unanticipated, severe, and possibly related to study procedures, and all serious adverse events among CET participants, as they occur. The DSMC will review cumulative data no less than twice per year.
7. **Analyzing safety data.** Given the modest sample size in this pilot study, we will focus on effect sizes rather than tests of significance when comparing adverse event rates in the two CET conditions. Any unanticipated or serious adverse events in either condition will be thoroughly assessed and examined.
8. **Conditions that trigger immediate suspension of the research.** The CET will be suspended immediately if data suggest there are unanticipated, severe problems associated with treatment in the CET. The NIH will be notified within 5 days if the PI deems it necessary to suspend the study. In the case of a temporary suspension, the PI will develop a plan for continuation of the study and discuss this plan with NIH in a reasonable time frame.
9. **How the study team will adhere to reportable event reporting requirements.** Any reportable events that are unexpected, immediately life-threatening or severely debilitating, and probably caused by study medication will be reported within 1 business day. If new information about study medication risks that was not previously known to investigators or participants is discovered, investigators will prepare a change of protocol with revised study documents or withdraw affected drugs from the protocol within 14 business days. Likewise, the research team will report to the IRB within 14 business days any of the following: failures to obtain properly informed consent for the CET; dosing errors in medication dispensing; unexpected harms to participants or others that are probably related to the study procedures; noncompliance that could affect participants' rights, welfare, or safety; reportable audit findings; breach of confidentiality; failure to suspend study activities during a participant's known incarceration; and unresolved participant complaints. Breaches of confidentiality of PHI will also be reported to the HIPAA privacy officer.

24.0 Economic Burden to Participants

24.1 **Costs to participants.**

The only costs that participants may incur are cell-phone charges for minutes spent on phone calls for Wisconsin Tobacco Quit Line (WTQL) services, qualitative interviews, or CET counseling or assessment calls. Participants may incur co-pays if they elect to receive smoking cessation support from their healthcare team, rather than WTQL or CET treatment.

25.0 Resources Available

Will the research be conducted outside School of Medicine and Public Health or UW Hospitals and Clinics (e.g. the researcher does not have an SMPH research feasibility attestation for this study)?	☐ YES (complete 25.1) ☑ NO (remove text below, but retain this section)

25.1 **Resources available to conduct the research.**

1. **Recruitment.** There are more than 600 living patients with head and neck cancer and more than 800 patients with prostate cancer who use tobacco receiving care at UW-CCC. Given this, it is feasible to recruit 50 patients with cancer who use tobacco in to the CET, even if only head and neck and prostate cancer clinic patients are recruited. To increase the likelihood of recruiting enough people with a history of cancer to achieve the aims of the qualitative interviews (maximum 32), those without a tobacco use history will also be included.
2. **Timeline.** We anticipate completing recruitment within 2.5 years and all data collection within 3 years.
3. **Facilities.** We have sufficient private office space, secure and HIPAA-compliant computing infrastructure, computer workstations, and telephone equipment needed to conduct the proactive tobacco treatment outreach and the CET counseling sessions proposed. We also have locked medication storage areas and space and equipment needed to prepare participant mailings, including medication mailings, and to conduct quality assurance checks on all such mailings. We also have private exam rooms for collecting CO samples and a specially equipped private bathroom for collecting and cotinine-testing urine samples. We have locked cabinet space to store saliva samples in need of testing.
4. **Medical or psychological resources.** A study physician (Brian Williams, MD) and psychologist (Danielle McCarthy, Ph.D.) will be available to follow-up with participants who experience

adverse events of a medical or psychological nature, respectively.

5. **Process to ensure that all persons assisting with the research are adequately informed throughout the study. A**ll persons assisting in the research will be informed about the protocol during the informed consent process. The oral consent process will be supplemented by written information regarding the CET. Study personnel who obtain informed consent from participants will be trained to mastery of the protocol before consenting any participants. They will be guided through the oral consent process by a thoroughly tested REDCap database that will prompt each step in the consent process, and document completion of each step (with timestamping and change logging). Thorough quality assurance processes will ensure that consent processes are followed as per protocol.

26.0 Multi-Site Research

Not applicable.

27.0 References

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28.0 Appendices

Not applicable.