Study Protocol and Statistical Analysis Plan

Study Title: Breathe 2 Project 3: Comprehensive Chronic Care

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Title: Research Plan and Protocol: Breathe 2 Project 3: Comprehensive Chronic Care

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	7/8/2022	Revisions to cessation treatment attempt dose levels and minor editorial updates.	N
2	8/19/2022	Addition of annual post-cards, new cannabis assessment, revisions to biochemical abstinence assessments	Y
3	11/2/2022	Update inclusion criteria	Y
4	3/22/2023	Addition of text/email communications, and follow up assessment via online	N

5	5/2/2023	Change in PI from Dr. Fiore to Dr. Cook	Y
6	7/19/2023	Replace breath and urine testing with saliva cotinine testing	Y
7	10/12/2023	Add anabasine result to saliva cotinine testing	N

A. STUDY SUMMARY

Study Title	Breathe 2 Project 3: Comprehensive Chronic Care
Brief Summary	This study will address gaps in smoking treatment by comparing Standard Care (SC) with Comprehensive Chronic Care (CCC), a healthcare treatment approach designed to increase smoking treatment engagement and abstinence among primary care patients who smoke. This research will compare SC and CCC on criteria that are of great clinical and public health importance: long-term abstinence (primary outcome), treatment reach, and cost-effectiveness. Participation in the study will last 18 months (21 months maximum, if the person is not reached immediately for the final 18-month post-enrollment telephone follow-up).
Number of study sites	2 (UW Health and AdvocateAurora Health)
Study Design	This project is a 2-arm RCT
Primary Objective	**Aim 1:** To determine whether Comprehensive Chronic Care (CCC), relative to Standard Care (SC), significantly improves biochemically confirmed 7-day point-prevalence smoking abstinence at 18 months post-enrollment.
Secondary Objective(s)	**Aim 2:** To determine the effects of CCC relative to SC on: cost-effectiveness and 7-day point-prevalence smoking abstinence at 6- and 12-months (biochemically confirmed) post-enrollment. **Aim 3:** To compare CCC with SC on cessation treatment use over 18 months of treatment access.
Research Intervention(s)/ Investigational Agent(s)	Comprehensive Chronic Care (CCC) provides ongoing proactive outreach designed to provide support and information about evidence-based smoking treatment, with access to individually validated treatments that are appropriate for patients who are: 1) unwilling quit but willing

	to reduce; 2) ready to quit; and 3) recovering from an unsuccessful quit attempt. Standard Care (SC) involves one offer of cessation treatment (8 weeks of nicotine patch plus referral to the tobacco quit line).
Drugs/devices used on study (including any IND/IDE #)	Standard of Care nicotine patch and/or nicotine mini-lozenge will be available to participants who are medically eligible and who are interested in using during treatment for smoking cessation or reduction. The effectiveness of these standard of care agents is not being tested.
Study Population	Primary care patients who smoking cigarettes
Sample Size	N=1000
Study Duration for individual participants	Participation in the study will last 18 months (21 months maximum, if the person is not reached immediately for the final 18-month post-enrollment telephone follow-up).
Study Specific Abbreviations/ Definitions	Comprehensive Chronic Care (CCC) Standard Care (SC) Care Manager (CM) Center for Tobacco Research and Intervention (CTRI)

This project, Breathe 2, is a 2-arm RCT designed to evaluate whether Comprehensive Chronic Care, relative to Standard Care, increases smoking abstinence and treatment use in primary care patients who smoke. Adult patients who smoke daily at the time of enrollment will be eligible to participate, with no obligation to quit smoking or use treatment. Participants (*N*=1000) will be recruited in 8-14 primary care clinics in 2 healthcare systems by healthcare system staff (Care Managers) using an opt-out strategy to maximize inclusion and enhance the generalizability of the results. Participants who enter the study will be randomized to one of two treatments: 1) Comprehensive Chronic Care; CCC (*n*=600); or 2) Standard Care; SC (*n*=400). Those randomized to CCC will receive ongoing smoking treatment offers via the following routes: 1) Four Outreach Calls at 4, 8, 12, and 14 months post-study enrollment; and 2) Four texts and/or mailings over 14 months. These outreach contacts will offer cessation treatment for those interested in quitting (4 weeks pre-quit day + 12 weeks of post-quit day treatment) or smoking reduction treatment for those not ready to quit but willing to reduce their smoking (8 weeks of smoking reduction treatment). All treatment will be provided by trained UW-CTRI Health Counselors. Those who enter cessation treatment will receive treatment initiated assessment calls from UW-CTRI staff at 8- and 12-weeks following the target-quit day to evaluate smoking status. CCC participants who have an unsuccessful quit attempt will be encouraged to make a new quit attempt using cessation treatment provided by the study; those who decline additional cessation treatment will be offered reduction treatment. Participants

randomized to SC will receive one Outreach Call per year offering cessation treatment (8 weeks of nicotine patch and referral to Wisconsin Tobacco Quitline and/or Smokefree.txt). All participants can elect to engage in treatment (or not) at any time up to Month 14 of the 18-month study period. Participants in both groups may engage in treatment multiple times, consistent with good clinical care. In addition to a Baseline Assessment, all participants will complete Semi-Annual Follow-Up Assessments at Months 6, 12, and 18 post-study enrollment. The primary outcome is biochemically confirmed point-prevalence abstinence at 18 months post-enrollment. Secondary outcomes are: 7-day point-prevalence abstinence at months 6 and 12 post-enrollment, use of cessation treatment, and cost. Participation in the study will last 18 months (21 months maximum, if the person is not reached immediately for the final 18-month post-enrollment telephone follow-up). In addition, data on health status and healthcare utilization for all participants will be extracted from the EHR for up to 1-year pre-enrollment, and 4 years post-enrollment to inform economic analyses.

B. BACKGROUND

Smoking is the leading preventable cause of death and disease in the US[1]. Smoking cessation reduces the risk of cancer, cardiovascular disease, and stroke[2,3]. About 50-60% of persons who smoke will die prematurely of a smoking-related illness[4] if they don't quit. This makes the reduction of smoking prevalence a key public health priority in the US. Healthcare visits offer a prime opportunity to connect patients with smoking treatment because most smokers (about 70%) visit a primary care clinician each year[5]. Unfortunately, the vast majority of healthcare visits do not result in patients engaging in evidence-based treatment for their smoking[5, 6]. One reason for this is that cessation treatment is rarely offered in healthcare settings (<40% of patients report the being offered assistance quitting smoking, <15% report being offered follow-up for smoking by their primary care provider [5,7]). Even when cessation treatment is offered, patients rarely use it because most smokers (70-90%) are not ready to quit in the near future (e.g., [8]).

Research suggests that smoking treatment would be more effective if it comprised multiple *well validated* approaches to smoking treatment. First, these include smoking reduction treatment for those not ready to quit; such treatment increases both smoking treatment reach and abstinence rates in primary care patients[8,9]. Second, tobacco smoking is a chronic, relapsing condition: most individuals trying to quit smoking ultimately relapse[10,11]. Therefore, an optimal treatment would involve chronic care approaches that follow-up with individuals in order to encourage treatment re-engagement[12,13]. Otherwise, many individuals who use cessation treatment relapse and then disengage from treatment for months or years. Third, smoking treatment in primary care is typically offered to those making healthcare visits. However, many patients rarely make clinic visits and the motivation to quit is highly labile so that the treatment offer and the inclination to accept are not aligned. Therefore, repeated proactive outreach should be offered to engage or re-engage *all patients who smoke* in treatment that is appropriate for their current goals (i.e., reducing, quitting, recovering from relapse[14]). While all of these elements have been shown to be effective, they have never been integrated and their combined effects rigorously evaluated in a healthcare population and compared with standard care.

This study will address gaps in smoking treatment by comparing Standard Care (SC) with Comprehensive Chronic Care (CCC), a healthcare treatment approach designed to increase treatment engagement and abstinence among primary care patients who smoke. CCC provides ongoing proactive outreach designed to provide support and information about evidence-based smoking treatment, with facilitated access to individually validated treatments that are

appropriate for patients who are: 1) unwilling quit but willing to reduce; 2) ready to quit; and 3) recovering from an unsuccessful quit attempt. This research will compare SC (offer of cessation treatment once per year) and CCC on criteria that are of great clinical and public health importance: long-term abstinence (primary outcome), treatment reach, and cost-effectiveness.

C. STUDY OBJECTIVES AND ENDPOINS

This project is a 2-arm RCT designed to evaluate whether Comprehensive Chronic Care (CCC), relative to Standard Care (SC), increases smoking abstinence and treatment use in primary care patients who smoke. The aims are as follows:

Primary Aim

Aim 1: To determine whether Comprehensive Chronic Care (CCC), relative to Standard Care (SC), significantly improves biochemically confirmed 7-day point-prevalence smoking abstinence at 18 months post-enrollment.

Secondary Aims

Aim 2: To determine the effects of CCC relative to SC on: cost-effectiveness and 7-day point-prevalence smoking abstinence at 6- and 12-months (biochemically confirmed) post-enrollment.

Aim 3: To compare CCC with SC on cessation treatment use over 18 months of treatment access.

D. RECRUITMENT PROCEDURES

Participants (N=1000) will be patients from 8-14 large primary care clinics in two Wisconsin healthcare system that treat diverse populations of patients with a large percentage of smokers. UW Health is the integrated health system of the University of Wisconsin-Madison serving more than 600,000 patients each year in the Upper Midwest at six hospitals and more than 80 outpatient sites. Aurora Health Care (Aurora) is the largest healthcare delivery system in Wisconsin and serves ~1 million Wisconsin residents including Medicaid-eligible, commercially insured, and indigent patients in urban (e.g., Milwaukee) and suburban areas in eastern Wisconsin. We will continue enrolling within each health system until we reach our target enrollment (N=1000). However, we are using health system as a randomization variable to control for this variability in number of participants enrolled within each healthcare system.

All patients in the electronic health record (EHR) smoking registry for each participating clinic in the health systems will be notified that their clinic is offering information about treatment that can help people who smoke. The notification will be sent by mail just prior to the launch of recruitment in each clinic (see uploaded Clinic Launch Letter). This message lets patients know that tobacco care management is starting and that treatments for smoking are available for those who are interested in making changes to their smoking. Messaging will indicate that they will earn $40 for talking with a Care Manager to learn about smoking treatment resources in their clinic (including our study). They will be told that they do not need to enroll in the study or use any treatment to receive the $40. All study notifications will provide the name and number of a Care Manager to contact if interested in learning about the program, and the number to call to opt out of future Care Manager outreach. Patients in participating health clinics will also receive 2-4 annual postcards (depending on rate of study enrollment) reminding them that they can earn $40 for talking with a Care Manager about smoking treatment resources in their clinic (see uploaded recruitment postcard). 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.

Once the study has been launched at an adult primary care clinic, all clinic patients on the

smoking registry or who are identified as current cigarette smokers at clinic visits (whether face-to-face, or telemedicine visits) 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 patient requests to opt out in the EHR to suppress outreach at least until the next clinic visit or patient-initiated contact with the Care Manager. In addition, posters about Breathe 2 will be posted in participating clinics to encourage patients to talk to their primary care team about stop-smoking resources, including the Breathe 2 study.

Care Managers, who are healthcare system employees, will make at up to 5 phone call attempts to reach each patient who did not opt out, starting within 3 business days of the visit, at the patient telephone numbers in the EHR. When the Care Manager reaches a patient, s/he will explain that the healthcare system is reaching out to all patients who smoke to offer support and resources, including participation in the Breathe 2 study and that they will get $40 for listening to the treatment options and providing minimal information to allow us to provide payment. Care Mangers will then obtain oral consent to record the caller's identity and demographic information so that we can send the $40 payment. We must record who receives payment to reduce multiple claims. In addition, screening information for those who screen fail will be kept in a de-identifed form after the recruitment period to permit comparison between those who enter the study versus those who do not. We plan to keep screening information in an identifiable form through the end of the recruitment period (only while recruitment is ongoing) so that we can identify patients referred to the study more than once. This will permit evaluation of whether someone changes their screening answers, increasing safety of the trial. Once the recruitment period is over, we will de-identify screening data so we can assess the representativeness of those enrolled in the study relative to those not included in the study.

Patients who are interested in treatment from the clinic or the Wisconsin Tobacco Quit Line (WTQL) or state-appropriate quit line will be given the appropriate referrals. Patients who are interested in the Breathe 2 study will be given a brief description of this study and invited to complete a brief screening for the study (See uploaded Recruitment Call Script) to determine study eligibility. Please note that being medically eligible to use study medication is *not* required for study entry. Participants will be screened for medication eligibly if they elect to enter treatment. Participants who are not medically eligible to use study medications can still receive counseling as part of study treatment.

E. INCLUSION AND EXLUSION CRITERIA FOR STUDY PARTICIPATION

Inclusion criteria:

- Age 18 years or older
- On smoking registry at a participating clinic OR report current smoking at a clinic visit
- 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:

- Activated healthcare power of attorney or cognitive impairment that would preclude informed consent.

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

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

F. SPECIAL POPULATIONS

Study outreach, treatment provision, and assessment will be suspended during a participant's period of incarceration. However, we will not exclude 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). In addition, 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. 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 interventions, assessments, and compensation schedule should pose no more risk for those on parole or probation or those in institutionalized settings than for the general population as study procedures confer minimal risk and are entirely voluntary.

G. CONSENT

Those who pass the screening for the inclusion/exclusion criteria for study participation will be asked to complete an oral consent and HIPAA authorization process. During this process, the Care Manager will use the Study Information Sheet to guide discussion with prospective participants about all elements of elements of informed consent (see uploaded Oral Consent Procedures and Study Information Sheet). The discussion will involve 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 documented electronically in a REDCap database. Following enrollment for those who consent, study staff will send out a letter to the participant at the address provided that 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 (see Study Information Sheet).

This study involves remote outreach and treatment access, and interventions that offer minimal-risk (i.e., standard of care smoking treatments). Given these factors, an oral consent process is necessary for protecting 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 that one 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 and smoking treatment interventions that offer standard of care smoking treatment. We will, however, supplement the oral process with written documents. A Study Information Sheet will be mailed or emailed (participant's choice) to enrollees after they provide oral consent. If the patient requests written information about the study prior to the consent process, the Study Information form will be mailed or emailed to the patient, and an additional phone call will be scheduled for study consent.

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 the requirement of written consent and HIPAA authorization. Consent and HIPAA authorization procedures will be done 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 Study Information Sheet that will be mailed to the participant following 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.

Another consideration supporting the use of oral consent is that treatments being used are not experimental treatments; they are standard of care cessation and reduction treatments shown to be safe and effective in previous studies. We are not testing the effectiveness of the treatments offered in the study. Instead, we are testing whether offering different types of standard of care treatments as part of a package of treatments (as offered in Comprehensive Chronic Care), increases overall treatment use and abstinence. With respect to smoking pharmacotherapy, 8-26 weeks of combination NRT are FDA-approved regimens that are the recommended standard of clinical care for smoking cessation[15]. Moreover, use of prequit NRT for 8 weeks is an FDA-approved and recommended standard of care for those who are not ready to quit but are willing to reduce their smoking[15]. The UW Health Sciences IRB has previously deemed these over-the-counter nicotine replacement therapies, including combination NRT and mini-lozenge for smoking reduction as minimal risk. The cessation and reduction counseling offered has also been shown to be effective and is recommended by the US Public Health Service Guideline for Treating Tobacco Use and Dependence[15].

Patients who do not provide oral consent 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

H. BASELINE ASSESSMENT

Following oral consent, the 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 $30 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.

I. RANDOMIZATION

Randomization, which will occur immediately after oral consent and Baseline Assessment are completed, will be conducted by healthcare system Care Managers using the study REDCap database developed at UW-CTRI. Randomization to either CCC or SC will be blocked by clinic and patient-identified gender to ensure equitable distributions across conditions.

Following randomization, healthcare system Care Managers will describe the smoking treatments available to participants over the next 18 months (as determined by randomization to CCC or SC; see Interventions) and will ask whether the participant is interested in starting treatment. If the participant is not interested in starting treatment, the CM will give instructions about how to contact him/her when they are ready to initiate smoking treatment. Those in CCC will be informed that they will receive four Outreach Calls from a UW-CTRI Health Counselor offering treatment in about 4, 8, 12, and 14 months. Those in SC will be told that they will receive an Outreach Call offering treatment from a UW-CTRI Health Counselor in about 1 year. The participant will also be told that UW-CTRI research staff will be calling them in about 6 months for a brief assessment.

J. 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 with information about:
    a. Description of smoking treatments available for those randomized to either CCC or SC.
    b. Description of types of Outreach Calls offering smoking treatment and frequency of such outreach in either CCC or SC (depending on group assignment)
    c. Instructions about ways to contact the study to request treatment
    d. A reminder that UW-CTRI research staff will call every 6 months (months 6, 12, and 18) for a brief assessment (see uploaded Semi-Annual Assessments), and that $30 in compensation will be offered for completing the 6 and 12 month calls, and $50 in compensation will be offered for completing the 18 month call.
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).

K. INTERVENTIONS

Participants' assignment to either CCC or SC will determine: 1) the type of standard of care smoking treatments offered to patients (described below), and 2) the frequency and manner in which these standard of care smoking treatments are offered (described below). *Importantly, we are not evaluating the effectiveness of smoking treatments offered (cessation or reduction treatments).* Instead, we are evaluating whether CCC versus SC increases use of these standard of care smoking treatments and ultimately increases abstinence.

All enrollees in the study will receive a minimum of one Outreach Call offering treatment to promote utilization of available evidence-based smoking cessation treatment 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). Participants in both CCC and SC may engage in treatment multiple times, consistent with good clinical care.

Study medications will be administered only to those who meet eligibility criteria for the medication use *at the time they request treatment*. Eligibility to use nicotine replacement will be assessed by a Health Counselor (see uploaded NRT Use Screen) when a participant expresses interest in entering study treatment. To use medication provided by the study, participants must report no severe allergic reactions to nicotine patch or nicotine mini-lozenge, report not currently taking varenicline, report not currently taking bupropion for smoking cessation, no stroke, heart attack, or abnormal electro cardiogram within the past four weeks, and women with childbearing potential must not be pregnant or breastfeeding and must be willing 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. If a participant becomes pregnant, that is a critical time for them to quit smoking which is something that the cessation counseling in this study can support. If a participant becomes pregnant, they will not be administered study medications. If a participant who has initiated treatment becomes pregnant, they will be instructed to stop any use of study medications.

Participants who are not eligible to use study medication or who decline use of NRT will still be able to receive counseling as part of their smoking treatment. *Thus, access to counseling is not dependent on medication eligibility or election.*

Participants who decide to enter treatment and who provide consent to have counseling sessions recorded (see uploaded Oral Consent Procedures) will be reminded that counseling sessions will be audio recorded. They will be told that recordings are being collected for quality assurance purposes to train health counselors and to ensure that treatment is consistent for everyone.

Comprehensive Chronic Care (CCC)

Those randomized to CCC will receive smoking treatment offers via the following routes: 1) Four Outreach Calls from a Health Counselor at 4, 8, 12, and 14 months post-study enrollment; 2) Four texts and/or mailings (depending on healthcare system preferences) over 14 months. These outreach contacts will offer cessation treatment (4 weeks pre-cessation + 12 weeks of cessation treatment; described below) or reduction treatment (8 weeks of smoking reduction treatment; described below).

When participants report interest in entering treatment, Health Counselors will assess for NRT eligibility (described above), set up a treatment call schedule and provide instructions regarding how to use study medications (if participant is eligible and willing to take medication). Medications will be mailed following this call, along with a handout that describes: 1) when to

begin taking study medication; 2) the doses involved; 3) how and when to obtain medication; 4) complete instructions on proper medication use, including information from the package insert; and 5) contact information if they have questions regarding their medication and/or symptoms they experience.

Reduction Treatment. Consistent with standard of care, smoking reduction treatment involves fast-acting nicotine replacement therapy (nicotine mini-lozenge) accompanied by phone counseling. *The effectiveness of reduction treatment is not being tested.*

Reduction Counseling. Reduction counseling (see uploaded Reduction Counseling Protocol) involves 4, 15-20 minute phone counseling sessions over an 8-week period (Weeks 0, 2, 4, and 8 post-treatment initiation; see Table 1). During the initial call and subsequent counseling calls, the HC will work with participants to develop strategies for changing smoking patterns such as reducing cigarettes, increasing time between cigarettes, delaying smoking, or eliminating smoking in specific situations. The counseling will emphasize the development of smoking control skills via feasible, specific, and graded assignments involving the modification of smoking patterns. The HC will explicitly address pragmatic issues such as work contexts, smoking policies, smokers at home, and habits that interfere with the development of new smoking control skills.

Nicotine Replacement Therapy (NRT). Participants will be mailed the 2-mg mini-lozenges. Participants will be instructed to use the product for 8 weeks in a scheduled manner consistent with the 2008 PHS Guideline[15]; they will be instructed to use one mini-lozenge every 1-2 hours and up to 12 daily, with a goal of using at least 5 daily. Participants will be mailed 8 weeks of medication prior to the first reduction counseling session. They will also be mailed an information sheet that conveys all medication instructions as well as a phone number to call if they have concerning side effects or other questions about their medication. Using an uploaded adverse events protocol, Health Counselors will assess medication use and side effects at all reduction treatment counseling sessions (Treatment Assessments at Weeks 2, 4, and 8; Table 1).

Table 1. Schedule of Treatment Contacts for Reduction Treatment

Week	0	2	4	8
Phone Counseling	X	X	X	X
Treatment Assessments	X	X	X	X
Adverse Events	X	X	X	X

Cessation Treatment. Consistent with standard of care, cessation treatment involves evidence-based cessation counseling and combination nicotine replacement therapy (nicotine patch plus nicotine mini-lozenge). The cessation treatment is based on recommendations in the 2008 PHS Guideline[11]. *The effectiveness of cessation treatment is not being tested.*

Cessation Counseling. Cessation counseling (see uploaded Cessation Counseling Protocol) will comprise four 15-25-minute counseling sessions occurring 1 week prequit, during the first week post-target quit day (TQD), and during Weeks 2 and 4 post-TQD (see Table 2). During the first counseling call, the HC and participant will set the TQD and create a quit plan that will be mailed to the participant following the call. Postquit sessions will involve anticipating high-risk situations, coping with craving, providing intra-treatment support, and dealing with a lapse/relapse.

Nicotine Replacement Therapy (NRT). Cessation treatment will involve using the nicotine patch for up to 4 weeks prior to the TQD and combination NRT (patch + nicotine mini-lozenge; C-NRT) for 12 weeks starting on the TQD. Participants who smoke 5 or more cigarettes will use

14-mg patches for up to 4 weeks prior to the TQD (while they are still smoking) and not a higher dose patch, to reduce the risk of adverse events. Those who smoke 1-4 cigarettes per day will be given 7mg patches for up to 4 weeks prior to the TQD. Consistent with standard dosing and package insert instructions for the cessation phase, 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. Participants who smoke 1-4 cigarettes/day will be given 7mg patches for 12 weeks. To reduce the risk of adverse effects, all participants will receive 2-mg mini-lozenges for the 12-week cessation period. 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.

Cessation Treatment Following an Unsuccessful Quit Attempt. By definition, for this study, a quit attempt will last a minimum of 4 weeks. If participants report smoking at any point after 4 weeks post-TQD, they will be encouraged to make a new quit attempt using cessation treatment provided by the study (Note that smoking during the first 4 weeks of a quit attempt will be addressed as part of the current quit attempt – such as encouraging participants to recommit to quitting if they lapse or set another quit attempt right away if they relapse). Smoking status following a quit attempt will be assessed during the week 4 post-TQD counseling call and the cessation treatment assessment calls (Weeks 8 & 12 Treatment Assessment calls post TQD; see Table 2), and study Outreach Calls and Follow-Up Assessments. Anyone reporting smoking at these timepoints will be offered the opportunity to re-engage in cessation treatment. Participants will also be encouraged to call their HC if they relapse following a quit attempt if they are ready to make another quit attempt. Participants will be informed that for any subsequent quit attempts (after their initial quit attempt), they will receive four cessation counseling sessions (as described above in cessation counseling; see Table 2) and 26 weeks of combination nicotine replacement therapy. Both the counseling and medication offered is in-line with standard of care. Consistent with standard of care, for those who smoke >10 cigs/day=22 weeks of 21 mg, 2 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches, along with 2-mg nicotine mini-lozenges. For those who smoke 5-10 cigs/day=24 weeks of 14 mg and 2 weeks of 7 mg nicotine patches along with 2-mg mini-lozenges. Those who smoke 1-4 cigarettes/day will be given 7mg patches for 26 weeks. To reduce the risk of adverse effects, all participants will receive 2 mg mini-lozenges, rather than dosing mini-lozenges based on time to first cigarette (per package insert - those who smoke within 30 minutes should use 4 mg mini-lozenges). Participants will be encouraged to use an average of 9 mini-lozenges per day.

For all quit attempts, participants using NRT will be provided with instructions on proper NRT use and on how and when to obtain the medication refills. Participants will initially be mailed a 2-month supply of NRT. They will be instructed to call the study medication line to get each additional 2 month supply (for 16 weeks for first quit attempt; 26 weeks for subsequent quit attempts). Using the uploaded Adverse Events Protocol, Health Counselors will assess medication side effects at all cessation counseling sessions (Treatment Assessments at -1, 1, 2, and 4 weeks post-TQD) and during the 8 and 12-week post-TQD assessment calls (see Treatment Assessments; Table 2).

Table 2. Schedule of Treatment Contacts for Cessation Treatment

Week	-1	TQD+1	2	4	8	12
Phone Counseling	X	X	X	X		
Treatment Assessments	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X

Standard Care

Standard Care participants will receive an Outreach Call offering cessation treatment at 12 months post-treatment enrollment (in addition to cessation treatment offer during the study enrollment call), ensuring that evidence-based treatment is offered annually to every participant. During the study enrollment call and the 12 Month Outreach Call, participants will be offered cessation treatment involving 8 weeks of nicotine patch provided by the study and referral to Wisconsin tobacco Quitline and/or Smokefree.txt. Participants who decide to enter cessation treatment will work with Health Counselors to set a quit date and will receive a quit plan worksheet in the mail for them to complete to support their quit attempt. They will then be referred to the Wisconsin Tobacco Quit Line, where they will receive one proactive counseling call. Participants can call the Quit Line for additional counseling sessions.

Participants who smoke >10 cigarettes/day will start with a 21 mg patch on their quit day, and use for 4 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 5-10 cigarettes/day will be given 6 weeks of 14 mg patches and then 2 weeks of 7 mg patches. Participants who smoke 1-4 cigarettes/day will be given 7mg patches for 8 weeks.

All Standard Care participants will be given complete instructions on proper nicotine patch use and on how and when to obtain the next month's supply of medication. Participants will initially be mailed a 1-month supply of patches and will be instructed to call a study medication line to get each additional 1-month supply of the medication. Using the uploaded adverse events protocol, Health Counselors will assess medication side effects during a brief safely assessment call 2 weeks post-TQD.

L. ASSESSMENTS

Baseline Assessment, which will last 10-15 minutes, will be conducted when the participant is enrolled in the study. (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, perceptions about the impact of Covid-19 on their life and their smoking, 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 $30 for completing the baseline assessment.

Semi-Annual Follow-Up Assessment, which will last 10-15 minutes (See uploaded Semi-Annual Follow-Up and List of EHR Data to Be Extracted), will be conducted via phone at 6, 12, and 18 months post study enrollment. At these semi-annual assessments, smoking status, use of study treatment, quitting attitudes, self-efficacy, experiences (including withdrawal and social support related to quitting), use of all nicotine products, and extrinsic/intrinsic motivation will be assessed. EHR and pharmacy data on healthcare utilization and smoking status changes will also be extracted. Self-reported satisfaction with healthcare and any smoking cessation treatments used during the study will be assessed. Participants will earn $30 for completing the 6 and 12 month semi-annual assessments; they will earn $50 for completing the 18-month assessment. 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 (see uploaded Follow-Up Unable to Reach Mailer). If we cannot reach participants by phone for the Follow-Up Assessments, we will send a letter with a form to return in a self-addressed stamped envelope,

and/or via text/email if the participant has consented to text/email communications, to indicate their smoking status and any smoking treatment they have used (see uploaded Follow-Up Assessment Letter). Participants can also provide responses to the follow-up assessment questions online via QR code. The QR code will direct subjects to a REDCap survey that will gather the same questions listed in the follow-up assessment letter. Participants who access the survey link will be asked to provide minimal identifying information (e.g., last name, phone number), but the ICTR Redcap database has restricted access that is only available to study team members.

Cannabis Use Assessment. Cannabis use will be assessed at the Baseline Assessment and the 6, 12, and 18 month Semi-Annual Follow-Up Assessments. This assessment will evaluate frequency and mode of use, patterns of use with cigarettes, reasons for use, and motivation to stop using cannabis.

Biochemical Abstinence Assessments. Participants who report no smoking in the past 7 days at the 12- and 18-month post-enrollment interviews will be asked to complete a brief, 30-minute call to assess smoking, tobacco, and smoked marijuana use since the telephone interview and to provide saliva for biochemical testing to verify abstinence from smoking. Saliva testing will be completed via a home collection kit mailed to subjects. Participants who report abstinence in the last 7 days at this call but have a cotinine level >10ng/mL, anabasine level greater than 2ng/mL, or who do not provide a cotinine result will be considered to be smoking. In order to achieve a high level of abstinence verification, participants will receive $50 for returning the saliva sample kit for biochemical abstinence assessment. .

Treatment Assessments (See uploaded Treatment Assessments). Participants will receive a brief 5-minute assessment during all treatment contacts (for cessation and reduction treatment). During these treatment contacts, patient self-report of smoking, treatment use, and experiences (including withdrawal symptoms) will be assessed, along with any adverse events that occurred since the beginning of treatment (see Tables 1 & 2). In addition, CCC participants who enter cessation treatment will receive additional treatment assessment calls at Weeks 8 & 12 post TQD to assess smoking status and assess adverse events. Participant utilization of treatment will be assessed by tracking how many calls the participant completed and how much medication they report using.

Health Counselor Adherence to Treatment. To enhance intervention fidelity, intervention delivery will be assessed via supervisory review of recorded smoking treatment counseling calls delivered by UW-CTRI Health Counselors, with feedback regarding performance to enhance fidelity, as needed.

M. PROMOTING CONTINUED EXPERIMENTAL PARTICIPATION

To enhance follow-up interview completion rates, the following communication routes will be used: texting, mailing, and automated phone calls (depending on their communication preferences as noted in the EHR and during enrollment). We will also use study call scheduling flexibility and continued interaction with the same HC for each round of treatment. In addition, for consented participants who we are not able to reach using contact information obtained at the baseline and subsequent calls, the CM will check in the EHR for updated contact information. If there is no updated information, we will call and/or send a letter to the alternate contacts provided by the participant, designated as a contact for this specific situation.

Compensation: Compensation offered for completing assessments ($30 for the Baseline Assessment, $30 each for the 6 and 12-month Semi-Annual Follow-Up calls, and $50 for the final 18-month Semi-Annual Follow-Up call). They will be paid $50 for returning each saliva sample for biochemical abstinence assessment at 12- and 18-month post-study enrollment. Participants who miss their 6 or 12-month assessment calls may complete the assessment by mail or online and receive $15 for their time. Participants who miss their 18-month follow-up call may complete the assessment by mail or online and receive $25 for their time.

Withdrawal of Participants

Participants will be withdrawn from study participation if their involvement in the study poses a safety risk to their health or wellbeing, or if the participant fails to comply with the requirements of the study. Participants can withdraw from the study via written or verbal communication with study staff. All data obtained prior to study withdrawal will be used in data analysis. No data will be collected after a participant withdraws from the study.

N. DATA MANAGEMENT, TRANSMISSION AND STORAGE

Personnel from both the healthcare systems and UW-CTRI will 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 Care Managers who are both health system employees and study personnel. Care Managers will have security templates in the EHR that permit them to enter research records, update smoking status, and/or exchange secure in-basket messages with primary care providers regarding serious adverse events, or medication discontinuation due to side effects.

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 18-month 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 study 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).

Delivery of intensive treatment and follow-up data collection procedures and collation of data from multiple sources/sites is necessary for thorough program evaluation. To achieve the study aims, UW-CTRI investigators require access to identifiable patient data. Identifiers will be destroyed at study closure or at the time of publication. 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.

O. STATISTICAL CONSIDERATIONS

Statistical Power

Sample size (N=1000) was based on the power needed to detect significant differences in 18-month abstinence, our primary aim. We used SAS PROC POWER to identify the necessary sample size to ensure that comparisons of CCC (n=600) versus SC (n=400) would have sufficient power to detect an 8% increment in abstinence (≥ .80, 2-tailed test, $\alpha < .05$), the minimum effect size we believe would be cost-effective and of clinical and public health significance for an intervention of the CCC intensity. We assume that the rate of 18-month biochemically confirmed abstinence for those in SC will range from 6-10%. Power estimates for an 8% effect of CCC relative to SC on biochemically confirmed abstinence at 18 months relative to the projected SC rates exceed .8 (at alpha .05) with a sample of 1000 participants.

Handling of Missing Data

The intent-to-treat principle with the assumption of missing=smoking will be used for abstinence analyses but will be supplemented with sensitivity analyses and multiple imputation for missing data to support scientific rigor[16]. The latter models will assume that 80% of dropouts return to smoking and that abstinence likelihood is related to baseline participant covariates as per our prior research[8,17,18]. For the treatment use outcome, there will be no missing data because treatment use will be automatically recorded in the database.

Analysis Plan

Primary Aim

Aim 1: To determine whether Comprehensive Chronic Care (CCC), relative to Standard Care (SC), significantly improves biochemically confirmed 7-day point-prevalence smoking abstinence at 18 months.

Group differences in abstinence at 18 months will be evaluated using logistic regression. In analyses of the primary outcome, we will not use covariate adjustment because we wish to see the extent to which treatment effects are robust with regard to variation across diverse person factors and because the use of such covariates can produce biases and interpretive challenges. Thus, we will analyze treatment effects among diverse smokers as they present in real life, not whether such effects occur in a statistically adjusted sample. However, we will use both sensitivity tests and covariate adjustment in secondary analyses to determine the robustness of the findings obtained in primary outcome analyses. Such variables will include age, gender, race, mental health diagnosis, smoking heaviness, time-to-first cigarette of the day, use of other treatments or participation in prior smoking cessation research, and educational attainment. The variables will also be used in moderation analyses to determine if the effectiveness of the SC and CCC conditions varies as a function of person factors. As noted, analyses with the assumption of missing=smoking will be supplemented with sensitivity analyses and multiple imputation for missing data. Finally, distributions of outcome variables will be carefully examined to determine the need for transformation or appropriate modeling (e.g., via a Poisson distribution).

Secondary Aims

Aim 2: To determine the effects of CCC relative to SC on: cost-effectiveness, and 7-day point-prevalence smoking abstinence at 6- and 12-months.

As described above, group differences in abstinence at 18 months will be evaluated using logistic regression.

Cost-effectiveness analyses will compare CCC with SC. We will determine total cost for both intervention arms and incremental cost-effectiveness ratio (ICER)[84], or cost per additional person who quits smoking, for the CCC vs. SC. Incremental resource costs related to the CCC intervention include Health Counselor/staff time, administration, staff training, recruitment, and medication. We will use methods recommended by the United States Panel on Cost-Effectiveness in Health and Medicine, consistent with our prior research[85,86]. We will measure costs from a societal perspective using direct observational data of health system resource use[87]. Cost estimates will be converted to a common year and effectiveness will be assessed through biochemically verified abstinence at the 18-month follow-up. The ICER is calculated as the difference in total costs between CCC and SC divided by the difference in 24-month quit rates. 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). The abstinence self-reports will be biochemically confirmed reports at 12 months but not at 6 months.

Aim 3: To compare CCC with SC on cessation treatment use over 18 months of treatment access.

Group differences in cessation treatment use will be evaluated using logistic regression analysis. Treatment use will be defined as making at least one treatment contact (initiating >0 treatment calls with reach coded as binary [use vs. no use], which would reflect cessation or reduction treatment in CCC and cessation treatment in SC). We will also examine the use of cessation treatment only in the two conditions, again coded as binary.

P. 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). If the elect to use treatment, they could benefit by reducing their smoking or quitting. Although patients 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 people who smoke by identifying a treatment approach for expanding the reach and effectiveness of standard of care smoking treatments that are available 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 (one Baseline Assessment and three Semi-Annual Follow-Up assessments; plus, for those in CCC who enter cessation treatment, a 5-10 minute assessment at 8 and 12 weeks post TQD, and 2) minimal-risk, non-invasive informational and supportive interventions to promote smoking reduction and cessation and use of FDA-approved smoking treatments that represent 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. 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 given to participants in this study 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 and available over the counter. Patients will provide oral informed consent for NRT, and monitoring for adverse effects is in place. Providing saliva samples 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 at 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 participants will have the ability to decline or withdraw from the study and any study activities at any time. Risks associated with use of 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.

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. 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, a UW-CTRI employee. 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.

To protect against violations of privacy, patients will first have the option to opt out of the program, at study launch and at the clinic. Those who opt out will not receive a call from a Care Manager for recruiting and offers of smoking cessation treatment.

Routine adverse event assessment will only occur in the context of treatment episodes, given the minimal and informational nature of the outreach calls offering treatment and research assessments. Adverse events that occur during all smoking treatment contacts. Adverse events reported by patients will be assessed fully and reported to the IRB 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. 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 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 NRT at all. The nicotine mini-lozenge dose dispensed to participants who initiate Combination NRT (patch + mini-lozenge) 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).

Participants will be alerted to possible withdrawal effects in the mailed Welcome Packet sent after enrollment and again at the time they decide to use smoking treatment 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 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 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 whether a chronic care approach to smoking (CCC treatment) improves treatment use and abstinence relative to SC. The risks associated with the use of nicotine replacement therapy are minor relative to the risks of continued smoking, given that NRT is available over the counter. If successful, this CCC 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 from 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 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 (Cook) is responsible for routine monitoring of study progress. This includes scheduled meetings with study staff and healthcare system 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, and rates of allocation to experimental

conditions by clinic, sex, and eligibility for treatment (to ensure the randomization scheme is coordinated and balanced as intended). The PI will also routinely monitor 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), and rates of missing data in assessments. This will continue throughout the 42-month data collection period. 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 for the study 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 NRT use 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 treatment or assessment contacts 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 emerge during the study will be assessed fully and reported. If an SAE might be related to study drug use, both the Food and Drug Administration (FDA) and the manufacturer will be notified within 5 days of investigators becoming aware of the event. Examples of SAEs would be untoward medical or intervention occurrences that result in death, are life-threatening, require hospitalization or prolonging of existing hospitalization, create persistent or significant disability/incapacity, or involve congenital abnormality/birth defects. Unanticipated problems will be monitored and reported to the DSMC. 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 treatment outreach strategies with 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.

Individual study results or assessments will not be shared directly with participants or their physicians. However, the electronic health records may be updated to reflect a change in their smoking status (i.e, they quit smoking). Aggregate results from this research will be shared with the scientific community and our research collaborators. The findings form this research will also be shared upon request with study participants

ClinicalTrials.gov Requirements

This research project will be registered with clinical trials.gov prior to the enrollment of the first subject. Final data (including outcomes and adverse events) will be reported to clinicaltrials.gov within 1 year of the conclusion of the trial.

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