Study Protocol

Official Title: Health Systems Reach Interventions Project

NCT Number: NCT04199117

Document Date: 10/12/2023

Title: Research Plan and Protocol: Breathe 2 Project 2: Centralized Health System Interventions to Enhance Reach: A Factorial Screening Experiment (HS Reach Interventions)

Principal Investigator: Danielle E. McCarthy (University of Wisconsin School of Medicine and Public Health, Department of Medicine, Center for Tobacco Research and Intervention)

Protocol Version: October 12, 2023

Funding Sponsor: National Cancer Institute, National Institutes of Health, Grant 2P01CA180945

Research Plan and Protocol: Health System Reach Interventions Study

August 2, 2021 Update: Parts of the protocol pertaining to provision of varenicline to participants randomly assigned to have access to intensive treatment will be modified due to recent problems with the supply of varenicline. These problems are related to the recent discovery of a novel nitrosamine, N-nitroso-varenicline, at levels above the recommended FDA acceptable daily intake (ADI) threshold for human drugs. Although this novel nitrosamine is not known to be carcinogenic, it is being treated as a possible carcinogen similar to other complex nitrosamines. This prompted the manufacturer of varenicline (Pfizer) to recall several lots of varenicline in which the novel nitrosamine exceeded their ADI level. As of 7/22/2021, discrepancies between the FDA ADI (37 ng) and the ADI that Pfizer advocates and used as the basis of its voluntary recall (185 ng) have not been resolved. Details regarding this issue are provided in FDA alerts accessible at https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-and-press-announcements-nitrosamine-varenicline-chantix.

This issue prompted the investigators to suspend recruitment for the study beginning on June 25, 2021 and to modify the protocol to ensure we do not dispense varenicline from lots that have not yet been tested to ensure they are at or below the acceptable daily intake (ADI) level for nitrosamines set by the FDA. We are now seeking IRB approval to modify consent scripts and documents, and other scripts and letters pertinent to varenicline treatment, so we can resume study activities. At this time, we seek to resume recruitment, enrollment, intervention, and follow-up activities with modifications as noted below.

We want to alert participants to the possible unavailability of varenicline due to a possible safety concern, as we will not dispense varenicline until we are sure that the medication we have in stock is below the FDA ADI. That is, we will NOT resume dispensing varenicline to participants in this study until we are assured that the medication is within FDA guidelines for nitrosamines. The global pause on distribution of varenicline has caused shortages of the medication, so we may not be able to get new deliveries of varenicline known to be below the FDA ADI for some time (likely months). To convey this to participants, scripts and letters that describe the treatments available to participants eligible for intensive treatment with varenicline (due to randomization and passing screening for intensive medication eligibility) will be amended to note that recent problems with the supply of varenicline due to a possible safety concern have occurred and that varenicline availability cannot be guaranteed.

The one participant in the study who was dispensed varenicline prior to the June 2021 recall of varenicline has already been called and informed about possible exposure to nitrosamines in varenicline, and advised to stop using the medication. This participant will also be offered alternative treatment (combination NRT) because their varenicline treatment was disrupted, as described in CP012.

I. SIGNIFICANCE

Despite a large decline in smoking prevalence, 15% of US adults (~37 million people) continue to smoke[1]. Healthcare settings are excellent places to engage smokers in evidence-based care that can double or triple abstinence rates[2], as most smokers (roughly 70%) visit primary care clinics each year[2]. Epidemiological and healthcare system data show that smoking cessation

interventions are rarely offered in healthcare settings, however[3-16](<40% of patients report the being offered assistance quitting smoking, <15% report being offered follow-up for smoking by their primary care provider[6,17]). Long-term access to treatment and follow-up are critical to the treatment of tobacco use as a chronic, relapsing condition[18,19]. At the population level, only about 5% of smokers who try to quit use Public Health Service Guideline-recommended treatment each year (both counseling and pharmacotherapy[20]). Healthcare systems have unrealized potential to improve treatment reach markedly, given their existing intervention infrastructure.

Healthcare systems are adopting care-management, population-health approaches to manage common chronic conditions (e.g., diabetes, hypertension)[21-23], but still undertreat smoking[24]. Similar infrastructure, expertise, and personnel can be used to treat smoking as a chronic condition, however. Proactive approaches to promoting smoking cessation treatment and treating tobacco use as a chronic condition have shown promise in recent years[18,19]. Repeated proactive outreach to patients who smoke may be one good way to leverage the reach of healthcare systems among smokers to address *the chief limitation on the impact of smoking treatments, their very low rates of use*. Although researchers have explored ways to extend smoking treatment reach in healthcare[25-28], rates of treatment use remain low[29-32]. Thus, there is a pressing need to effectively and efficiently increase smoking treatment reach in healthcare.

Data support care management[25,33-35], periodic telephone outreach[36-38], and warm handoffs that immediately connect those interested in quitting with treatment[39] as ways to enhance the reach of chronic disease management interventions, but we do not yet know which chronic interventions for smoking work best to connect smokers with evidence-based cessation treatment, alone or in combination (and which are to be avoided due to antagonistic interactions). We also do not yet know how can we best promote use of the most effective treatments (vs. less intensive cessation treatment). This project will address these questions and generate new data on healthcare system interventions that effectively and efficiently increase treatment reach among outpatients who smoke.

This project will use a factorial experiment (Table 1) to test the main and interactive effects of 3 centralized, healthcare system-delivered intervention components designed to enhance use of either standard care or more intensive, evidence-based cessation treatments. Standard care comprises referral to a toll-free state tobacco quitline offering a starter kit of nicotine replacement therapy and a single proactive counseling call to all Wisconsin residents who smoke, and/or referral to a primary care provider for brief smoking cessation advice/counseling and medication. More intensive treatment comprises varenicline or combination nicotine replacement therapy (NRT) with three counseling calls. Access to more intensive treatment (among those who meet medical eligibility criteria for varenicline and/or combination NRT use) will be randomly assigned on a

Table 1. Study Design: 2x2x2x2 Factorial Screening Experiment

Participants: Adult daily smokers in primary care not willing to quit within the next 30 days • **Experimental sample:** Target sample size of 300 patients eligible to use C-NRT* and/or varenicline and willing to be randomized to 4th factor below • ~416 patients eligible for neither C-NRT nor varenicline
Intervention Components: **1.** Incentives ($40 for each 1st counseling call in up to 4 rounds of treatment over 2 years, maximum $160) vs. none **2.** Semi-annual automated, tailored mailed and electronic-health-record outreach promoting treatment vs. generic letters **3.** Semi-annual proactive telephone-delivered care management (outreach and motivational intervention) vs. none **4.** Access to intensive care (12 weeks of either C-NRT or varenicline, with 3 counseling calls) vs. standard care (counseling and medication from quitline and/or patient's primary care provider)
Outcome: Any use of smoking cessation treatment in the 1st year of enrollment and over 2 years of enrollment (primary) and abstinence (secondary)
Final Product: Optimized reach interventions to promote smoking cessation treatment utilization that will be evaluated in an RCT

*C-NRT= Combination Nicotine Replacement Therapy (patch + mini-lozenge)

4th experimental factor (see Table 1). The factorial design will allow us to determine how well each intervention (incentives for initiating smoking cessation treatment, automated tailored outreach via letter and electronic message, and proactive telephone-delivered care manager motivational support) works overall (i.e., the main effects), and to identify particularly promising combinations of reach-focused interventions for both standard and more intensive smoking cessation treatment (i.e., interaction effects) in real-world healthcare settings. The intervention components selected for this experiment target patients directly and can be implemented centrally and remotely by chronic care management specialists, with minimal disruption to routine clinical care. In this way, these patient-level interventions have strong potential for adoption and effectiveness in healthcare settings, as supplements to primary care efforts to address tobacco use.

The proposed study was designed with dissemination in mind, and will be implemented in a pragmatic manner, but with appropriate controls to protect human subjects and permit strong inferences regarding the success and impact of the experimental manipulations. Overall, the objective is to conduct pragmatic and dissemination-ready research about effective, efficient, and acceptable ways to enhance the reach of stop-smoking treatments by enhancing access to and promotion of treatments.

II. GOALS/AIMS

This project will use an efficient 2x2x2x2 factorial design (Table 1) to identify reach-focused intervention components that either singly, or in combination, increase patient use of evidence-based smoking cessation treatment over 2 years of availability and, by extending treatment reach, reduce smoking prevalence 2 years after enrollment. All adult patients who smoke daily, but who are ***not willing to enter smoking cessation treatment*** at the time of enrollment (the vast majority of smokers[40]) will be eligible to participate, with no obligation to quit smoking or use treatment. Participants (*N*=240-300) will be recruited in 4-12 primary care clinics in 2 healthcare systems by system staff using an opt-out strategy[41] to maximize inclusion and enhance dissemination and the generalizability of results. (Roughly 60 additional patients who do not meet eligibility criteria for intensive counseling and medication with either combination NRT or varenicline will be included in the study but will not be part of the experimental sample.)

This will be the first factorial experiment in healthcare settings to test interventions designed to extend the reach of varied smoking cessation treatments in primary care patients who are not initially willing to make an aided quit attempt (see Table 1). This rigorous and efficient factorial design will address the following aims:

Primary Aims

1. To **create an optimized reach intervention package** by identifying intervention components that increase cessation treatment reach especially well, at low cost, at 1-year follow-up.
2. To estimate the **main and interactive effects** of the intervention components on cumulative treatment **reach over 2 years** of treatment access.

Secondary Aims

1. To estimate the main and interactive effects of intervention components on **abstinence** at 2-year follow-up.
2. To identify the degree to which intervention component effects on 2-year abstinence are **mediated by increases in cessation treatment reach.**
3. To assess the **cost-effectiveness** of intervention components in promoting reach and abstinence.
4. To identify patient and clinic **moderators** of intervention component effects on reach and abstinence.

III. METHODS

Design Overview. In this factorial experiment (see Table 1), participants (not willing to enter cessation treatment at the time of enrollment) recruited by phone after initial outreach or primary care visits in or telemedicine appointments with participating clinics in UW Health and AdvocateAurora Health will be screened, consented, and randomized over the phone to one of 16 conditions resulting from the crossing of the 4 experimental factors in this 2 (incentives on vs. off) x 2 (tailored vs. generic outreach letters) x 2 (care manager calls on vs. off) x 2 (access to intensive treatment on vs. off) design. Participants who request treatment for smoking cessation over the next 2 years will do so through a Tobacco Care Manager who will coordinate referrals to a tobacco quitline (the Wisconsin Tobacco Quit Line (WTQL) for Wisconsin residents) and/or the patient's primary care provider, as preferred by the patient in the standard care conditions. Tobacco Care Managers will also coordinate scheduling with a UW-CTRI Health Counselor for intensive smoking cessation treatment. Participants will have access to either standard or intensive smoking cessation treatment for 24 months, and will receive outreach promoting smoking cessation twice per year from enrollment to 22 months post-enrollment. Participants will be asked to complete brief (10-20-minute) follow-up telephone interviews 6, 12, 18, and 24 months after enrollment. Those claiming abstinence at the 12- and 24-month post-enrollment phone interviews will be asked to return to their primary care clinic to complete breath, urine, and/or saliva testing to verify abstinence from combustible tobacco. This will entail providing breath samples for carbon monoxide testing and/or a urine or saliva sample for immediate cotinine/anabasine testing (no samples will be stored). Participants may also be asked to collect a saliva sample at home and return it in the mail. If a participant sets a target stop-smoking date as part of a smoking cessation treatment episode (either standard or intensive treatment), the participant will be asked to complete telephone follow-up interviews 3, 12, and 26 weeks post-target-quit-day, as well. Participation in the study will last 24 months (27 months maximum, if the person is not reached immediately for the final 24-month post-enrollment telephone follow-up or visit). In addition, data on health status and healthcare utilization for participants who do vs. do not use stop-smoking treatment and quit smoking will be extracted from the EHR for up to 1 year pre-enrollment, and 4 years post-enrollment to inform economic analyses for Aim 3 and moderation analyses for Aim 4.

A. Recruitment, inclusion and exclusion

Up to 2600 adult participants will be recruited from 4-12 participating primary care clinics over 6-15 months. First, all patients who meet criteria for the smoking registry in the electronic health record (EHR) will be notified that the clinic is offering help in quitting smoking. The notification will be sent by mail and supplemented by secure EHR patient portal (e.g., MyChart) message just prior to the launch of recruitment in each clinic. This message is a way to let patients know that tobacco care management is starting, that treatments (study-related and standard care) for quitting smoking are available, and to give patients a way to opt out of future Tobacco Care Manager phone outreach. All study notifications will provide the name and number of a Tobacco Care Manager to contact if interested in quitting, and the number to call to opt out of future Tobacco Care Manager outreach. Tobacco Care Managers will be healthcare system employees who are also members of the study team who have completed all relevant human subjects research, HIPAA, and good clinical practice trainings and been added to the study team in ARROW.

Second, all patients on the smoking registry or identified as current cigarette smokers at clinician visits (whether face-to-face, video visits, or telemedicine visits) at participating adult primary care clinics (which adds the patient to the smoking registry) will be told by clinic staff that they can expect a call from the care management outreach program within a few business days of their visit. All patients will have the right to opt out of such outreach. Medical Assistants

will be trained to record such patient requests to opt out in the EHR to suppress outreach at least until the next clinic visit or patient-initiated contact with the Tobacco Care Manager. Offering advice to quit smoking and assistance in quitting and follow-up are the current recommended standard of care in outpatient care. The introduction of the Tobacco Care Manager who will provide phone follow-up to all adult patients who smoke is new, however, and is not part of standard clinical practice and is new to this study. Although the Tobacco Care Manager role as the centralized means of offering smoking cessation treatment is new, the process of advising patients to quit, assessing interest in quitting, and offering assistance in quitting is the recommended standard clinical practice at UW Health, AdvocateAurora and elsewhere. In addition, posters about Breathe2 will be posted in clinics to encourage patients to talk to their primary care team about stop-smoking resources, including Breathe 2 studies.

Next, a Tobacco Care Manager, who is a healthcare system employee, will make at least 3 phone call attempts to reach each smoker (who did not opt out) beginning within 3 business days of the visit, at the patient telephone numbers in the EHR. When the Tobacco Care Manager reaches a smoker, s/he will explain that the healthcare system is reaching out to all smokers to offer support and resources to help them protect their health. The Tobacco Care Manager will advise all patients who smoke to quit, will let them know that s/he can offer help in quitting, and will ask if patients are interested in quitting within the next 30 days. If patients answer yes, they will be routed to cessation resources and invited to screen for a smoking cessation study (UWHSIRB Protocol #2019-0054) and will be ineligible for the Health System (HS) Reach Interventions Study described in the present protocol. Patients who are not ready to quit within 30 days will be given a brief description of this study and invited to complete a brief screening for the study (See uploaded Recruitment Call Script) for the following inclusion/exclusion criteria:

Inclusion criteria for study participation:

- Age > 17 years.
- On smoking registry at a participating clinic
- Smoked cigarettes every day in the past 30 days (with or without other forms of tobacco or nicotine).
- Able to participate in informed consent activities (e.g., reports understanding the nature of the study and consent)
- Able to speak and read English.

Exclusion criteria for study participation:

- Opted out of recruitment at the most recent clinic visit, or by patient-initiated contact.
- Willing to quit smoking within the next 30 days at recruitment call (these patients are referred for treatment or invited to be in a cessation study IRB# 2019-0054).
- Activated healthcare power of attorney or cognitive impairment that would preclude informed consent.

Those who agree to and pass the screening for the inclusion/exclusion criteria for study participation will be asked to complete an oral consent and HIPAA authorization process next. Those who decline the screening invitation, do not meet eligibility criteria, or do not provide oral consent for study participation 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).

Those who consent to the study will then be asked to complete a baseline assessment, including screening for initial eligibility for intensive treatment medication regimen, as shown below. Of the up to 2600 participants in this study, we anticipate that up to 1800 (target N=300) will meet additional criteria for randomization to access to intensive treatment with either varenicline or combination nicotine patch and mini-lozenge treatment. To be randomized to intensive vs. standard treatment access, a participant needs to meet medical eligibility criteria

for one of the intensive treatments (varenicline or combination nicotine patch and mini-lozenge), not both. Those who are eligible for both will be able to choose which regimen they want to use to quit smoking (pending approval of that regimen by a primary care provider at the time treatment is requested). Initial inclusion/exclusion criteria for randomization to access to intensive treatment or standard care are:

Inclusion criteria for access to intensive treatment (randomization on 4th factor):

- Smoke at least 5 cigarettes per day on average for at least 6 months at enrollment.
- Ability to meet screening criteria for one or both of the enhanced medication regimens, varenicline and/or combination NRT.

Exclusion criteria for access to intensive treatment (randomization on 4th factor):

- Among women with childbearing potential: pregnancy, breastfeeding, or unwillingness to use an approved method of birth control (these include: abstinence, condoms, diaphragm, birth control pills or injectable contraceptive (e.g., Depo-Provera), IUD, hysterectomy, tubal ligation, sterilization, vasectomy, or being more than 2 years post-menopausal) while receiving study medication. This will be assessed via self-report at the time a participant requests intensive treatment and participants who report this will not be eligible for study-provided varenicline or combination NRT.In addition, Tobacco Care Managers will look for pregnancy indicators in the patient's chart at the time a request is sent to the primary care provider to review patient eligibility for varenicline and/or combination NRT. If a Tobacco Care Manager sees that a patient is currently pregnant, s/he/they will not place the order.
- Contraindications to both varenicline and nicotine patch and mini-lozenge. These contraindications are listed by agent below. To be excluded, a person would have to have a contraindication in both the 2nd and 3rd columns below.

Table 2. Exclusion criteria for access to intensive treatment

Contraindication	*Varenicline*	*Nicotine patch & mini-lozenge*
Severe renal disease	X	
Allergic or severe adverse reaction to varenicline	X	
Allergic or severe adverse reaction to nicotine patch		X
Allergic or severe adverse reaction to nicotine lozenges or mini-lozenges		X
Suicide attempt in past 10 years	X	X
Current treatment for schizophrenia or a psychotic disorder	X	X

Because we seek to evaluate interventions that will promote use of evidence-based treatment, and thereby abstinence from smoking, from the full range of adult daily smokers who are not immediately ready to quit, we will not exclude members of vulnerable populations, including pregnant women (for whom quitting smoking is an important goal for the health of both mother and child) or those on parole or probation (this will not be assessed, as it is not directly relevant to the study and does not materially alter the risk to benefit ratio of participation). Individuals who are in institutional living situations (e.g., in assisted living facilities) will also be eligible, if they are adults, smoke daily, present at the host clinics for primary care, and are considered competent to make healthcare decisions according to existing healthcare system protocols and procedures. Tobacco Care Managers will be trained to check this information and to only seek oral consent from those capable of providing fully informed oral consent.

None of these vulnerable populations will be specifically targeted in recruitment. The proposed reach interventions, assessments, and compensation schedule should pose no more risk for

pregnant women, those on parole or probation, or those in institutionalized settings than for the general population, as study procedures confer minimal risk, are informational in nature, and are entirely voluntary. The risks of intensive treatment will be addressed in the informed consent process for those who agree to randomization to treatment intensity and are eligible for this (pregnant and breastfeeding women will be ineligible for intensive treatment).

In addition, the compensation offered for completing assessments ($20 for the baseline assessment and $10-$20 for each semi-annual and post-cessation follow-up assessment (not counseling) call and $50 for 12- and 24-month post-enrollment visits for biochemical validation of abstinence from smoking), which is available to all enrolled participants, regardless of assigned experimental condition, are modest. Likewise, the incentives for completing an initial counseling session ($40) available to half the enrolled participants on the basis of random assignment to an incentive condition are modest and unlikely to be undue inducements to participation, even in vulnerable populations. Excluding members of these vulnerable populations is not warranted for their protection, would instead unjustly prevent their involvement in a minimal-risk program offering benefit (information about and the opportunity to connect with evidence-based smoking treatment at no personal cost, apart from telephone charges where applicable) to all participants. In addition, while the study does not target incarcerated individuals, some participants may be incarcerated during the period of study involvement. All study outreach, treatment provision, and assessment will be suspended during a participant's period of incarceration.

B. Consent

For this study, a two-tiered consent process will be used. First, all prospective participants who meet inclusion criteria and who do not endorse exclusion criteria for study participation will be read an oral consent script by a healthcare system Tobacco Care Manager (see uploaded Recruitment Call script). The consent script read to participants over the phone conveys the key points regarding study procedures; risks; and participant rights, protections, and benefits in accessible, lay language. Prospective participants will be given an opportunity to ask questions and raise concerns during this process, which will be addressed prior to assessing participant consent to participate in the study. Informed consent for study participation will be formally documented electronically in a REDCap database. Following enrollment for those who consent, study staff will send out a letter in hard copy to the participant at the address provided (see uploaded Study Information Sheet). This letter will remind the participant of study procedures and will include a detailed study information sheet containing all required elements of informed consent and HIPAA authorization.

For those participants randomized to intensive treatment access upon enrollment, their enrollment packet will also contain an Intensive Treatment Information Sheet (see upload) containing required additional elements of consent and HIPAA authorization relevant to intensive study treatment. This will serve as an additional resource for those participants who elect to initiate intensive smoking cessation treatment at some future point during the study.

If and when a patient requests stop-smoking treatment, the Tobacco Care Manager or a UW-CTRI staff member will go through the Treatment Initiation Screen and Consent script over the phone. Those randomly assigned to the standard care condition will be offered referral to the Wisconsin Tobacco Quit Line (WTQL) and/or referral to their primary care provider. Those randomly assigned to the incentive condition will be reminded that they can earn $40 by completing a first counseling call with the WTQL. Participants randomized to standard care are free to choose whatever treatment the WTQL or their primary care providers recommend, or that they choose to pursue outside of the treatment study (e.g., over the counter medication).

For example, a participant randomized to standard care in the study who gets a prescription for varenicline from their primary care provider will still be retained in the study, but the medication will not be provided by the study (it will be accessed, and paid for, in the usual means in clinical practice).

For those randomized to access to intensive treatment, the Tobacco Care Manager or UW-CTRI staffer will obtain oral assent to screen for current eligibility for varenicline and/or combination NRT (depending on their initial eligibility at enrollment—only the medications(s) for which the person met prerequisites at enrollment will be considered as options), will conduct this screening, and will then obtain oral consent to begin intensive treatment over the phone (see uploaded Treatment Initiation Screen and Consent). Those who were randomly assigned to receive incentives for treatment initiation will be reminded that they can earn $40 by completing a first counseling call with a UW-CTRI quit coach. Medication and UW-CTRI health-counselor delivered telephone counseling will not be dispensed to patients unless they provide oral consent for intensive treatment. Medications also will not be dispensed until the patient's primary care provider has had a chance to review and decline a request for the patient to begin the medications for which they are eligible according to the study protocol. Because we: anticipate that not all participants will request smoking cessation treatment during the study, want medication screening to be done at the time of the smoking cessation attempt, and want to minimize burden on primary care providers, medication requests for combination NRT or varenicline will be sent to primary care providers only after a participant has requested intensive treatment, assented to and passed eligibility screening, and consented to intensive treatment over the phone. Those in the intensive treatment condition who are not eligible for either combination NRT or varenicline will still have access to 3 sessions of UW-CTRI quit coach counseling, as will those who are eligible but decline to use combination NRT or varenicline. Access to counseling is not dependent on medication eligibility or election. Adverse events will be assessed among all those who initiate stop-smoking treatment at phone follow-up interviews 3, 12, and 26 weeks post-target quit date. In addition, adverse events will be assessed among those in intensive treatment during the quit coach counseling calls 1 week pre-quit, 1 day post-quit, and 1 week post-quit.

Access to medication is not limited to those in the conditions receiving incentives; all the study manipulations including access to incentives and access to intensive treatment are independent and fully crossed in this factorial design.

Given the remote nature of the outreach and treatment access interventions to be evaluated in this study, an oral consent process is the most likely to protect the external validity of the findings by ensuring that they resemble real-world practices in wellness and prevention interventions. Collecting consent over the phone also reduces the risk that we will inadvertently bias the sample toward the most motivated, stable, or affluent members of the target population by requiring face-to-face or mailed consent processes. Mailing a written consent form and waiting for this to be returned would result in an evaluation study sample that is less representative of the target population (i.e., selecting for those most motivated or most stably motivated, which is particularly problematic given the focus of this project on trying to engage adult patients who are not initially motivated in smoking cessation). Attempting to collect electronic or written consent at clinic visits would be a major challenge in terms of training and human subjects research training certification of clinic staff, and in terms of integration of the consent process into clinic workflows. A clinic-based consent process could also yield a biased sample (e.g., those who can least afford to miss work may be least likely to agree to hear about the study at a clinic visit). As such, introducing a delay or logistical barriers in the consent

process for the sole purpose of documenting written informed consent would undercut the knowledge to be gained by this minimal risk study without substantially enhancing subject protections. Requiring written informed consent and HIPAA authorization for study participation would reduce the real-world relevance of this study designed to evaluate real-world remotely delivered outreach interventions to increase smoking cessation quit attempts and success. We will, however, supplement the oral process with written documents (a Study Information Sheet mailed to enrollees after providing oral consent for the randomized reach interventions and standard treatment, plus an Intensive Treatment Information Sheet for enrollees randomized to this condition. The latter will be reviewed with participants if they request intensive treatment prior to delivery of that treatment), and primary care providers will review patient medical eligibility for combination NRT and varenicline treatment before any study medication is dispensed.

For these reasons, we also propose to use an altered HIPAA authorization because it would be impracticable to obtain authorization with all elements required under the HIPAA Privacy Rule over the phone to conduct our research study. We also seek to waive some of the required elements of consent and HIPAA authorization over the phone in order to reduce participant burden and to enhance comprehension of the material read to participants, without omitting any key information pertinent to risks, rights, or protections. Consent and HIPAA authorization over the phone will cover the collection of data from the electronic health record and the Wisconsin Tobacco Quit Line for research purposes. The mailed Study Information Sheet that will follow the telephone enrollment and oral consent process will include all required elements of consent and HIPAA authorization (including a statement regarding how long permission to use the PHI will last, how to withdraw permission for PHI use, and the mandatory statement that the PHI could be redisclosed without subjects' permission in the consent/authorization and enrollment process). The study information sheet also details how to withdraw from the study and revoke authorization to use PHI, without penalty or punishment. Likewise, the Intensive Treatment Information Sheet mailed to participants in the intensive treatment condition at enrollment (prior to intensive treatment delivery) will similarly cover all required elements of consent and HIPAA authorization.

Other considerations also support the use of oral consent to participate in this study and to extract data from the electronic health record (EHR) for intervention and research purposes. For those receiving tailored outreach letters, the tailoring will be based on demographic information and administrative data on clinic and assigned primary care provider from the EHR. The level of risk involved is also low, and the study will evaluate ways to enhance minimal risk reach-focused interventions to increase the number of patients who smoke who attempt to quit and use available smoking cessation treatments. The intensive treatment medication and counseling regimens are also minimal risk. These are not experimental treatments; they are good clinical practice shown to be safe and effective in previous studies. First, 12 weeks of combination NRT or varencline are FDA-approved regimens that are the recommended standard of clinical care for smoking cessation. The UW Health Sciences IRB has previously deemed nicotine replacement therapy, including combination NRT as minimal risk. Varenicline has a similar risk profile to NRT. Among adults with or without psychiatric conditions, a large multi-site trial of varenicline, bupropion, nicotine patch therapy, and placebo demonstrated that varenicline has superior efficacy without increased rates of neuropsychiatric adverse events or serious adverse events of any kind, relative to placebo, even among those with psychosis, anxiety, or mood disorders[42-43]. Previous studies at UW conducted by Dr. Fiore and colleagues have similarly shown that both combination NRT and varenicline are well tolerated. In a randomized clinical trial of 12 weeks of pharmacotherapy in 1086 adult smokers (N=241 who received nicotine

patches only, N=421 who received nicotine patches and nicotine lozenges, and N=424 who received varenicline), only one serious medication-related adverse event (an allergic reaction to varenicline) occurred[44]. This is 0.24% of those assigned to varenicline, and 0.12% of all those assigned to varenicline or combination NRT. In an ongoing trial of the effects of extending varenicline treatment to 26 weeks and adding nicotine patch therapy to varenicline (IRB protocol #: 2017-0404), only 2 out of 1251 (0.15%) consented participants who initiated 12 weeks of varenicline treatment have experienced serious adverse events possibly related to study medication. In the current study, to ensure that varenicline can be safely used, we will use the same inclusion/exclusion criteria used in IRB protocol #: 2017-0404 to determine eligibility for varenicline at the time of treatment request, and will additionally require approval of the primary care provider prior to dispensing either combination NRT or varenicline to study participants who consent to intensive treatment. In addition, the data to be collected are not particularly sensitive and will be securely transmitted and stored.

With regard to compensation and incentives, the Consent Script and mailed Study Information Sheet will make clear distinctions between compensation for completing study follow-up assessments (available in all conditions), and incentives for treatment engagement (available to those in only half of conditions). This is important for the sake of transparency, but also to prevent attrition among those randomized to conditions that offer no incentives for using smoking cessation treatments.

C. Baseline assessment

Following oral consent, a healthcare system Tobacco Care Manager will: conduct a brief baseline assessment (see uploaded Baseline Assessment) and collect information on 1-3 contacts who could help study staff get in touch with participants who move or experience phone interruptions (with participant consent). Participants will receive $20 for completing this assessment.

The Care Manager will also ask if the participant gives the study permission to stay in touch with them and send them reminders about upcoming study contacts during the study via email and/or text message. The Care Manager will remind them that email and text messaging are generally not a secure way to communicate about their health as there are many ways for unauthorized users to access email and text messages. The Care Manager will also inform them that they do not have to provide their email address or text message number to participate in this study.

D. Randomization

Randomization will occur immediately after oral consent and baseline data are collected and will be conducted by healthcare system Tobacco Care Managers using randomization tables developed at UW-CTRI. Randomization will be blocked by clinic, patient-identified gender, and eligibility for randomization to intensive treatment access to ensure equitable distributions across conditions. Enrollees who meet initial eligibility for intensive treatment will be randomized to 1 of 16 conditions (see Table 3), while those who do not meet these criteria (e.g., those with a history of severe renal disease and allergic reaction to NRT) will be randomized to 1 of the first 8 conditions shown below (because the 4th factor, access to intensive treatment, will not apply to them; they will have access to counseling and medication, if appropriate, from the quitline and/or their primary care provider). No placebo will be used in this pragmatic trial. Every enrollee will receive advice to quit smoking and information about resources available to help

them quit smoking no less than 2 times per year for 2 years. All enrollees who want stop-smoking treatment at some point in the 2-year study will have access to no less than a single smoking cessation counseling session and a 2-week supply of a single nicotine replacement therapy (if medically eligible for nicotine medication).

Following randomization, healthcare system Tobacco Care Managers will describe the stop-smoking treatments available to participants over the next 2 years (as determined by eligibility for and randomized access to intensive treatment condition), and will give instructions about how to contact him/her when ready to initiate smoking treatment. Those randomized to the incentive conditions will be told that they will receive $40 for completing a first smoking cessation counseling session if/when they decide to enter treatment (they can earn the incentive up to twice per year [four times maximum] over the 2-year study). The Tobacco Care Manager will also remind the participant that the study team will be reaching out in 6 months to conduct a brief follow-up assessment interview and the healthcare system will reach out again via letter in 6 months to provide information about resources and support available to quit smoking. If the person is randomized to a care management condition, the Care Manager will also schedule a 15-minute phone call for a motivational intervention within the next 2 weeks (with the option to complete the call immediately, if the participant is interested in doing so).

Table 3. Conditions (cells) to which participants will be randomized*

Cell	Incentives for treatment initiation	Automated tailored letters 2x/year	Care Manager Outreach 2x/year	Access to Intensive Treatment
1.	Off	Generic	Off	Off
2.	On	Generic	Off	Off
3.	Off	Tailored	Off	Off
4.	On	Tailored	Off	Off
5.	Off	Generic	On	Off
6.	On	Generic	On	Off
7.	Off	Tailored	On	Off
8.	On	Tailored	On	Off
9.	Off	Generic	Off	On
10.	On	Generic	Off	On
11.	Off	Tailored	Off	On
12.	On	Tailored	Off	On
13.	Off	Generic	On	On
14.	On	Generic	On	On
15.	Off	Tailored	On	On
16.	On	Tailored	On	On

* Those meeting initial criteria for access to intensive treatment will be randomized to all 16 cells; those ineligible for intensive treatment will be randomized to only the first 8 cells.

E. Welcome mailing

Following the enrollment call, study staff will mail enrollees a welcome package containing the following (samples of which are uploaded with the application):

1. A study Welcome Letter and a Treatment Offer Letter with information about:
    a. Available smoking cessation treatments and evidence of their effectiveness. In the tailored letter condition, this information will be tailored and personalized.
    b. Instructions about ways to contact the Care Manager to request treatment.
    c. Incentives available, how to earn them, and how and when they will be paid (if

applicable, as randomly assigned on the incentives factor).
   d. A reminder that the Tobacco Care Manager will call within 2 weeks of enrollment and again 5, 10, 16, and 22 months post enrollment to talk about smoking, quitting, and available resources (if applicable, as randomly assigned on the Care Manager outreach factor).
   e. A reminder that participants will receive a letter about stop smoking resources at enrollment (with enrollment packet) and at months 6, 12, 18, and 22 (in all conditions).
   f. A reminder that participants will be called by UW-CTRI research staff every 6 months to complete follow-up interviews regarding smoking and quitting, and that $20 in compensation will be offered for completing each of these calls.
2. A copy of the study information sheet containing all the information agreed to over the phone, and additional details covering all required elements of consent and HIPAA authorization (see uploaded Study Information Sheet).
3. A copy of an Intensive Treatment Information Sheet for varenicline and/or combination nicotine patch and nicotine mini-lozenge treatment for those randomly assigned to have access to intensive treatment when ready to quit.
4. A business card and a magnet showing how to contact the Tobacco Care Manager if participants decide they would like to quit (see uploaded Care Manager Magnets Cards).

F. Study treatments and experimental conditions

All enrollees in the study will receive a minimum of 5 outreach contacts in the form of letters describing available stop-smoking resources (at enrollment, 6, 12, 18, and 22 post-enrollment) to promote utilization of available evidence-based smoking cessation treatments offered at no cost to the participant (apart from possible cell phone minute charges if the participant receives study- or treatment-related calls on a cell phone). Every participant will be offered some form of evidence-based treatment, as even those who are not eligible for or randomized to access to intensive treatment will be offered referral to a tobacco quit line that, in Wisconsin, offers proactive counseling and (for those medically eligible) a 2-week starter-kit supply of a nicotine replacement therapy. Tobacco Care Managers will also offer to alert enrollees' primary care providers when enrollees are interested in quitting (i.e., coordination of care).

Some participants will receive additional or modified outreach, as randomly assigned. Some will receive incentives to use smoking cessation counseling, some will receive automated tailored letters and MyChart messages (if MyChart active) promoting smoking cessation treatment use, and some will receive a motivational intervention and care management delivered by phone. These experimental interventions are described in detail below.

Incentives. In 2 of our recent studies[45,46], incentive-driven increases in counseling use mediated incentive effects on abstinence in Medicaid-insured smokers. Given the significant savings associated with smoking cessation[47], modest incentives *to use treatment* may well be cost-effective if they drive increased quitting. Modest incentives ($25 or $50) also improve attendance at primary care visits[48]. Thus, evidence supports modest, utilization-contingent incentives for use of both smoking cessation and primary care treatment. The proposed project will be the first to examine incentives to use smoking treatment (rather than achieve abstinence) in primary care.

Half of participants will be assigned to receive incentives while the other half will not. Incentives will be tied to readily observable *initiation* of treatment (i.e., completion of a quitline or health counselor counseling call). A single $40 incentive *per round* will be offered to spur treatment initiation. The $40 incentive was selected based on the promising results of earlier work that

used $30 incentives to improve counseling completion, and through this pathway, abstinence rates among low-income smokers. A slightly larger incentive will be used here due to the greater diversity in socioeconomic status of the proposed sample, and because only 1 incentive is available per treatment round. Participants will be limited to 2 rounds of treatment per year (as per Affordable Care Act guidelines[49]), for a maximum of $160 over the 2-year study. Participants will be paid by mailed check or gift card. Incentives are not contingent on medication use, as medication use is subject to medical eligibility and too difficult to verify. Those in the incentive condition will be told of these incentives at enrollment and reminded of them at months 6, 12, 18, and 22 post-enrollment.

Automated Tailored Outreach*.* Repeated, proactive outreach to patients who smoke increases use of smoking-cessation treatment[18,50-53]. A recent proactive campaign based on a smoker registry yielded a 30% response rate[52], markedly higher than population treatment use rates[54-56]. One promising strategy to improve receptivity to treatment invitations is tailoring and personalizing content[57-61]. Tailoring involves crafting messages for specific individuals based on their characteristics (e.g., age, gender[62]). Personalization involves identifying the source of the message (i.e., the provider, team, or system sending the message[62]). Tailoring and personalization increase smoking abstinence among healthcare system patients interested in quitting[62], but the degree to which these approaches enhance treatment reach is less clear and will be evaluated in this study.

Half of participants will be assigned to receive proactive outreach tailored to sex, age, assigned primary care provider, and assigned clinic, as recorded in the EHR and confirmed at enrollment. Messages will be tailored to only these variables to foster dissemination. This outreach, personalized with pictures and messages from the Tobacco Care Manager, clinic, and primary care provider will promote the use of available interventions (as determined by eligibility and random assignment). Those in the mailing-only ("Off") control condition will receive non-tailored mailed letters noting available treatments and how to access them twice per year (at enrollment, month 6, month 12, month 18, and month 22). Participants in the "On" condition will receive communications on the same schedule, via both mail and MyChart (if MyChart active). Each letter/message will have a different theme, but all will provide information about available treatments and how to access them, as shown in the uploaded Sample Letters.

Care Management**.** Healthcare systems are increasingly adopting disease/care management approaches to improve the clinical management of costly chronic conditions such as diabetes and depression[36-38,63]. Care management involves continuing (i.e., longitudinal) care with proactive outreach, patient education and support, and coordination of care[61,62]. In this study, a Tobacco Care Manager will provide a manual-guided motivational enhancement intervention known to increase motivation to quit smoking[66]. Tobacco dependence Care Management models have been tested in 2 RCTs[18,19], both of which suggested that proactive chronic disease management improves both treatment use and abstinence over at least 18 months.

In the current study, half of the sample will be assigned to care management and receive live phone calls from the Tobacco Care Manager within 2 weeks of enrollment and again at 5, 10, 16, and 22 months post-enrollment. Tobacco Care Managers will be healthcare system employees and study team members trained in tobacco dependence treatment and certified in human subjects research and HIPAA training. Training manuals and documentation templates will be provided to enhance real-world implementation potential and quality assurance/intervention fidelity. Tobacco Care Managers will follow a protocol to provide support, information, and motivational interviewing strategies, delivered via phone (see uploaded Care Management Counseling Protocol) comprising 5 10-15-minute sessions (within 2 weeks of enrollment and at months 5, 10, 16, and 22). Treatment options and ways to initiate treatment and seek Care Manager support will be discussed at every call. We will strive to keep patients with the same Care Manager for 2 years to foster rapport and trust. Care Managers will document contact attempts and a random sample of phone sessions will be audiotaped for

fidelity coding (among those who consented to such recording, see consent for audio recording in the Study Recruitment Call Script). The half of the sample assigned to the "off" condition will receive no Care Manager outreach beyond enrollment.

Access to Intensive Treatment. Half of the participants who meet initial eligibility for intensive treatment will be randomized to have access to intensive treatment, with patient choice among intensive treatments (if eligible for both standard dosing of a 12-week regimen of varenicline and combination nicotine patch and mini-lozenge). At the time a patient requests treatment, the Tobacco Care Manager will send a medication order for the patient's primary care provider to review and order, if the primary care provider considers this a safe and appropriate medication for the patient. Intensive treatment will involve three 15-minute phone counseling sessions delivered 1 week prequit, on the day after the target quit day, and 1 week postquit, following a standard protocol (see uploaded Cessation Counseling Protocol). These sessions will be offered by bachelor's level UW-CTRI Health Counselors. The remaining half of the experimental sample will be randomly assigned to standard care (referral to the Primary Care Provider and referral to a tobacco quit line, which for Wisconsin residents comprises a single 20-minute proactive cessation counseling call from a trained quit coach and, if medically eligible, a 2-week supply of a nicotine monotherapy dispensed by the quit line, at no cost to the smoker). Data from the WTQL will note the patient's quit date, counseling use, and medications dispensed for those referred to the WTQL. Quit line use will also be assessed via self-report at semi-annual follow-ups.

Dosing for the medication regimens will follow standard dosing procedures as follows: Participants approved to take varenicline will receive one 0.5 mg pill for the first 3 days, starting 7 days prior to the target quit day (TQD). They will then use one 0.5 mg pill twice daily for the next 4 days. After the first week of study medication ramp up, participants will use one 1 mg pill twice daily until 11 weeks post-TQD. Participants approved to take combination nicotine patch and nicotine mini-lozenge treatment will receive 12 weeks of nicotine patches and nicotine mini-lozenges starting on the target quit day (TQD). Consistent with standard dosing and package insert instructions, Participants who smoke 10 or more cigarettes/day will start with a 21 mg patch for 8 weeks, and then titrate down to a 14 mg patch for 2 weeks and then a 7 mg patch for 2 weeks. Participants who smoke 5-9 cigarettes/day will be given 10 weeks of 14 mg patches and then 2 weeks of 7 mg patches. To reduce the risk of adverse effects, all participants receiving combination NRT will receive 2 mg mini-lozenges. This is a lower dose of nicotine mini-lozenges than used in standard dosing in which those who smoke within 30 minutes are given 4 mg mini-lozenges. Participants who smoke fewer than 5 cigarettes per day will not be eligible for intensive treatment with either varenicline or combination NRT.

Adverse events associated with stop-smoking treatment will be assessed at every post-cessation follow-up (3, 12, and 26 weeks post-target quit date) and at every intensive treatment quit coach counseling call with a UW-CTRI quit coach (1 week pre-quit, 1 day post-quit, 1 week post-quit). Follow-up assessors and UW-CTRI quit coaches will follow the uploaded adverse event protocol and will notify the Tobacco Care Manager of adverse events that may be study related so that the Tobacco Care Manager can inform the primary care provider of this and coordinate care as needed.

G. Detailed study procedures: recruitment and retention

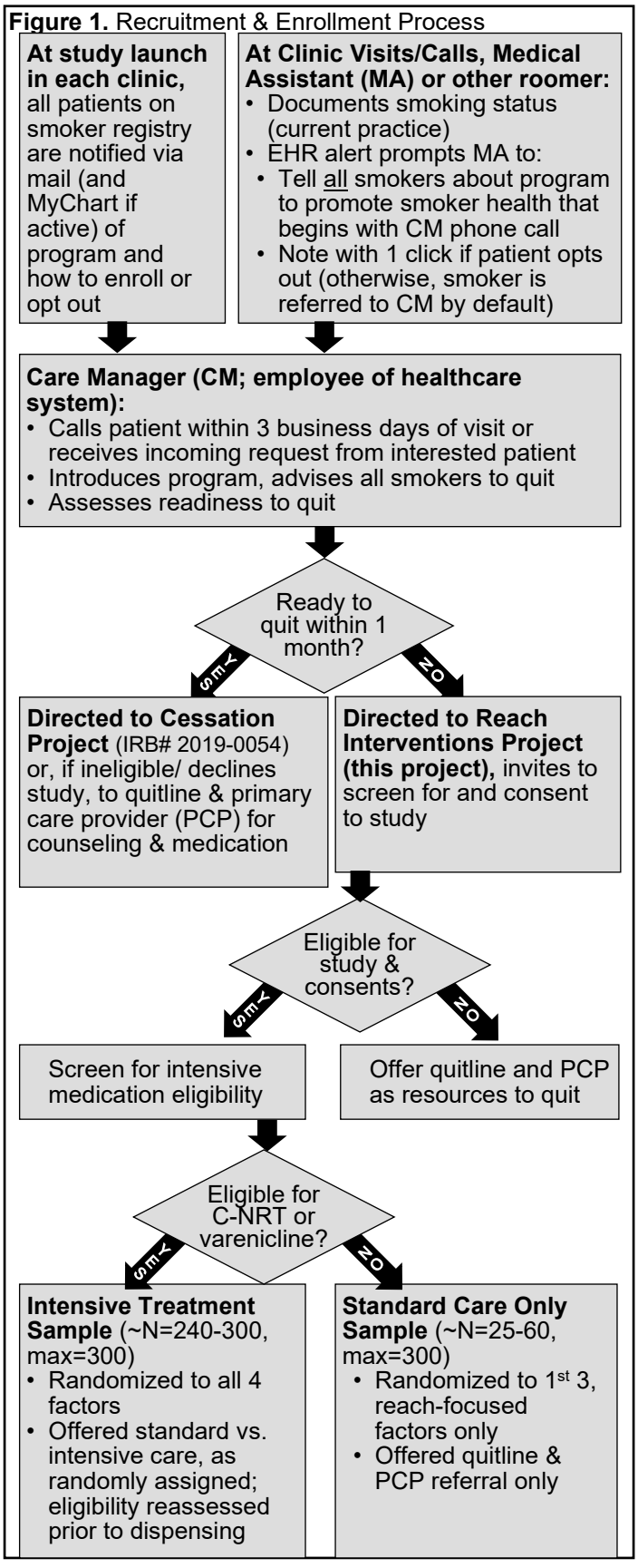
As noted in the flow diagram in Figure 1, recruitment will occur in healthcare systems. We will recruit participants via 2 routes. First, at the launch of recruitment in each clinic, and quarterly thereafter, we will alert all adult patients on the EHR smoker registry at participating clinics that a Tobacco Care Manager will be available to offer information and resources to any and all patients who want to quit smoking, and that opportunities to participate in research studies

offering compensation also exist. This notice will be delivered in the patient's preferred communication modality (mailed letter and in the secure EHR message portal MyChart; see the uploaded Recruitment Letter and MyChart Message content). These notices will also instruct patients to call or MyChart message the Care Manager if they would like to opt out of future Care Manager outreach.

Second, for all adult primary care patients on the smoker registry who present at participating primary care clinics or participate in primary care video visits or telemedicine calls with a primary care provider affiliated with a participating clinic, an EHR alert will prompt clinic staff assessing tobacco use and vital signs (typically this is a Medical Assistant or Licensed Practical Nurse) to advise all smokers to quit and tell the patient to expect a call within the next few days from a Tobacco Care Manager who will offer information about resources available to help them quit smoking now or in the future. Clinic staff will be trained how to respond to the EHR alert, present information on Care Manager outreach to the patient, answer patient questions about Care Manager outreach, and note if the patient opts out of telephone outreach from the Care Manager.

For clinic patients who do not opt out of Care Manager outreach, the Care Manager will proactively call the patient at the numbers listed in the EHR (beginning with the patient's preferred number) and will leave messages according to their consent for voicemail messages on file (see uploaded Recruitment Call Script for sample messages). Care Managers will make attempts to call the patient on varying days and at varying times of day, over no more than 30 days. The first call will typically occur within 3 days of the most recent visit to a participating clinic.

Figure 1. Recruitment & Enrollment Process



Healthcare system Tobacco Care Managers will deliver the reach-focused interventions in this study. For those who tell the Care Manager that they are ready to quit within 30 days at any point during the 24-month follow-up period, the Care Manager will coordinate access to either standard care (quit line and/or primary care provider referral) or intensive smoking cessation treatment depending on experimental condition. Coordinating standard care means providing referral to a state quit line (typically the Wisconsin Tobacco Quit Line), for patients who agree to this, and/or sending a message to the patient's primary care provider in the EHR to let the provider know the patient wants help in quitting smoking. Coordinating intensive treatment means screening for current eligibility for varenicline or combination NRT and obtaining oral consent for intensive treatment. For those who consent, the Care Manager will schedule a first session with an UW-CTRI health counselor and send a request for Primary Care Provider review for varenicline or combination NRT.

UW-CTRI personnel will be responsible for: conducting telephone follow-up interviews 6, 12, 18, and 24 months post-enrollment; conducting in-clinic visits with patients to verify claimed abstinence 12- and 24-months post-enrollment via biochemical testing (breath CO, urine, and/or saliva testing without biobanking); delivering three sessions of telephone counseling to those in the intensive cessation treatment conditions who initiate treatment; and conducting telephone follow-up interviews 3, 12, and 26 weeks after a patient's target quit day (for those who set a quit day during the study).

Personnel from both the healthcare systems and UW-CTRI will therefore have contact with study participants and/or their data. Coordination of all activities will be led by UW-CTRI and UW-CTRI will perform all data analyses. All data transmissions to UW-CTRI will occur via secure, HIPAA-compliant means via capture in REDCap or SFTP or Box file transfers. Data about study participation shared by UW-CTRI with health system primary care teams will occur via similar secure means or manual electronic health record (EHR) entry by Tobacco Care Managers who are both health system employees and study personnel. Tobacco Care Managers will have security templates in the EHR that permit them to enter research records, update smoking status, enter telephone encounters regarding study medications and route these to primary care providers, and/or exchange secure inbasket messages with primary care providers regarding medication requests, serious adverse events, or medication discontinuation due to side effects.

Assessment Plan

1. Baseline assessment (See uploaded Baseline Assessment and uploaded List of EHR Data to Be Extracted). At enrollment, Care Managers will assess patient age, sex, race, ethnicity, contact information, communication preferences, educational attainment, self-reported psychiatric history, tobacco use history and smoking cessation history, motivation and self-efficacy related to quitting smoking, attitudes about and beliefs regarding smoking cessation treatments, and self-assessed health. EHR data regarding chronic medical conditions and healthcare utilization over the past year will be extracted, as well. Participants will earn $20 for completing the baseline assessment.

2. Semi-Annual assessment (See uploaded Semi-Annual Follow-Up and List of EHR Data to Be Extracted). At these follow-ups, patient self-report of smoking, treatment use, and quitting attitudes, beliefs, and experiences (including withdrawal and social support related to quitting) will be assessed and EHR and pharmacy data on healthcare utilization and smoking status changes will be extracted. Participants will earn $20 for each of 4 10-20-minute semi-annual follow-up phone interviews assessing smoking status, treatment use,

and candidate mediators of intervention effects on treatment initiation and abstinence (e.g., extrinsic/intrinsic motivation, self-efficacy, perceived social support, and treatment use). Self-reported satisfaction with healthcare and with the interventions provided in the study and any smoking cessation treatments used during the study will be assessed, as well. In addition, participants who report no smoking in the past 7 days at the 12- and 24-month post-enrollment interviews will be asked to return to a participating primary care clinic to complete a brief visit to assess smoking, tobacco, and smoked marijuana use since the telephone interview and to provide breath, urine, and/or saliva samples for biochemical testing to verify abstinence from smoking. Breath testing will be completed using the commercially available Micro+Smokerlyzer® from Bedfont Scientific Ltd. This biochemical verification procedure presents minimal risk, as it requires only that participants hold their breath for 15 seconds before blowing into a CO detector and that the participant provide a urine or saliva sample for immediate testing for cotinine/anabasine via NicAlert® (Nymox Corporation, Hasbrouck Heights, NJ) test strip in an effort to verify self-reported abstinence from nicotine. Participants who do not come into the clinic may be asked to collect a saliva sample at home and mail it back to the study team instead. In order to achieve a high level of abstinence verification, and in light of participant travel involved, participants will receive $50 for completing this visit. If we are unable to reach participants, we will send letters and emails or texts (if they have given permission for this) reminding them about these follow-ups. At 12 and 24 months post-enrollment, if we cannot reach people by phone, we will send a letter with a form to return in a self-addressed stamped envelope to indicate their smoking status and any use of treatment in the past 6 months.

3. Post-quit attempt assessment (See uploaded Post Treatment Follow-Up assessment). Those who request smoking cessation treatment through a Care Manager will be asked to complete 10-20 minute telephone interviews 3, 12, and 26 weeks post-target-quit day and paid $10 for these calls (this payment is low to avoid interfering with the incentive manipulation). At these follow-ups, patient self-report of smoking, treatment use, and quitting attitudes, beliefs, and experiences (including withdrawal and social support related to quitting) will be assessed, along with any adverse events that occurred since the beginning of cessation treatment. In addition, participant utilization of treatment will be assessed by tracking how many calls or visits the participant completed and how much medication they report using.

To enhance intervention fidelity, intervention delivery will be assessed via supervisory review of recorded motivational interventions by the Care Manager and smoking cessation counseling calls delivered by UW-CTRI Health Counselors, with feedback regarding performance to enhance fidelity, as needed.

To enhance follow-up interview and visit completion rates, participants will be texted, mailed, sent MyChart reminders or automated phone calls (depending on their communication preferences as noted in the EHR and during enrollment).

Data management, transmission and storage

Data will be transferred from the EHR to research databases for use in tailoring and personalizing outreach (as randomly assigned) and tracking recruitment, participant healthcare utilization, smoking cessation treatment, and changes in smoking status, insurance type, or health status over the course of the 2-year study. Both healthcare systems maintain secure, HIPAA-compliant electronic health records for their operations and have mechanisms and processes in place to extract and encrypt data from the EHR for research purposes. Staff at UW-CTRI will receive data on enrollees who have provided consent for such data sharing as

part of the oral consent process. The data to be extracted from the EHR for the purposes of reach-focused interventions and assessment are shown in the uploaded List of EHR Data to Be Extracted. The research office will also receive data from the Wisconsin Tobacco Quit Line regarding services those in Standard Care received (i.e., did they complete the counseling call, were they sent any smoking cessation medications).

Although this program will evaluate interventions delivered by healthcare system personnel (Tobacco Care Managers), delivery of intensive treatment and follow-up data collection procedures and collation of data from multiple sources/sites necessary for thorough program evaluation are the responsibility of the UW-CTRI study investigators. To achieve the study aims, UW-CTRI investigators require access to identifiable patient data. At UW-CTRI, all study data will be stored in a HIPAA-compliant and secure manner on Department of Medicine servers with UW-CTRI-controlled password access. Staff trained in human subjects research and HIPAA compliance will link these datasets using a random subject identifier and will then de-identify the data for analyses.

Treatment procedures description

The reach-focused interventions to be evaluated in this study will be delivered by healthcare system Tobacco Care Managers and/or UW-CTRI personnel. In addition to recruiting, screening, consenting, randomizing, and informing enrollees about available treatments at enrollment, healthcare system Care Managers will be responsible for live outreach via telephone to provide motivational interventions to promote cessation and treatment use (as randomly assigned), and to coordinate care for participants who request smoking cessation treatment during the study (including seeking approval of medications by primary care providers and updating patient records to reflect treatment use and changes in smoking status). UW-CTRI personnel and health system Care Managers will work together to prepare and disseminate automated semi-annual mailed/electronic outreach materials (e.g., UW-CTRI personnel will mail letters, but Care Managers who have access to the EHR patient message portal will need to send MyChart messages). UW-CTRI personnel will be responsible for conducting follow-up interviews, including semi-annual interviews and post-target-quit-date follow-up interviews, and will alert Care Managers to any requests for treatment that occur during these telephone interviews. UW-CTRI Health Counselors will track completion of intensive treatment counseling calls and use of quit line services to determine whether or not a patient in the incentive condition is owed a $40 incentive. UW-CTRI staff will process incentive payments and letters (see uploaded Incentive Letter).

Standard (*vs.* intensive) treatment procedures will involve an offer of referral to standard quit line (e.g., Wisconsin Tobacco Quit Line, or WTQL) care. The WTQL offers all Wisconsin residents who smoke and want to quit within 30 days a single 20-minute counseling call (plus *ad hoc* calls as initiated by the participant) and a 2-week supply of an over-the-counter nicotine replacement therapy (for those who meet WTQL eligibility criteria for this medication, or have documented approval for the medication from their own physician). The WTQL mails medications to the participant's home, with instructions in proper use. This is the standard treatment protocol for the WTQL and will not be modified for this study. Another option for standard treatment is for the Care Manager to notify the participant's primary care provider that the participant has set a quit date and would like to talk about medication and support to help them quit. Participants may elect to accept one or both of these interventions, and the Care Manager will make the quit line referral and/or send an electronic message to the primary care provider via the EHR, as requested by the participant.

Requests for intensive treatment that come in from participants randomly assigned to have access to such treatment will be handled initially by the health system Tobacco Care Manager,

who will help the participant select a quit day within the next 30 days and then schedule a first phone counseling session with an UW-CTRI Health Counselor for one week prior to the target quit day. The Care Manager will record this quit date in a study database and will conduct a brief medication eligibility interview to determine whether the patient meets eligibility criteria for varenicline and/or combination nicotine patch and mini-lozenge therapy, and to determine what dose of nicotine patch is appropriate for those eligible for combination nicotine replacement therapy, at the time of the call. Care Managers will facilitate treatment for participants during their first 98 weeks (22.5 months) of enrollment and will provide standard treatment referral information to those who request treatment after that time or who request treatment more than 2 times per year or 4 times total during the study. See the uploaded Treatment Initiation Screen and Consent document. The Care Manager will collect oral consent for intensive treatment and ask those who consent and are eligible for both medications which medication they would prefer. The Care Manager will then draft a pending order for all the medications for which the consented participant meets eligibility criteria and will note in a message to the primary care provider which medication the participant would prefer. Primary care providers will be asked to review these medication orders (both the preferred medication and the alternative, if the preferred medication is deemed unsuitable for the patient by the provider) within 3 business days. Only patients with primary care providers in an active BREATHE 2 clinic will be eligible for intensive treatment medication, as the Tobacco Care Manager will not be able to seek approval for medication orders outside these clinics. Participants who have switched to an external primary care provider will be offered standard care instead. When a primary care provider approves a medication order, the Care Manager will note this in the study database and the UW-CTRI team will mail a starter medication kit and instructions to the participant's preferred mailing address (see uploaded medication instructions). Care Managers or UW-CTRI staff will notify the participant whether or not the medication has been approved by their provider and is being mailed to them. If a participant is eligible and approved for both varenicline and combination NRT, the participant's preferred treatment will be dispensed (so long as both regimens are available at the time treatment is initiated; see the 8/2/2021 update above). If a participant reports a soy allergy at the time of treatment request, soy-free mini-lozenges will be dispensed. Medication instructions mailed with medications will note how to request refills (as medications will be mailed in one-month supplies). In addition, either automated calls or text messages (for those who consent to receive text messages in the study) will be sent to alert participants when they can request medication refills.

Additional telephone counseling will be provided by UW-CTRI Health Counselors on the day after the target quit day, and one week following the target quit day. Health Counselors will be trained and supervised by licensed psychologists. Audio recordings of at least 10% of sessions will be reviewed and coded for fidelity. See the uploaded Cessation Counseling Protocol.

Analysis Plan

Ongoing study monitoring. Ongoing analyses to monitor study progress, patient flow, retention, and fidelity will be conducted for quality assurance. Patient flow through the recruitment process will be tracked carefully and descriptive statistics will be used to characterize the subsamples of participants who are fully enrolled and those who are lost at each step in the process, and whether this differs by clinic, Care Manager, or demographics. This will allow us to identify, and if need be, adjust for differences in retention due to patient-, clinic-, or Care Manager-level factors. Fidelity in telephone sessions delivered by Care Managers and Health Counselors will be monitored. Adverse events will be assessed and queried (see Adverse Event Protocol in the Post-Treatment Follow-Up assessment). Analyses will be conducted by UW-CTRI personnel using data collected from the EHR and data collected from the health system Care Manager (to

determine the number of patients eligible for referral to the Care Manager, the number and proportion who opt out, and the proportion retained through each step of the enrollment process, and the representativeness of the enrolled sample). Data collected via telephone interview by the Care Manager and UW-CTRI Health Counselor will be used to track retention and intervention delivery and fidelity.

Aim 1. To develop an optimized package of health system interventions to promote smoking cessation treatment reach among patients not initially willing to quit, logistic regression analyses will be conducted with binary treatment initiation over 1 year of study enrollment as the primary outcome, in the primary sample randomized on all 4 experimental factors. Effect size estimates will be generated and all main and all 2-way, 3-way, and 4-way interactive effects will be tested as predictors in the logistic regression model. In addition, the magnitude of the difference in treatment initiation rates between the most promising intervention conditions and the cell in which all the intervention components are off will be used to generate an upper limit estimate of optimized reach intervention package effects. Exploratory analyses will be conducted adjusted for covariates known to be predictive of treatment use. Exploratory sensitivity analyses will be conducted to estimate intervention component effects across a range of assumptions regarding missing outcome data. We anticipate that 25% of follow-up data will be missing and will examine the robustness of results across intent-to-treat and less stringent assumptions regarding missingness (i.e., that 90%, 80%, or 70% of missing cases are smoking) in sensitivity analyses. We may also use multiple imputation and examine the consistency of results across multiply imputed datasets and those imputed using the simple methods already described. This analysis will use data collected via UW-CTRI staff during follow-up telephone interviews supplemented by data regarding smoking cessation attempts and treatment utilization extracted from the EHR and the WTQL.

Aim 2. To assess the cumulative main and interactive effects of each intervention component on binary treatment initiation over 2 years of study enrollment, logistic regressions predicting any treatment initiation (defined as completing a first counseling session, the primary outcome at a more distal endpoint) will address this aim, first in the ~240-300 patients (max 300) eligible for intensive treatment to examine all 4 intervention components, and then, separately, in the ~30-60 (max 60) participants who do not meet criteria for access to intensive treatment. As in the analyses for Aim 1, effect coding will be used to ensure the independence of the main and interactive effects in this balanced design, exploratory analyses will be conducted with adjustment for covariates, and exploratory sensitivity analyses will examine the robustness of results across a range of missing data assumptions.

In addition to the binary logistic regression described above, exploratory logistic regression models will estimate intervention component main and interactive effects on treatment completion (all 3 counseling sessions and medication initiation) among those randomly assigned to have access to intensive treatment with C-NRT or varenicline and counseling. This exploratory analysis will quantify the effects of the informational/motivational intervention components on the dose of evidence-based treatment received by participants over 2 years. Effect coding, covariate adjustment, and sensitivity analyses will be used, as described above. Exploratory descriptive analyses of the frequency and temporal patterns of treatment use will also be conducted (e.g., to explore whether C-NRT use tends to follow varenicline more often than the reverse, to see whether C-NRT is more likely to be repeated than varenicline use). As for Aim 1, this analysis will use data collected via UW-CTRI staff during follow-up telephone interviews supplemented by data regarding smoking cessation attempts and treatment utilization extracted from the EHR.

Secondary Aim 1. Although the primary outcome in this study is treatment reach, the ultimate objective of this project is to help more smokers stop smoking. A key secondary binary logistic regression analysis in this project will estimate reach-focused intervention component effects on end-of-study 7-day point-prevalence abstinence confirmed by CO testing, and, if CO is elevated,

salivary cotinine/anabasine testing, among those claiming abstinence. This analysis will estimate the main and interactive effects of the intervention components on end-of-study (2-year) 7-day point-prevalence abstinence rates (as ascertained by self-report and biochemically confirmed). The primary analysis will be an unadjusted, intent-to-treat analysis, but this will be followed by exploratory adjusted models and sensitivity analyses. This analysis will use data collected by personnel during the final semi-annual follow-up telephone interview plus the biochemical confirmation visit (for those claiming abstinence), supplemented by data on smoking status extracted from the EHR.

Additional, exploratory analyses will examine the 7-day point-prevalence abstinence rates at 3 time points following each round of treatment initiated with the Tobacco Care Managers (3, 12, and 26 weeks post-target-quit-day), for up to 4 rounds of treatment. Exploratory descriptive analyses will summarize abstinence rates at each time point, and the effects of intervention components on these abstinence rates will be explored, both within and across rounds of treatment. This analysis will use data collected by UW-CTRI personnel during the post-quit follow-up telephone interviews.

Secondary Aim 2*.* The degree to which intervention component effects on abstinence are mediated by treatment use will be examined via formal mediation analysis. These tertiary outcome models will examine the extent to which intervention component effects on 7-day point-prevalence abstinence after 2 years of enrollment are mediated by initiation of treatment in the preceding 2 years. Enrollees eligible for intensive treatment will be the primary sample for these analyses, with exploratory replication in those not eligible for intensive treatment. To examine mechanisms of specific intervention effects on the primary outcomes of interest, additional, exploratory models will examine the extent to which intervention components affect quitting motivation, self-efficacy, and perceived intra-treatment social support, and the degree to which these candidate mediators are associated with treatment initiation and point-prevalence abstinence at the end of the study. Within each treatment episode, the degree to which short-term abstinence (3-, 12-, or 26-weeks postquit) is mediated by reductions in withdrawal will also be explored.

Secondary Aim 3*.* We will attempt to estimate total (service, administrative, medication, utilization, patient out-of-pocket) costs of implementing the reach interventions in the study (e.g., costs related to administration, training, supervision, recruitment, medication screening) and each specific intervention component (and combination thereof) as tertiary outcomes for the project, without including any costs related only to research activities. First-year and second-year costs will be estimated separately in order to generate cost estimates after 1 year of implementation (and compare these with program costs of the usual fax-to-quit care approach in place prior to study launch), and to separately estimate program maintenance costs. To generate stable estimates of short and longer-term costs and savings, we will extract data on healthcare utilization from 1 year pre-enrollment to up to 4 years post-enrollment (maximum of 5 years total). These tertiary analyses will inform optimization of health system reach interventions and provide healthcare systems that may adopt reach interventions estimates of both initial and maintenance costs, overall, and by intervention component. We will compute total costs, and costs by category, and then use these cost data to compute cost per treatment initiation (the primary outcome of this study), cost per quit (the secondary, abstinence outcome), and costs per Quality Adjusted Life Years gained (QALYs[67]) by each intervention component. These analyses will help to assess intervention component efficiency in terms of promoting reach, abstinence (effectiveness), and quality of life. We may also conduct exploratory analyses to estimate net monetary benefit (NMB) when considering the added costs of the reach intervention components, and the monetized value of their QALYs gains. In addition, we may use incremental cost-effectiveness ratios (ICERs)[68,69] to assess intervention component efficiency in promoting reach, and, separately, abstinence. These exploratory cost-effectiveness methods will be computed in the primary sample of participants eligible for intensive treatment access, where the costs of standard care and both forms of intensive treatment will be

computed and analyzed. We will conduct an exploratory replication of these cost-effectiveness analyses in the sample of patients eligible only for standard care who may differ systematically from those eligible for intensive treatment. In addition, we will use EHR-extracted data on healthcare utilization for participants who do vs. do not use smoking cessation treatment, and those who do vs. do not quit smoking to estimate potential savings resulting from implementation of each reach intervention (and combination of interventions) in exploratory analyses. We may also conduct probabilistic sensitivity analyses across a range of assumptions to account for uncertainty[70,71]. Healthcare system budget impact analyses may be conducted to help healthcare systems gauge the affordability of the most promising, cost-effective reach interventions[72]. This analysis will use data extracted from the EHR and from UW-CTRI research databases regarding intervention delivery and external estimates of Medicaid costs of healthcare system staff time and procedures.

Secondary Aim 4. To explore moderators of reach intervention responses, we will introduce individual differences (sex, age, race/ethnicity, education, insurance type, time-to-first-cigarette, quitting history, chronic conditions, healthcare utilization in the year prior to enrollment, and mental illness history) to the models described above for Aims 1-3. In addition to testing interactions between candidate moderators and reach intervention component main and interactive effects in logistic regression models of treatment use and abstinence, we may conduct regression tree analyses to identify subpopulations of smokers defined by compound characteristics that differ maximally on treatment initiation and abstinence outcomes and subgroups that vary in intervention response. These exploratory analyses can help to identify patients that may benefit especially from particular reach intervention components or combinations thereof. These analyses will use data collected at baseline, follow-up, and via the EHR.

Supplemental Models. Exploratory GEE models may examine intervention component effects on the pattern of treatment initiation and abstinence across the 4 semi-annual follow-up waves. Additional, exploratory latent class analyses may examine patterns of engagement and abstinence in 6-month epochs over 2 years, conditional on intervention components and combinations. These supplemental analyses will be exploratory and hypothesis generating. Their results may facilitate interpretation of interaction effects in the primary analyses and inform refinement of optimized combinations of reach-focused system interventions.

Covariates. All models described above will be conducted and reported with and without adjustment for healthcare system or clinic and factors known to be associated with treatment engagement (e.g., sex, age, medical comorbidities related to smoking, healthcare utilization[73-77]). Covariates will be removed from final adjusted models if not significantly related to the dependent variable to enhance model parsimony.

Power and Sample Size

The target sample size for participants eligible for randomization to intensive treatment access (*N*=1664) was selected based on estimates of the flow of patients through clinics in a 9-month period and the number needed to detect at least an 8% increment in both treatment reach (defined here as initiation or completion of treatment) and 2-year abstinence rates, as we consider 8% to be a clinically meaningful increment in both reach and abstinence. Power estimates for main effects of each intervention component across a range of possible base rates in treatment use (from 5 to 65%) and abstinence (from 5 to 30%) exceed .9 (at alpha .05) with a sample of 1664 participants. Power to detect simple main effects (i.e., to interpret interactions) exceeds .7 for all but one combination of base rates and effect sizes at N=1664.

Power will be lower in the sample of smokers who do not meet all eligibility criteria for randomization to intensive treatment access (we estimate this to be roughly 416 participants, but may be as high as 800 participants), but this sample will be sufficiently large to generate

upper-bound estimates of effect sizes for intervention component, component-by-component interaction, and mediator and moderator effects.

July 2022 update to sample size based on recruitment challenges

Initially, the sample size was N=1664 to provide adequate power to detect hypothesized effects (8% increments in treatment reach, or initiation of assisted quit attempts, and 8% increments in abstinence 2-years after enrollment). Given difficulties in recruitment using the current model, we recognize that this sample size is not feasible to achieve during the study period. As such, we have now revised our goals for this study and now propose a sample of 240-300 participants. This will ensure that at least 15 participants are in each cell of the experimental design, sufficient to yield stable estimates of effect sizes in this factorial design. Although this sample size will not provide adequate power to test hypothesized effects, it will be sufficient to generate effect size estimates and ranges, and to identify interventions and intervention combinations with promising effect sizes for future study.

H. Human Subjects Protections and Data Sharing

Describe any potential direct benefits to subjects. If there are no direct benefits, state this.

Every participant in the study will be given information about ways to access at least 1 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 and care management). Although smokers could access this care outside of the study, we know that only about 1-2% of smokers use a quit line and only about 5% use both medication and counseling. As such, the proposed study will offer all participants the benefit of information about treatment options and a low-barrier method of initiating treatment (i.e., by phone).

Describe the potential benefits of this research to society.

The proposed research also has the potential to benefit other smokers by identifying highly effective health system reach interventions that expand the reach of existing lower- and higher-intensity treatments and are feasible, cost-effective, and potentially sustainable in primary care settings. This work has the potential to accelerate the translation of clinical research on smoking interventions into healthcare practice and thereby reduce morbidity and mortality associated with smoking.

To promote public access to the results of this research, and thus its potential benefits, the study will be registered as a clinical trial at ClinicalTrials.gov, with information about the study purpose, experimental design, outcomes, and analyses available to the general public (with results posted within one year of study closing, as required).

Describe any potential psychosocial risks to subjects, such as psychological stress or confidentiality risks (including risk to reputation, economic risks, and legal risks).

This project poses minimal risk to participants, as it entails only 1) limited data collection (up to 5 semi-annual phone assessments with two possible 5-minute visits over 2 years for all enrollees, plus 3 brief (10 to 20 minute) treatment-initiated assessments for each of up to 4 rounds of treatment among those who elect to initiate treatment) and 2) minimal-risk, non-invasive informational and supportive interventions to promote smoking cessation and use of FDA-approved smoking treatments that meet or exceed the current standards of care.

The chief risks involved are loss of privacy and breach of confidentiality. Although we will take several steps to protect participant privacy (including, importantly, honoring patient requests not

to be contacted), we cannot guarantee that patients may not experience an invasion of privacy. Some patients may perceive tailored outreach letters from the health system (tailored on demographics such as sex and age, and on primary care provider and clinic) as violating privacy, for example. Likewise, we cannot guarantee the confidentiality of the information collected directly from participants. Although we will not collect sensitive data directly aside from asking about marijuana use, some data (i.e., substance use disorder diagnoses) may be included in deidentified extracted EHR data.

The outreach messages and motivational support given to participants in this project are unlikely to induce psychological distress, as they will be positive in tone and will focus on resources available to participants to support their efforts to change. The treatments provided are FDA-approved. The intensive pharmacotherapies will be administered only after patients are authorized by their PCPs to receive such treatment, patients provide oral informed consent for such treatment, and monitoring for adverse effects is in place. Providing breath samples for carbon monoxide and/or providing saliva or urine for cotinine/anabasine testing carries minimal risk, as these are minimally invasive procedures.

It is important to note that all patients will have access to evidence-based smoking cessation treatment at no cost (through their primary care provider and/or a quit line that offers evidence-based cessation treatment no cost to callers) and that receiving such treatment is not contingent on consenting to this study. It is also important to note that all patients will have the ability to decline or withdraw from the study and any study activities at any time. Risks associated with use of intensive treatments will be addressed by screening for contraindications prior to administering medications and by explaining these risks in the informed consent process for those who consent to such treatment. The risks associated with nicotine replacement distributed by a tobacco quit line or smoking cessation treatments provided by primary care providers will be addressed according to standard quit line or healthcare system protocols and procedures.

Describe how ALL the risks of the study will be minimized.

To protect against breach of confidentiality or violations of privacy, we will ensure that data are stored on secure, encrypted servers at all participating sites, and that transfer of data between clinics and the UW-CTRI research team are conducted via HIPAA-compliant means. Communication with patients via the MyChart patient portal will likewise be conducted in HIPAA-compliant ways that conform to healthcare system standards. 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 maintained by the data manager. 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. Data will be stripped of direct identifiers (limited datasets) or completely de-identified prior to sharing with others outside the IRB-approved research team.

To protect against violations of privacy, patients will first have the option to opt out of the program, at study launch and quarterly thereafter, at the clinic. Those who opt out will not receive a call from a Tobacco Care Manager for recruiting and offers of smoking cessation treatment. In addition, potentially sensitive information from the EHR (e.g., depression or substance use status) will not be used to tailor automated outreach letters among those who consent to participation in this study. Only demographic and care team information will be used for tailoring and personalization.

If, in the course of the study, participants reveal important clinical information to their Tobacco Care Manager (e.g., during motivational intervention calls), the Care Manager, who will be an employee of the healthcare system, will be able to communicate directly with the patient's

primary care team (e.g., if a patient notes that they are coughing up blood) via the EHR and will advise the patient to seek care from their care team or emergency care, as appropriate.

Routine adverse event assessment will not occur in this study, except in the context of smoking cessation treatment episodes, given the minimal and informational nature of the health system reach interventions and research assessments. Adverse events that occur during smoking cessation treatment will be assessed during post-quit-day follow-ups (3, 12, and 26 weeks post-quit day). Adverse events reported by patients will be assessed fully and reported to the IRB, the host healthcare system, and if appropriate (i.e., if serious or necessitating a change in the protocol) to the study sponsor and FDA, in a timely manner, as specified by pertinent guidelines and regulations.

To minimize adverse events, study medications will be administered only to those who meet eligibility criteria at the time they request treatment and set a quit day in the next 30 days. In addition, study medications will be dispensed in a manner fully consistent with product labels, clear patient instructions will be provided, and standard dosing regimens will be used. Patients who elect to use combination NRT (nicotine patch + mini-lozenges) and who smoke 5-9 cigarettes per day will receive a lower dose regimen of nicotine patches (14-mg for 10 weeks, 7-mg for 2 weeks) than those who smoke 10 or more cigarettes per day (21-mg for 8 weeks, 14-mg for 2 weeks, 7-mg for 2 weeks). Those who smoke fewer than 5 cigarettes per day will not have access to combination NRT at all. The nicotine mini-lozenge dose dispensed to participants who initiate C-NRT will be the lower, 2-mg, dose to minimize side effects of mini-lozenge use. Mini-lozenge use frequency recommendations will also follow labeling (1 mini-lozenge every 1-2 hours for 6 weeks, every 2-4 hours for 3 weeks, and every 4-8 hours for 3 weeks). Varenicline will be dispensed in 1-week packs (rather than as loose pills) to facilitate proper dosing and will start with 0.5 mg per day for 3 days, 0.5 mg twice per day (8 hours apart) for 4 days, and then 1 mg twice per day for the following 11 weeks.

Participants will be alerted to possible withdrawal effects in the mailed welcome packet sent after enrollment and again at the time they consent to smoking cessation treatment (among those who request such treatment during the 2 year study) and will be offered medication to manage these symptoms (if medically eligible), and will be advised that these symptoms are typically mild and temporary. Both Wisconsin Tobacco Quit Line counseling and the counseling delivered by UW-CTRI Health Counselors in the intensive treatment condition address ways to manage withdrawal.

Explain why the risks to the subjects are reasonable in relation to the anticipated benefits.

This study carries minimal risk. None of the reach-focused interventions to be deployed poses significant risk above and beyond standard treatment and every participant will be offered access to at least one form of evidence-based smoking cessation treatment. Those who receive FDA-approved medication in the course of the study will be screened for contraindications and will provide consent for treatment prior to medication dispensing (even at the Wisconsin Tobacco Quit Line). No information about illegal behavior except for marijuana use will be entered in databases. The risk of someone's identity becoming known to unauthorized persons is low. This risk is outweighed by the benefits of quitting smoking for any individual, and the benefit to society of having fewer people use tobacco products. This research has the potential to benefit smokers in the future by helping to identify optimal combinations of remotely delivered interventions to promote use of smoking cessation treatments for broader dissemination. The proposed project will accelerate refinement of treatments with broad reach and low barriers to access using an efficient factorial research design. The risks associated with the use of nicotine replacement therapy and varenicline are minor relative to the risks of continued smoking ,

particularly with careful medication eligibility screening as proposed here. If successful, this treatment approach could be used more broadly to reduce the considerable financial and personal costs associated with smoking-related disease. Therefore, the potential gain in knowledge regarding treatments and mechanisms of change associated with the proposed study outweigh the risks of participation.

Describe the provisions in place to identify and address unanticipated problems or complications.

The Project Lead and Principal Investigators (PIs) will be responsible for routinely monitoring study progress. UW-CTRI has an adverse event monitoring protocol and team in place and will alert the study Project Lead and PIs to adverse events among study participants who receive smoking cessation treatment. Any data safety concerns will be reported to the Project Lead and PIs immediately and addressed. We will report any unanticipated problems to the IRB according to posted guidelines. A full data safety and monitoring plan is included at the end of this protocol.

Describe the precautions that will be used to ensure subject *privacy* is protected

Collection of sensitive information about subjects will be limited to the amount necessary to achieve the aims of the research. Participants will not be asked to disclose any information about illegal behavior except for marijuana use.

Describe the measures that will be implemented by your research team to safeguard the identifiable subject information from unauthorized use or disclosure for both paper and electronic forms of information. Include how and where data will be stored.

Participant study data will be collected by Tobacco Care Managers and 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 (either a secure FTP site or a secure interface to the EHR). A Certificate of Confidentiality will be issued for the study.

Required patient identifying data will be stored in a separate file linked to all study data via a study identifier. Confidentiality of participant data and information will be accomplished by using participant numbers as unique identifiers, allowing us to keep participant data separate from identifying information. At UW-CTRI, data generated through study participation and data obtained from the EHR or the quit line (with patient consent) will be stored in secure databases under protections and procedures consistent with the guidelines and regulations of the UW School of Medicine and Public Health (UW-SMPH). Outside access is available only via an encrypted connection to the Department of Medicine Citrix server located at the UW Clinical Science Center in Madison. The servers at the UW-CTRI Madison office are physically secured in a locked room. Data backups are created nightly and stored in a locked safe. Significant safeguards have been implemented to protect data including virus and adware protection, firewall, access controls and encryption when appropriate such as wireless and remote access. All UW-CTRI staff members have completed HIPAA and human subjects training and are aware of the sensitivity of study-related data. The UW SMPH has developed school-wide data security policies and procedures. UW-CTRI data security policies and procedures conform to those of the SMPH. UW-CTRI will use an enterprise-level REDCap database that supports audit trails such as access, change logging, and more sophisticated access control for managing and tracking user access privileges. No publications or presentations resulting from this research program will contain any identifying information about individual participants. Following cleaning

and verification of data at the conclusion of the study, all research data will be placed in a de-identified data set at UW-CTRI.

Data Safety and Monitoring Plan

The Data Safety and Monitoring Plan (DSMP) covers all research activities in this proposed project. All investigators must agree to comply with the procedures outlined in this DSMP. This DSMP does not reduce any investigator's obligation to comply with the requirements of the Institutional Review Board (IRB) at his/her home institution or the IRB of any collaborating organizations.

Monitoring the progress of trials and the safety of participants. The Principal Investigator (McCarthy) is responsible for routine monitoring of study progress. This includes scheduled meetings with study staff and healthcare system Tobacco Care Managers and their supervisors (weekly during the first 2 months of the study, and monthly thereafter); review of deidentified, aggregate reports on: patient referral and opt-out rates from clinics, enrollment rates for this project, rates of and reasons for ineligibility or declines, accrual rates in both the experimental and standard-care-only samples, and rates of allocation to experimental conditions by clinic, sex, and eligibility for intensive treatment (to ensure the randomization scheme is coordinated and balanced as intended). The PI will also routinely monitor Tobacco Care Manager patient contact rates, follow-up assessment completion rates and timeliness, rates of and reasons for patient withdrawal from the study, rates of outreach message acknowledgement/acceptance (e.g., rates of letters returned, secure EHR messages unopened), and rates of missing data in assessments. To verify that incentives are being delivered as intended, the PI will review monthly reports on UW-CTRI Health Counselor-delivered counseling session completion and quit line referral results (which note the number of counseling sessions completed), and compare these against incentive processing records. This will continue throughout the 33-month data collection period. Prior to and quarterly following the launch, the PI will review outreach materials produced for test patients to make sure that the content, format, and periodicity of these tailored outreach materials are implemented as intended. Similar testing with Tobacco Care Manager outreach for care management purposes will occur quarterly following launch to promote fidelity to the care management protocol and to address drift that may occur over time. The PI will troubleshoot difficulties in this area with the Tobacco Care Managers and their supervisors, as needed. In addition, the PI will monitor incoming follow-up data to ensure that assessors are capturing this data as fully and accurately as possible, and to troubleshoot problems with the data collection instruments or procedures, as needed. As such, the PI will implement routine monitoring procedures to assess progress and fidelity in terms of recruitment, retention, randomization, intervention delivery fidelity, and follow-up. In addition, the PL (a licensed Clinical Psychologist) will review all incoming adverse events no less than weekly, and will evaluate and address serious adverse events within 24 hours, in consultation with the PI (a Physician).

To facilitate participant safety, all study participants will receive no less than access to standard of care smoking cessation care. Those who do not meet eligibility criteria for enhanced pharmacotherapy (combination NRT or varenicline) or do not consent to such treatments, will be referred to a quit line that administers evidence-based cessation counseling and NRT monotherapy. State and national quit lines have standing protocols for screening for medical contraindications for nicotine replacement therapy. The Wisconsin Tobacco Quit Line screens for pregnancy; recent heart attack, stroke, or transient-ischemic-attack; rapid/irregular heartbeat requiring lifestyle modification or medication; severe or worsening angina; and past negative reactions to NRT, and has a standard protocol for addressing adverse events. Those who initiate intensive C-NRT or varenicline treatment (which is subject to primary care provider review) will be counseled in proper use of the medication, monitored for adverse events, and

advised to reduce or stop medication if treatment-related adverse events occur. Any adverse events reported during contact with a Tobacco Care Manager or during follow-up assessments will be fully assessed, addressed, and reported promptly to the PL and PIs, and, if study-related, to the DSMB, the IRB, and, if serious or necessitating protocol changes, NCI. Should either excessive risk to study participants and/or convincing evidence of lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit. When taking that step, the investigators will consult with the IRB and NCI.

Plans for assuring compliance with requirements regarding the reporting of adverse events. This DSMP requires that investigators 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 come to light 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. These 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 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. The PL and PIs have 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.

Plans for assuring that any action resulting in a temporary or permanent suspension of an NIH-funded clinical trial is reported to the NIH grant program director responsible for the grant. The NIH grant program director will be notified within 5 days if the PI deems it necessary to suspend the clinical trial. In the case of a temporary suspension, the PI and PL will develop a plan for continuation of the study and discuss this plan with the NIH grant program director in a reasonable time frame.

Plans for assuring data accuracy and confidentiality and protocol compliance. The PI will develop and implement protocols for assuring UW-CTRI data collection accuracy and protocol compliance, with the support of the Administrative and Data Analysis Cores. Study protocols will include data verification and protocol compliance checks. The PI will also be responsible for ensuring that the data for the project are securely transferred from participating healthcare systems 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 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 the presence of 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, the UW-CTRI and the 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 the data systems described in the proposal 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 PIs and UW-CTRI IT Manager. To further protect confidentiality, only the UW-CTRI IT Manager will be permitted to transmit data to the SFTP server. Finally, the Department of Medicine employs extensive data backup and server redundancy procedures and performs full backups to tape weekly of all servers, along with incremental and daily backups.

Data and Safety Monitoring Committee. In addition to the protections outlined in the DSMP (above), all research activities conforming to the NIH definition of a clinical trial will also have an independent Data Safety and Monitoring Committee (DSMC). This application includes a Phase III clinical trial using communication and motivation strategies with strong theoretical rationales and promising empirical support in human research, and offering FDA-approved smoking cessation therapies prescribed in a manner consistent with FDA-approved labeling. The DSMP specifies overall monitoring that will be conducted by the PI, including timely reporting of AEs and SAEs. Every 6 months, the DSMC will convene to review the overall safety data, as well as data on safety summarized by treatment condition. As per NIH guidelines, the objective of these reviews will be to determine whether continued conduct of the trial poses any undue risk for participants.

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 this project's research activities. Dr. Cleary is joined on the DSMC by Dr. James Sosman and Dr. Burke Richmond. Dr. Sosman is Associate Professor of Medicine and Medical Director of the HIV/AIDS Comprehensive Care Program at UW Hospital and Clinics who has previously collaborated on a clinical trial of smoking cessation with UW-CTRI. Dr. Richmond is an otolaryngologist who has served on independent DSMCs for Phase II and III trials involving a nicotine vaccine. Neither has direct involvement with any of the proposed research. The PI will report to the DSMC; the three DSMC members will be unblinded as to treatment conditions and will make the final determinations as to study continuation.

References

1. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults - United States, 2005-2015. *MMWR Morb Mortal Wkly Rep.* 2016;65(44):1205-1211.
2. Fiore MC, Jaen CR, Baker TB, et al. *Treating tobacco use and dependence: 2008 update.* Rockville, MD: U.S. Department of Health and Human Services, U.S. Public Health Service; 2008.
3. Danesh D, Paskett ED, Ferketich AK. Disparities in receipt of advice to quit smoking from health care providers: 2010 National Health Interview Survey. *Prev Chronic Dis.* 2014;11:E131.
4. Borland R, Li L, Driezen P, et al. Cessation assistance reported by smokers in 15 countries participating in the International Tobacco Control (ITC) policy evaluation surveys. *Addiction.* 2012;107(1):197-205.
5. Keith DR, Stanton CA, Gaalema DE, et al. Disparities in US healthcare provider screening and advice for cessation across chronic medical conditions and tobacco products. *J Gen Intern Med.* 2017;32(9):974-980.
6. Papadakis S, Gharib M, Hambleton J, Reid RD, Assi R, Pipe AL. Delivering evidence-based smoking cessation treatment in primary care practice: experience of Ontario family health teams. *Can Fam Physician.* 2014;60(7):e362-371.
7. Aquilino ML, Farris KB, Zillich AJ, Lowe JB. Smoking-cessation services in Iowa community pharmacies. *Pharmacotherapy.* 2003;23(5):666-673.
8. Braun BL, Fowles JB, Solberg LI, Kind EA, Lando H, Pine D. Smoking-related attitudes and clinical practices of medical personnel in Minnesota. *Am J Prev Med.* 2004;27(4):316-322.
9. Jamal A, Dube SR, Malarcher AM, Shaw L, Engstrom MC. Tobacco use screening and counseling during physician office visits among adults--National Ambulatory Medical Care Survey and National Health Interview Survey, United States, 2005-2009. *MMWR.* 2012;61 Suppl:38-45.
10. Conroy MB, Majchrzak NE, Silverman CB, et al. Measuring provider adherence to tobacco treatment guidelines: a comparison of electronic medical record review, patient survey, and provider survey. *Nicotine Tob Res.* 2005;7 Suppl 1:S35-43.
11. Park ER, Gareen IF, Japuntich S, et al. Primary care provider-delivered smoking cessation interventions and smoking cessation among participants in the National Lung Screening Trial. *JAMA Intern Med.* 2015;175(9):1509-1516.
12. Curry SJ, Orleans CT, Keller P, Fiore M. Promoting smoking cessation in the healthcare environment: 10 years later. *Am J Prev Med.* 2006;31(3):269-272.
13. Thorndike AN, Regan S, Rigotti NA. The treatment of smoking by US physicians during ambulatory visits: 1994 2003. *Am J Public Health.* 2007;97(10):1878-1883.
14. McIlvain HE, Backer EL, Crabtree BF, Lacy N. Physician attitudes and the use of office-based activities for tobacco control. *Fam Med.* 2002;34(2):114-119.
15. Schnoll RA, Rukstalis M, Wileyto EP, Shields AE. Smoking cessation treatment by primary care physicians: An update and call for training. *Am J Prev Med.* 2006;31(3):233-239.
16. Ferketich AK, Khan Y, Wewers ME. Are physicians asking about tobacco use and assisting with cessation? Results from the 2001-2004 national ambulatory medical care survey (NAMCS). *Prev Med.* 2006;43(6):472-476.
17. Quinn VP, Hollis JF, Smith KS, et al. Effectiveness of the 5-As tobacco cessation treatments in nine HMOs. *J Gen Intern Med.* 2009;24(2):149-154.

18. Joseph AM, Fu SS, Lindgren B, et al. Chronic disease management for tobacco dependence: a randomized, controlled trial. *Arch Intern Med.* 2011;171(21):1894-1900.
19. Ellerbeck EF, Mahnken JD, Cupertino AP, et al. Effect of varying levels of disease management on smoking cessation: a randomized trial. *Ann Intern Med.* 2009;150(7):437-446.
20. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting Smoking Among Adults - United States, 2000-2015. *MMWR Morb Mortal Wkly Rep.* 2017;65(52):1457-1464.
21. Elliott WJ. The economic impact of hypertension. *J Clin Hypertens (Greenwich).* 2003;5(3 Suppl 2):3-13.
22. Agency for Health Care Research and Quality. Expenditures for hypertension among adults age 18 and older, 2010: estimates for the U.S. civilian noninstitutionalized population. 2013. https://meps.ahrq.gov/data_files/publications/st404/stat404.shtml. Accessed 21 Sep 2017.
23. NCD Risk Factor Collaboration. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet.* 2016;387(10027):1513-1530.
24. Bernstein SL, Yu S, Post LA, Dziura J, Rigotti NA. Undertreatment of tobacco use relative to other chronic conditions. *Am J Public Health.* 2013;103(8):e59-65.
25. Papadakis S, McDonald P, Mullen KA, Reid R, Skulsky K, Pipe A. Strategies to increase the delivery of smoking cessation treatments in primary care settings: a systematic review and meta-analysis. *Prev Med.* 2010;51(3-4):199-213.
26. Bandi P, Cokkinides VE, Virgo KS, Ward EM. The receipt and utilization of effective clinical smoking cessation services in subgroups of the insured and uninsured populations in the USA. *J Behav Health Serv Res.* 2012;39(2):202-213.
27. Smith SS, Keller PA, Kobinsky KH, et al. Enhancing tobacco quitline effectiveness: identifying a superior pharmacotherapy adjuvant. *Nicotine Tob Res.* 2013;15(3):718-728.
28. Adsit RT, Fox BM, Tsiolis T, et al. Using the electronic health record to connect primary care patients to evidence-based telephonic tobacco quitline services: a closed-loop demonstration project. *Transl Behav Med.* 2014;4(3):324-332.
29. Thomas D, Abramson MJ, Bonevski B, George J. System change interventions for smoking cessation. *Cochrane Database Syst Rev.* 2017;2:CD010742.
30. Mena JA, Ampadu GG, Prochaska JO. The influence of engagement and satisfaction on smoking cessation interventions: a qualitative study. *Subst Use Misuse.* 2017;52(3):322-331.
31. Campbell KA, Cooper S, Fahy SJ, et al. 'Opt-out' referrals after identifying pregnant smokers using exhaled air carbon monoxide: impact on engagement with smoking cessation support. *Tob Control.* 2017;26(3):300-306.
32. Piper ME, Baker TB, Mermelstein R, et al. Recruiting and engaging smokers in treatment in a primary care setting: developing a chronic care model implemented through a modified electronic health record. *Transl Behav Med.* 2013;3(3):253-263.
33. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA.* 2002;288(22):2836-2845.
34. Gilbody S, Whitty P, Grimshaw J, Thomas R. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *JAMA.* 2003;289(23):3145-3151.
35. Renders CM, Valk GD, Griffin S, Wagner EH, Eijk JT, Assendelft WJ. Interventions to improve the management of diabetes mellitus in primary care, outpatient and community settings. *Cochrane Database Syst Rev.* 2001(1):CD001481.

36. Skov-Ettrup LS, Dalum P, Bech M, Tolstrup JS. The effectiveness of telephone counselling and internet- and text-message-based support for smoking cessation: results from a randomized controlled trial. *Addiction.* 2016;111(7):1257-1266.
37. Graham AL, Papandonatos GD, Cobb CO, et al. Internet and telephone treatment for smoking cessation: mediators and moderators of short-term abstinence. *Nicotine Tob Res.* 2015;17(3):299-308.
38. McGrath CA, Zak CL, Baldwin K, Lutfiyya MN. Smoking cessation in primary care: implementation of a proactive telephone intervention. *J Am Assoc Nurse Pract.* 2014;26(5):248-254.
39. Richter KP, Faseru B, Shireman TI, et al. Warm handoff versus fax referral for lnking hospitalized smokers to quitlines. *Am J Prev Med.* 2016;51(4):587-596.
40. Papadakis S, Tulloch HE, Gharib M, Pipe AL. Profile of tobacco users identified in primary care practice and predictors of readiness to quit: a cross-sectional survey. *CMAJ Open.* 2016;4(1):E41-47.
41. Richter KP, Ellerbeck EF. It's time to change the default for tobacco treatment. *Addiction.* 2015;110(3):381-386.
42. Anthenelli RM, Benowitz NL, West R, St Aubin L, McRae T, Lawrence D, Ascher J, Russ C, Krishen A, Evins AE. Neuropsychiatric safety and efficacy of varenicline, bupropion, and nicotine patch in smokers with and without psychiatric disorders (EAGLES): a double-blind, randomised, placebo-controlled clinical trial. The Lancet. 2016 Jun 18;387(10037):2507-20.
43. Evins AE, Benowitz NL, West R, Russ C, McRae T, Lawrence D, Krishen A, St Aubin L, Maravic MC, Anthenelli RM. Neuropsychiatric Safety and Efficacy of Varenicline, Bupropion, and Nicotine Patch in Smokers With Psychotic, Anxiety, and Mood Disorders in the EAGLES Trial. Journal of clinical psychopharmacology. 2019 Mar 1;39(2):108-16.
44. Baker TB, Piper ME, Stein JH, et al. Effects of Nicotine Patch vs Varenicline vs Combination Nicotine Replacement Therapy on Smoking Cessation at 26 Weeks: A Randomized Clinical Trial. *JAMA*. 2016;315(4):371–379. doi:10.1001/jama.2015.19284
45. Baker TB, Fraser DL, Kobinsky K, et al. A randomized controlled trial of financial incentives to low income pregnant women to engage in smoking cessation treatment: Effects on post-birth abstinence. *J Consult Clin Psychol.* 2018;86(5):464-473.
46. Fraser DL, Fiore MC, Kobinsky K, et al. A randomized trial of incentives for smoking treatment in Medicaid members. *Am J Prev Med.* 2017;53(6):754-763.
47. Ku L, Bruen BK, Steinmetz E, Bysshe T. Medicaid tobacco cessation: big gaps remain in efforts to get smokers to quit. *Health Aff (Millwood).* 2016;35(1):62-70.
48. Bradley CJ, Neumark D. Small cash incentives can encourage primary care visits by low-income people with new health care coverage. *Health Aff (Millwood).* 2017;36(8):1376-1384.
49. McAfee T, Babb S, McNabb S, Fiore MC. Helping smokers quit--opportunities created by the Affordable Care Act. *N Engl J Med.* 2015;372(1):5-7.
50. Sherman SE, Takahashi N, Kalra P, et al. Care coordination to increase referrals to smoking cessation telephone counseling: a demonstration project. *Am J Manag Care.* 2008;14(3):141-148.
51. Hammett P, Fu SS, Nelson D, et al. A proactive smoking cessation intervention for socioeconomically disadvantaged smokers: the role of smoking-related stigma. *Nicotine Tob Res.* 2017.
52. Fu SS, van Ryn M, Sherman SE, et al. Proactive tobacco treatment and population-level cessation: a pragmatic randomized clinical trial. *JAMA Intern Med.* 2014;174(5):671-677.

53. Cupertino AP, Mahnken JD, Richter K, et al. Long-term engagement in smoking cessation counseling among rural smokers. *J Health Care Poor Underserved.* 2007;18(4 Suppl):39-51.
54. Cummins SE, Bailey L, Campbell S, Koon-Kirby C, Zhu SH. Tobacco cessation quitlines in North America: a descriptive study. *Tob Control.* 2007;16 Suppl 1:i9-15.
55. Kahende J, Malarcher A, England L, et al. Utilization of smoking cessation medication benefits among medicaid fee-for-service enrollees 1999-2008. *PLoS One.* 2017;12(2):e0170381.
56. Centers for Disease Control and Prevention. Quitting smoking among adults - United States 2001-2010. *MMWR.* 2011;60(44):1513-1519.
57. de Vries H, Kremers SP, Smeets T, Brug J, Eijmael K. The effectiveness of tailored feedback and action plans in an intervention addressing multiple health behaviors. *Am J Health Promot.* 2008;22(6):417-425.
58. Strecher VJ. Computer-tailored smoking cessation materials: a review and discussion. *Patient Educ Couns.* 1999;36(2):107-117.
59. Abroms LC, Ahuja M, Kodl Y, et al. Text2Quit: results from a pilot test of a personalized, interactive mobile health smoking cessation program. *J Health Commun.* 2012;17 Suppl 1:44-53.
60. Balmford J, Borland R, Benda P. Patterns of use of an automated interactive personalized coaching program for smoking cessation. *J Med Internet Res.* 2008;10(5):e54.
61. Borland R, Balmford J, Segan C, Livingston P, Owen N. The effectiveness of personalized smoking cessation strategies for callers to a Quitline service. *Addiction.* 2003;98(6):837-846.
62. Strecher VJ, McClure JB, Alexander GL, et al. Web-based smoking-cessation programs: results of a randomized trial. *Am J Prev Med.* 2008;34(5):373-381.
63. Bodenheimer T, Wagner EH, Grumbach K. Improving primary care for patients with chronic illness: the chronic care model, Part 2. *JAMA.* 2002;288(15):1909-1914.
64. Burke MV, Ebbert JO, Schroeder DR, McFadden DD, Hays JT. Treatment outcomes from a specialist model for treating tobacco use disorder in a medical center. *Medicine (Baltimore).* 2015;94(44):e1903.
65. Sheffer CE, Payne T, Ostroff JS, Jolicoeur D. Increasing the quality and availability of evidence-based treatment for tobacco dependence through unified certification of tobacco treatment specialists. *J Smoking Cessation.* 2014;11(4):229-235.
66. Bock BC, Papandonatos GD, de Dios MA, et al. Tobacco cessation among low-income smokers: motivational enhancement and nicotine patch treatment. *Nicotine Tob Res.* 2014;16(4):413-422.
67. Stapleton JA, West R. A direct method and ICER tables for the estimation of the cost-effectiveness of smoking cessation interventions in general populations: application to a new cytisine trial and other examples. *Nicotine Tob Res.* 2012;14(4):463-471.
68. Chen S, Zhao H. Estimating incremental cost-effectiveness ratios and their confidence intervals with different terminating events for survival time and costs. *Biostatistics.* 2013;14(3):422-432.
69. Caponnetto P, Keller E, Bruno CM, Polosa R. Handling relapse in smoking cessation: strategies and recommendations. *Intern Emerg Med.* 2013;8(1):7-12.
70. O'Hagan A, Stevenson M, Madan J. Monte Carlo probabilistic sensitivity analysis for patient level simulation models: efficient estimation of mean and variance using ANOVA. *Health Econ.* 2007;16(10):1009-1023.
71. Claxton K, Sculpher M, McCabe C, et al. Probabilistic sensitivity analysis for NICE technology assessment: not an optional extra. *Health Econ.* 2005;14(4):339-347.

72. Bilinski A, Neumann P, Cohen J, Thorat T, McDaniel K, Salomon JA. When cost-effective interventions are unaffordable: Integrating cost-effectiveness and budget impact in priority setting for global health programs. *PLoS Med.* 2017;14(10):e1002397.
73. Smith PH, Bessette AJ, Weinberger AH, Sheffer CE, McKee SA. Sex/gender differences in smoking cessation: A review. *Prev Med.* 2016;92:135-140.
74. Smith PH, Kasza KA, Hyland A, et al. Gender differences in medication use and cigarette smoking cessation: results from the International Tobacco Control Four Country Survey. *Nicotine Tob Res.* 2015;17(4):463-472.
75. Allen AM, Oncken C, Hatsukami D. Women and smoking: the effect of gender on the epidemiology, health effects, and cessation of smoking. *Current addiction reports.* 2014;1(1):53-60.
76. Kehlet M, Schroeder TV, Tonnesen H. The Gold Standard Program for smoking cessation is effective for participants over 60 years of age. *Int J Environ Res Public Health.* 2015;12(3):2574-2587.
77. Hastings SN, Whitson HE, Sloane R, Landerman LR, Horney C, Johnson KS. Using the past to predict the future: latent class analysis of patterns of health service use of older adults in the emergency department. *J Am Geriatr Soc.* 2014;62(4):711-715.