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BREATHE 2 cluster-randomized trial of health system changes to increase reach of smoking cessation treatments

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BREATHE 2 cluster-randomized trial of health system changes to increase reach of smoking cessation treatments

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REVISION HISTORY

Revision #	Version Date	Summary of Changes	Consent Change?
1	8/1/2022	Responses to pre-review comments	Yes
2	1/6/2023	Removal of an exclusion criterion for correctional facility addresses based on infeasibility	No
3	2/24/2023	Responses to pre-review comments to CP001	No
4	6/26/2023	Change study enrollment to 13,000	No
5	2/8/24	Removal of Cessation trial #2019-0054 as a treatment option as of 2/23/24 due to recruitment closure	No

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1.0 Study Summary

Study Title	BREATHE 2 Clinic Outreach Study
Brief Summary	This 2-arm cluster-randomized clinical trial will compare a standard approach to smoking cessation treatment outreach in adult primary care to an enhanced approach offering more frequent outreach, multiple ways to request treatment, and a broader array of treatment options. We hypothesize that enhanced care comprising quarterly outreach offering both standard person-to-person treatment options (quitline services, care from a primary care provider, phone coaching and medication through a clinical trial) and self-guided quitting support via nicotine sampling (2 week supplies of nicotine replacement therapies) and enrollment in text-message based cessation support (via SmokefreeTXT or other Smokefree.gov text-message programs) will attract more adult primary care patients to treatment and will help more patients achieve abstinence from smoking, as indicated by a change in their smoking status from current to former smoking in their electronic health records. Up to 13,000 adult patients who receive primary care at 10 participating clinics and whose electronic health records suggest they smoke will receive smoking cessation treatment outreach for up to 18 months, unless they opt out of participation. [Note: this trial has not been registered at clinicaltrials.gov yet, but will be registered there after IRB approval and prior to enrollment of participants].
Number of study sites	2 study sites; 10 participating primary care clinics (5 at UW Health, 5 at Advocate Aurora Health)
Study Design	2-arm cluster-randomized controlled trial
Primary Objective	1. To use a cluster-randomized controlled trial to evaluate a reach intervention package designed to increase cessation treatment reach especially well, at low cost, at 1-year follow-up. 2. To estimate the effects of randomized reach intervention package on cumulative treatment reach over 18 months of treatment access.
Secondary Objective(s)	1. To estimate the effects of the enhanced reach intervention on abstinence at 12 and 18-month follow-ups. 2. To identify the degree to which intervention effects on 2-year abstinence are mediated by increases in cessation treatment reach. 3. To assess the cost-effectiveness of the reach intervention in promoting reach and abstinence. 4. To identify patient and clinic moderators of intervention effects on reach and abstinence.
Research Intervention(s)/	1. Standard care approach comprising initial outreach at the launch of the program and calls from Tobacco Care Managers 1-3 days after a qualifying primary care visit

Investigational Agent(s)	(no more than once per month and until 2/23/24) offering 3 person-to-person smoking treatment options - Wisconsin Tobacco Quit Line - Referral back to the Primary Care Provider - Screening/enrollment in a separate smoking cessation treatment study (IRB protocol #2019-0054) until 2/23/24 when #2019-0054 closes recruitment 2. Enhanced care comprising Standard care as described above (initial letter, calls from Tobacco Care Managers 1-3 days after qualifying primary care visits no more than once per month (and until 2/23/24), 3 person-to-person treatment options (1a-1c), plus quarterly outreach via letter and applicable patient-preferred modalities (including EHR patient portal, e-mail, text messages, website) offering two additional treatment options: - Nicotine sampling (patients can request 2 weeks starter kits of any 2 of the following nicotine replacement therapies (patch, gum in any available flavor, mini-lozenge in any available flavor), even if they are not ready to set a quit date - Facilitated enrollment in SmokefreeTXT (if ready to set a quit date in 14 days), Practice Quit (if ready to abstain 1-5 days but not quit permanently) or Daily Challenges (if not ready to quit, but willing to make some changes)
Drugs/devices used on study (including any IND/IDE #)	FDA-approved over-the-counter nicotine patch, gum, and mini-lozenge samples (2 week supplies)
Study Population	Adult primary care patients who smoke cigarettes
Sample Size	13,000
Study Duration for individual participants	18 months
Study Specific Abbreviations/Definitions	EBST=evidence-based smoking treatment; EHR=electronic health record; NCI=National Cancer Institute; NRT=nicotine replacement therapy; PCP=primary care provider TCM=Tobacco Care Manager; WTQL=Wisconsin Tobacco QuitLine

Note: Include only elements relevant to this study.

2.0 Background

2.1 Gaps in current knowledge.

Despite a large decline in smoking prevalence, 13% of US adults (~37 million people) continue to smoke (Cornelius et al., 2019). In addition, although more than half of adults who smoke in the US try to quit smoking each year, only 5% who try to quit use recommended treatment combining pharmacotherapy and psychosocial support (Babb et al., 2017). This problem persists despite advances in treatment options and accessibility. Efforts to increase smoking cessation treatment access at the population level through public programs (e.g., tobacco quitlines), public policy (e.g., the Affordable Care Act, the Joint Commission), and healthcare system change [e.g., smoking as a vital sign, Ask-Advise-Connect models (Vidrine et al., 2013)] have yielded important, but modest benefits [US Department of Health and Human Services (USDHHS), 2020]. The primary care context offers a propitious opportunity to provide smoking treatment, but even when using proactive models of EHR-facilitated quitline referral (e.g., eReferral), only about 5% of eligible patients engage in quitline services (Baker et al., 2021; Fiore et al., 2019). Moreover, the reach of quitlines appears to be waning as incoming calls to the quitline are declining [North American Quitline Consortium (NAQC), 2022], and reluctance to take phone calls and engage in person-to-person counseling appears to be growing (Smith et al., 2015; Morphet et al., 2015; Halladay et al., 2015).

Healthcare settings are excellent places to engage smokers in evidence-based smoking treatment (EBST), as most smokers (roughly 75%) visit primary care clinics each year (King et al., 2013). Epidemiological and healthcare system data show that smoking cessation interventions are rarely offered in healthcare settings, however (<40% of patients report being offered assistance quitting smoking, <15% report being offered follow-up for smoking by their primary care provider) (Borland et al., 2012; Control et al., 2005; Jamal et al., 2012; Keith et al., 2017; Papadakis et al., 2014; Park et al., 2015; Quinn et al., 2009). Long-term access to treatment and follow-up are critical to the treatment of tobacco use as a chronic, relapsing condition (Ellerbeck et al., 2009; Fiore et al., 2008; Joseph et al., 2011). 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) (Agency for Health Care Research and Quality, 2013; Elliott, 2003; NCF Risk Factor Collaboration, 2016), but still undertreat smoking (Bernstein et al., 2013). 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 (Ellerbeck et al., 2009; Joseph et al., 2011; McCarthy et al., 2022). 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 (Adsit et al., 2014; Bandi et al., 2012; Papadakis et al., 2010; Smith et al., 2013), rates of treatment use remain low (Campbell et al., 2017; Mena et al., 2017; Piper et al., 2013; Thomas et al., 2017). Thus, there is a pressing need to effectively and efficiently increase smoking treatment reach in healthcare.

Mobile, digital, and remote treatment tools have tremendous potential to increase the reach of EBST, particularly if proactive offers for such low-barrier treatments can be incorporated into primary care. Offering an array of EBST (e.g., beyond just physician advice and tobacco quitline referral) may also attract more patients to treatment. Although tobacco quitlines deliver EBST 24/7 at no cost to users with few logistical barriers, their reach is not increasing. In fact, the rates at which people call the quitline, or return quitline-initiated calls, are declining (NAQC, 2022). This may reflect a broader trend away from person-to-person communication to digitally mediated connections (Albert et al., 2020; Meek, 2022). Although face-to-face and synchronous telephone or video communication are the dominant modes of communication in healthcare settings, other modes and models of care delivery are possible and may help to reach patients reluctant to engage in person-to-person treatment, or to set a date to quit smoking within the next month (a prerequisite for quitline coaching and medication).

The proposed cluster-randomized controlled trial will evaluate a package of health system changes designed to reduce barriers to EBST utilization and to increase patient demand for such treatments. Adult primary care patients who do not opt out of the study at 10 clinics in 2 healthcare systems will receive either a standard EBST outreach and treatment model (n=4 clinics) or an enhanced outreach and treatment model (n=6 clinics) over 18 months to assess the extent to which enhanced care increases treatment reach (primary outcome) and abstinence (secondary outcome), and the degree to which enhanced care is cost-effective and has equitable or equity-enhancing effects across patient subpopulations. Recent research suggests that proactive treatment offers are cost-effective and that universal outreach reduces disparities in EBST treatment access (Baker et al., 2021; McCarthy et al., 2022; Mundt et al., 2022).

Importantly, the enhanced interventions to be tested can be implemented centrally and remotely by chronic care management specialists (as in McCarthy et al., 2022), with minimal disruption to routine primary care practices. 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 enhanced outreach and treatment package. 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.

2.2 *Preliminary data.*

The design of the proposed cluster-randomized clinical trial has been informed by several recent studies and one ongoing study. Our research group and others have demonstrated several important findings about the challenges of incorporating EBST into routine clinical care. First, many studies have shown that engaging clinicians in delivery of EBST during routine clinical care is very difficult (Papadakis et al., 2010). Although multicomponent system changes to facilitate clinician delivery of EBST help some, rates of offering EBST remain low, typically below 50%, even when counting brief (<3-minute) clinician counseling (Papadakis et al., 2010). Clinicians face many barriers to integrating EBST into their encounters with patients, and changing practice is difficult (Jaén et al., 1994; Vandetti et al., 2017; Vogt et al., 2005).

Second, several studies have demonstrated that proactive outreach to patients identified as currently smoking can increase the rate at which patients accept treatment referrals and initiate treatment. For example, three of our recent studies demonstrate that using EHR tools to prompt clinicians to offer smoking treatment during routine primary care clinical encounters (or at the bedside in inpatient units) meaningfully increases the rates at which adult patients who smoke are referred to tobacco quitline or other telephone-delivered services (Baker et al., 2021; Creswell et al., 2022; Fiore et al., 2019; McCarthy et al., 2022). Electronic referral to quitline services via the EHR in healthcare settings is rapidly being adopted by state tobacco quitlines and is becoming an accepted standard of care (NAQC, 2022). At the same time, we have found that fewer than a third of patients who accept a treatment referral actually initiate treatment (i.e., rates of accepting quitline services among those who consented to quitline referral are below 30% and are declining over time) (Baker et al., 2021; Fiore et al., 2019). These findings suggest that simply referring patients to external treatment services, such as tobacco quitlines, is feasible in real-world practice settings, but may have modest effects on population-level EBST reach due to high levels of attrition between referral and treatment initiation.

We recently found that combining proactive telephone outreach to all patients on a smoking registry and EHR prompts for primary care providers to address smoking during clinical encounters both doubled the rates at which patients on the registry received EBST and significantly increased the rates at which all smoking patients converted to former smoking (McCarthy et al., 2022). Proactive phone outreach reached at least 50% of patients eligible for calls from centralized Tobacco Care Managers and 1 out of 6 of those reached developed a quit plan (McCarthy et al., 2022). Both prompting clinicians to offer EBST and reaching out to patients by phone seem to reduce disparities in treatment access among historically undertreated populations (i.e., members of minoritized racial and ethnic groups and Medicaid-eligible patients) (McCarthy et al., 2022). Thus, preliminary data suggest that universal outreach to patients who smoke may have equity-enhancing effects on EBST reach, and may increase smoking quit rates, as well.

In an ongoing experiment (IRB protocol #2019-0939) that serves as the direct precursor for the proposed cluster-randomized trial, we have found that engaging patients who are not currently interested in quitting smoking in research on health system interventions to enhance EBST reach to be quite challenging. The ongoing study uses a telephone-based recruitment model that has had very low yield (it has taken more than 20 months to enroll 204 participants of a target sample of 1664, from a pool of more than 11,000 patients). This model also introduces a high risk of sampling bias in the experiment, as only patients most open to quitting and ready to consider EBST are likely to accept the initial study recruitment call that comes from a Tobacco Care Manager (TCM) at their health system, and then complete the 45-minute phone enrollment process for a 2-year study that involves at least 4 follow-up phone contacts. As such, our attempt to recruit for a factorial experiment that manipulates and evaluates patient-level interventions to promote use of EBST has demonstrated that this is not the best way to assess the population-level effects of health system changes to enhance EBST reach.

In light of this, we have designed the current proposal to rigorously assess health system interventions randomly assigned at the clinic-level using a client population sampling strategy in which: all patients who meet criteria for a smoking registry at a participating clinic will be considered enrolled unless they opt out; outcomes will be assessed via deidentified or limited EHR data rather than patient self-report; and treatment navigation and facilitation will be handled by health system TCMs rather than research personnel outside of the health system. Outreach to patients will occur both via distant means (mail or messaging in the patient portal in the EHR) and via phone outreach from health system TCMs, with the schedule and content of the outreach varying at the clinic rather than patient level.

In sum, several preliminary studies suggest that proactive outreach to all adult patients who smoke can increase treatment referrals and downstream treatment initiation in an equitable manner, but with considerable dropoff between referral and treatment (Baker et al., 2021). Embedding treatment in health systems via centralized tobacco care management services shows promise as a way to enhance treatment reach equitably, with less dropoff between accepting and initiating treatment (McCarthy et al, 2022). Recruiting adult primary care patients by phone for experimental studies of patient-focused interventions designed to increase EBST utilization has been challenging, however, and introduces sampling biases that undermine the validity of the experiments. As such, we propose a population health approach with clinic-level manipulation of outreach strategies and treatment options facilitated by health system TCMs in the current cluster-randomized clinical trial.

2.3 Background and significance.

Combustible cigarette smoking is the leading cause of preventable mortality in the US and causes more than 480,000 US deaths annually [Centers for

Disease Control and Prevention (CDC), 2022; USDHHS, 2014, 2020]. Effective treatments have been identified that double or triple the odds of quitting smoking successfully (Fiore et al., 2008). Despite this progress, a major challenge in smoking intervention in healthcare is that too few people use effective treatment when trying to quit (Babb et al., 2017). That is, while we have effective treatments, their reach is low, and healthcare visits lead to engagement in such treatments in a minority of cases (Baker et al., 2021; Papadakis et al., 2010). Population-based data show that, while more than half of US adults who smoke try to quit smoking each year, only about 5% of those trying to quit use both counseling and pharmacotherapy to help them quit (Babb et al., 2017). Even with state-of-the-art EHR systems to facilitate smoking intervention, typically 5% of patients or fewer are connected with smoking treatment in primary care clinics (Baker et al., 2021; Fiore et al., 2019). It is vital that we develop more effective strategies for engaging primary care patients in effective smoking treatment. About 75% of individuals who smoke make a primary care visit each year (King et al., 2013), and patients who smoke report that they are influenced by provider advice to quit (Halladay et al., 2015). Indeed, the World Health Organization (WHO) argues that primary care is the most suitable health setting for advising and supporting smoking cessation (Shibuya et al., 2003; WHO, 2015), as it provides frequent opportunities to help people quit (Lawson & Flocke, 2009; Ockene & Miller, 1997; WHO, 2018).

Integrating smoking cessation treatment in primary care has proven challenging, however. Studies indicate that many clinicians believe they lack training or expertise to intervene, have too little time to intervene, and lack effective treatment resources to which they can easily refer patients (Helgason & Lund, 2019; Ramsey et al., 2019; Rojewski et al., 2019; van Rossem et al., 2015). To overcome these barriers, some systems have adopted referral to external resources [i.e., Ask-Advise-Connect approaches (Vidrine et al., 2013)] as an alternative or complement to smoking treatment delivery in primary care encounters. State tobacco quitlines are a common external resource used by many health systems, and EHR-based quitline referral systems that both prompt and expedite referrals do increase rates of referral and quitline treatment utilization among adult primary care patients (NAQC, 2022). As noted above, however, fewer than 30% of quitline referred patients actually engage in quitline treatment, and these connection rates have been falling in recent years (Baker et al., 2021; Fiore et al., 2019; Tindle et al., 2016; Willet et al., 2009). While about 10-20% of patients who smoke agree to referral, only about 3-5% actually receive treatment (Albert et al., 2020; Baker et al., 2021; Fiore et al., 2019). Thus, there is still much room for improvement in efforts to connect adult primary care patients who smoke with EBST.

In addition, quitlines and most health system changes to support smoking treatment focus on smoking cessation treatments designed for people ready to make a quit attempt within the next 14-30 days. The many people who are not ready to quit within the next month often receive little more than brief

advice to quit (Papadakis et al., 2010). Although evidence-based strategies to increase quit attempts have been identified in the literature as efficacious ways to increase quit attempts (Carpenter et al., 2020; Cox et al., 2022), these have not yet been integrated into health system interventions designed to increase the reach of smoking treatments. For example, evidence indicates that nicotine sampling strategies in which people who smoke are encouraged to try nicotine replacement therapies even if not trying to quit can increase quit attempts, even with minimal advice or guidance (Burris et al., 2015; Carpenter et al., 2020). In addition, practice quitting for short periods of time also shows promise as a way to attract more people to make quit attempts and to fend off relapse during such attempts (Cox et al., 2022; McCarthy et al., 2016). To reach the many patients who have interest in quitting smoking at some point in the future, but who are not ready to try to quit within the next month (Petersen et al., 2017), we need to offer treatments that focus on helping people prepare to quit, rather than just focusing on the cessation phase of the quitting process (Baker et al., 2011).

Even among those who want to quit soon, offering treatment options that do not require person-to-person interactions or synchronous communication may enhance reach by attracting individuals who fear being disrespected or lectured to, feeling pressured to quit or shamed by smoking, or are reluctant to share personal information with strangers or relinquish personal agency in the quitting process (Halladay et al., 2015; Morphet et al., 2015; Smith et al., 2015). Texting programs such as the SmokefreeTXT program (and the Practice Quitting and Daily Challenge text-based programs for people not yet ready to quit) sponsored by the National Cancer Institute available at no cost to users throughout the US, may not activate such concerns (Morphett et al., 2015; Prutzman et al., 2021) and may be more acceptable than quitlines or interactions with their primary care providers to some patients. Similarly, nicotine sampling strategies that do not require person-to-person interactions (e.g., mailed medication samples) may appeal to a broad range of adults who are considering changing their smoking, even if they are not ready to set a quit date (Carpenter et al., 2020). As such, leveraging technology and asynchronous communication may be helpful in connecting more patients with treatment as people in the US migrate away from phone contact and toward digital connection (Meek, 2019).

The proposed trial will build on previous research that suggests that repeated proactive outreach to primary care patients who smoke offering a range of treatments to all patients who smoke, not just those ready to quit within 30 days, can meaningfully increase the rates at which adults try to quit smoking, and thereby increase the number who quit successfully (Ellerbeck et al., 2009; Joseph et al., 2011; McCarthy et al., 2022). The proposed trial will evaluate this expanded approach to EBST promotion against a robust standard care approach in which TCMs help patients navigate their smoking cessation treatment options. The programs will be compared in terms of their effectiveness and equity in connecting patients with EBST, and in terms of their efficiency and cost-effectiveness under real-world conditions.

In this way, the proposed trial will generate new knowledge about an augmented intervention approach that may enhance the population impact of readily available EBSTs by increasing their reach among adult primary care patients who smoke.

The proposed project will also address another important problem limiting the impact of EBST on population health. Although EBSTs are widely available at low or no cost, and covered by most insurance plans, including public program such as Medicaid, marked disparities in EBST access persist, and have even grown over recent decades as more effective treatments have been developed and disseminated (Jamal et al., 2016, 2018; Sheffer et al., 2012). Even though many tobacco quitline clients identify as socioeconomically disadvantaged, uninsured, or Medicaid-eligible, these populations are still underrepresented among quitline service recipients, as smoking prevalence in these groups is roughly double that of the general population (CDC, 2015; NAQC, 2022). Furthermore, members of minoritized racial and ethnic groups use treatment and succeed in quitting at lower rates than do members of non-minoritized groups, despite making more attempts to quit (Browning et al., 2008; Danesh et al., 2014; Fox & Sh[paw, 2014; Hiscock et al., 2012). These disparities in treatment access and quitting success likely contribute to inequities in the downstream toll of tobacco use in terms of disease, disability, and death and are critically important to address (CDC, 2015; Lehrer et al., 2014; Nordahl et al., 2014). Recent evidence suggests that health system changes that make offering EBST the default have the potential to close gaps in treatment reach across patient groups defined by demographics such as race and ethnicity or by insurance type (Baker et al., 2021; Creswell et al., 2022; McCarthy et al., 2022). Given this, the proposed trial will evaluate the enhanced outreach program in terms of its equity or representativeness of reach among patient groups, particularly historically underserved populations.

3.0 Study Objectives and Endpoints

3.1 Primary Aims

1. To use a cluster-randomized controlled trial to **evaluate a reach intervention package** designed to increase cessation treatment reach especially well, at low cost, at 1-year follow-up.
2. To estimate the effects of randomized reach intervention package on cumulative treatment **reach over 18 months** of treatment access.

Secondary Aims

3. To estimate the effects of the enhanced reach intervention on **abstinence** at 12 and 18-month follow-ups.
4. To identify the degree to which intervention effects on 2-year abstinence are **mediated by increases in cessation treatment reach**.

5. To assess the **cost-effectiveness** of the reach intervention in promoting reach and abstinence.
 6. To identify patient and clinic **moderators** of intervention effects on reach and abstinence.
- 3.2 We hypothesize that the enhanced reach intervention package will increase the rate at which adult primary care patients initiate smoking treatment over 12 and 18 months, relative to a standard care approach, and will do so in a manner that is cost-effective and equitable. We also hypothesize that increasing treatment reach through enhanced reach interventions will lead to increases in conversion from current to former smoking status in the EHR.
 - 3.3 The primary endpoints of interest are the rates at which adult primary care patients who receive smoking intervention offers initiate smoking treatment within 12 and 18 months of study entry. Secondary endpoints of interest are rates of achieving abstinence from smoking (as indicated by a change in smoking status from current to former smoking in the EHR) within 12 or 18 months of study entry, and costs and cost-effectiveness of the standard and enhanced reach intervention approaches.
 - 3.4 There are no primary or secondary safety endpoints in this minimal risk study of ways to enhance the reach of existing, FDA-approved and publicly available smoking cessation treatments.

4.0 Number of Participants

- 4.1 Up to 13,000 adult primary care patients from 10 clinics will participate.
- 4.2 We anticipate that up to 7% of patients notified about the program may opt out of participation, so the retained sample may range between 11,160 and 13,000 patients.
- 4.3 Participants will be considered enrolled in the study if they receive an initial study notification and do not opt out of or withdraw at any time during the study. All patients will have the option to opt out or withdraw and will be notified about this at study launch. Patients who opt out will not be replaced.

5.0 Inclusion and Exclusion Criteria

- 5.1 Patient inclusion and exclusion criteria include:
 - Adult age 18 years or older
 - Meet criteria for including on a smoking registry (based on current smoking status and/or recent diagnosis of nicotine dependence or treatment of nicotine dependence)
 - Being seen in a participating clinic in the past 1-3 years, as documented in the EHR
 - Having a valid address (e.g., street address, city, state, zip code)

- Not having a language other than English listed as their preferred language (people whose preferred language is missing will be included)

These criteria must be met at the time that initial launch letters are sent. Patients meeting these criteria at the time of launch will be considered enrolled unless they opt out (by communicating this to TCMs after receiving the study notification).

The research team will not keep screening data. Health system TCMs will keep a list of their patients who received launch letters in order to keep track of patients who opt out so they can ensure that patients who do not want to have their medical records included in the deidentified medical records study and/or do not want to receive EBST outreach will not be included in outreach efforts or EHR data extraction.

- 5.2 All patients who meet criteria for inclusion at the time that initial outreach letters are generated who do not opt out over the following 18 months will be included in the final sample.
- 5.3 The only exclusion criteria for the final study sample are:
 - Patient has an invalid address.
 - Patient has a preferred language other than English documented in the EHR
 - Patient had an activated power of attorney for healthcare or a legal guardian documented in the EHR at the time TCM phone outreach is due or if/when a patient seeks to join the communications and/or treatment substudy.
 - Patient opted out of the study within 18 months of initial outreach letter.
 - Patient clarification that they did not meet criteria for the smoking registry at the time of initial outreach (i.e., their smoking status was inaccurately documented in the EHR and the patient should not have been included in the registry).
 - Request from a patient's activated durable power or attorney for healthcare or legally authorized representative that the patient be excluded from mailed outreach and or EHR data extraction (in addition to TCM outreach and any substudy activities).
- 5.4 No specific population will be targeted or excluded on the basis of demographics or other characteristics beyond age (at least 18 years old), the criteria listed above, and receiving care at a participating clinic.

6.0 Special Populations

6.1 *Vulnerable Populations.* Because we seek to evaluate a health system intervention package that will promote use of EBST, and thereby abstinence from smoking, from the full range of adult patients who smoke cigarettes, 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 incarcerated at the time study initiation letters are mailed may also be incidentally included, as it is not possible to screen incarcerated individuals out of the mailing preparations, since this is not recorded as a discrete field in patient's electronic health records. 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 do not opt out (or have an activated power of attorney for health care or legally authorized representative opt out on their behalf).

None of these vulnerable populations will be specifically targeted in recruitment. The proposed reach interventions 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 follow extant standards of care, confer minimal risk, and are informational in nature. The risks of particular sub-study activities (e.g., using e-mail, text messages, or web-based forms of communication to communicate interest in treatment to TCMs) will be disclosed to participants, and active consent will be required before they engage in any of these forms of communication. The risks of FDA-approved over-the-counter nicotine replacement therapies that will be available at some clinics will be disclosed to participants before they consent to participating in this activity and request samples, and requesting patients will be screened prior to medication dispensing for medical eligibility (including pregnancy and breastfeeding status to ensure that people who are pregnant or breastfeeding are not sent samples). Impaired decision-making capacity will be assessed by checking the EHR to see if a durable power of attorney for health care is currently activated or if a legally authorized representative is responsible for patient care decisions. TCMs will check this before making any outbound phone calls for smoking treatment outreach, and at the time a patient requests either e-mail or text message communication or smoking treatment. Having either a power of attorney activated or an active legally authorized representative will preclude TCM phone outreach or inclusion for either of these substudies (i.e., people with an activated power of attorney for health care or a legally authorized representative noted in the EHR at the time of requests will not be permitted to participate in the substudies). Mailed outreach activities and EHR data collection will be conducted for all patients who meet the minimal inclusion/exclusion criteria articulated above.

If a TCM learns at any point in the study that a participant is currently incarcerated, their participation in the study (and any/all substudy activities

to which they may have consented when not incarcerated) will be suspended until the TCM learns that the participant is no longer incarcerated. That is, no study activities (e.g., consent to substudies, TCM-initiated contacts, automated mailings, etc.) will occur during a period of incarceration.

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

6.2 Vulnerable Populations. **Not applicable.**

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

6.3 Although we will not be targeting patients low in literacy, or those with visual or hearing impairments, it is possible that patients with these characteristics may be included. To ensure that literacy and sensory impairments do not impede understanding of the study or their right to opt out, initial outreach letters will be written in accessible language and will contain QR codes that patients can use to access audio recordings of the information in the letter.

Check all that apply.

- ☐ Non-English speaking participants
- ☒ Illiterate or Low Literacy participants
- ☒ Participants with visual or hearing impairments
- ☐ Status Relationship: Individuals with a status relationship with the PI or other study team members (e.g., employees, students, family members)

7.0 Recruitment Methods

7.1 Participants will be adult primary care patients at participating clinics identified based on review of health records. Analysts at the two health systems partnering in this research will compile reports of patients who are eligible for the proposed study based on their age, past-year tobacco use status, receipt of care at a participating clinic in the past year, preferred language, and valid address. These reports will be used to generate letters

mailed at study initiation that will inform patients about the nature, purpose, and risks of the study and provide them with instructions about how to opt out of the study if they prefer not to participate. In addition, in some clinics (those randomly assigned to the Enhanced Outreach arm of the trial) all participants who received the initial study letters and who did not later opt out/withdraw or get removed due to ineligibility or incarceration will receive quarterly postcards reminding them of their treatment options and ways to contact the TCM. These quarterly postcard mailings will thus serve as recruitment methods for the optional treatment and communication sub-studies in the Enhanced Outreach clinics.

- 7.2 Participants will be enrolled based on information contained in medical records unless they opt out of participation. Members of the research team will not access the EHR records that will be used to determine eligibility directly. Instead, analysts/report writers at the partnering health systems will prepare reports of eligible patients that will be used to generate initial study launch letters with instructions about ways to opt out by notifying TCMs at the participating health systems. As such, participant identification and notification regarding the study will be completed by healthcare system personnel.
- 7.3 Participants identified based on medical records review will be considered enrolled in the study if they do not notify a TCM that they would like to opt out in response to a mailed letter regarding their inclusion in the study. Patients (or their power of attorney or legally authorized representative) will have the opportunity to opt out at any point in the 18-month study. The letter will contain a QR code that recipients can scan to access an audio version of the content of the letter.
- 7.4 A mailed letter (uploaded with the application) will be sent to patients identified by EHR at study launch. The audio version of the mailed letter content will have essentially the same content, minus the addressee, salutation, and closing material (see uploaded script). The study notification mailing will occur once per clinic, at the time of study initiation. Recruitment will not be ongoing/rolling. Instead, all members of the cohort identified by EHR at the time of study initiation will be considered enrolled until and unless they opt out over the following 18 months. The only recruitment activity that will continue after opt-out enrollment in the parent study is promotion of treatment options and the communication substudy to participants who did not opt-out/withdraw from the parent study, and who were are not known to be ineligible (e.g., due to lack of baseline smoking or temporarily due to incarceration). This promotion will be achieved via mailings of postcards (uploaded with the application).
- 7.5 Participants will not be compensated.

8.0 Consent/Assent Process

- 8.1 Informed consent will not be obtained for either mailed outreach or proactive TCM outreach telephone calls to participants in this study. Instead, an opt-out recruitment approach will be used in an effort to enroll a representative cohort of patients in this minimal risk study, while also protecting patient autonomy by providing opportunities to opt out of outreach regarding available EBST and deidentified EHR data collection. Among those patients considered enrolled because they were sent a study notification and did not opt out of participation, some participants may choose to opt in to sub-study activities to gain access to EBST, with modified, remote informed consent collected via Qualtrics or REDCap survey or oral consent during phone calls with TCMs at participating health systems. Both online and oral options will be offered to maximize accessibility and convenience for participants, as the online version will be available at any time (not just during TCM working hours) and the oral version may be easier and more appealing to those with limited literacy or comfort with digital technology.

All enrolled participants will have the option to request EBST during the study. Those who elect to use standard treatment options to quit (WTQL services, referral back to their PCP) will not need to provide informed consent for human subjects research to initiate such treatments, as these treatments are available as the current standard of care in participating primary care clinics. Those who elect to receive treatment through a smoking cessation randomized clinical trial (IRB protocol # 2019-0054) will complete all invitation, screening, and consent procedures according to the IRB approved protocol for that study. These forms of treatment (WTQL, PCP referral, smoking cessation trial #2019-0054) will be available to all participants in the proposed cluster-randomized trial by calling a TCM at their host health system. Only those who do not have an activated power of attorney for healthcare or a legally authorized representative active, as noted in the EHR, at the time they request treatment will be able to consent to WTQL or to cessation trial #2019-0054. Note that cessation trial #2019-0054 will be removed as a treatment option as of 2/23/24 due to the closure of the trial's recruitment.

Patients in 5 of the 10 clinics in the cluster-randomized controlled trial will have access to additional means of requesting treatment, and additional treatment options, if they provided modified, remote consent for these activities at the time of treatment interest/initiation, and if they do not have an activated power of attorney for healthcare or a legally authorized representative noted in their EHR at the time of the treatment request.

These options include the following:

- The ability to fill out a treatment request online via a secure Qualtrics or REDCap survey viewable by only TCMs at their home health systems and the few research staff who maintain the Qualtrics

or REDCap survey and co-supervise the TCMs and are covered under agreements with the health systems (e.g., Business Associate Agreements). This treatment request survey is available via URL and QR code. The survey will be preceded by an online consent form, presented in both written and audio versions. Consent will be implied by choosing to open the survey after reading/hearing the consent information. Before participants consent, they will have the opportunity to submit any questions they may have in a brief question web-survey (uploaded), or by calling their TCM. The online consent form, online question survey form, and the treatment request survey are uploaded with this application. Within the survey, information about the nature and risks of each treatment option will be disclosed (in both written and audio form) and participants will have to confirm they have reviewed this information before completing brief treatment screening questions and requesting treatment. Both online and oral options are offered to maximize participant access to treatment and convenience. To ensure that people with compromised decision-making capacity do not receive treatment following an online consent, TCMs will check the EHR to see if a power of attorney for health care or a legally authorized representative is active at the time of the consent and treatment request before the request is fulfilled. TCMs can do this during phone calls with patients, and after online consents. Treatment requests will not be fulfilled for those with compromised decision-making status.

- The additional treatment options offered in these 5 clinics can be requested via phone call with the TCM or the secure Qualtrics or REDCap survey describe above. These self-guided treatment options will include:
 - Referral to or TCM-facilitated enrollment in one of three NCI-sponsored Smokefree.gov text messaging programs for people seeking to change their smoking:
 - SmokefreeTXT (a 6-8 week daily text message program for people willing to set a quit date in the next 14 days, offered at no-cost, apart from cell phone minutes or data charges for participants who do not have unlimited plans).
 - Practice Quit for people who are ready to practice quitting for up to 5 days, but are not ready to set a date to quit smoking permanently.
 - Daily Challenges for people who want to develop skills to help them change their smoking, but who are not ready to quit just yet.
 - Requesting free 2-week starter kits of 2 of the following FDA-approved over-the-counter nicotine replacement therapies (limit to 2 samples per quarter).

- Nicotine patches (with dose titrated to smoking heaviness, as per package insert)
 - Nicotine gum (with dose titrated to latency to smoking after waking, as per package insert, in a range of flavors)
 - Nicotine mini-lozenge (with dose titrated to latency to smoking after waking, as per package insert, in a range of flavors)
 - Medications will only be dispensed to people who consent to and complete an online or phone screening for medical eligibility and complete an online or phone consent for NRT sampling.
- The ability to opt into text and/or e-mail communication with the TCMs via Twilio and REDCap for outbound (REDCap-generated) quarterly communications, and university-owned phones and e-mail addresses for patient-initiated and two-way interactive communication between participants and TCMs. University-owned cell phones and e-mail will be used for all communication sub-study participants (i.e., those from both UW Health and AdvocateAurora Health). Different systems will be used for scheduled outreach activities (Twilio via REDCap) versus participant-initiated/2-way communication (university e-mail or cell phone) because of security risks that are raised by allowing direct participant interaction with the substudy REDCap database. To enhance the security of this database, we will not allow incoming messages to be imported. The study launch letter and the online version of the study launch information accessible via QR code and URL will both contain information about the option to communicate with TCMs via e-mail or texting. A secure Qualtrics form will be used to collect informed consent for two-way communication between participants and TCMs via e-mail and or text messages (see uploaded consent materials), in addition to an oral consent process conducted by TCMs over the phone (people can consent in either modality). Participants will have the opportunity to opt in to receiving treatment offers via these modalities, as well. All e-mail and text message communication is optional. We are offering these forms of communication to increase patient access to information about their treatment options (so they do not have to have their mailed letter on hand to review their options, and so they are not limited to requesting treatment during TCM working hours). Phone consents will not be completed with patients with an activated power of attorney or legally authorized representative, and online consents will not be accepted or acted upon if a patient has an active power of attorney or legally authorized representative at the time of consent.

- 8.2 We plan to use a streamlined consent process for treatment initiation and e-mail and/or text communication that will be highly accessible to participants. Given the minimal risk nature of these sub-study components, these consent processes will omit some standard components of consent processes. These online or oral consent processes will be followed up with a written study information sheet containing all relevant elements of consent, however.

Specifically, we seek a **waiver of informed consent for the proactive outreach** calls that TCMs will conduct, and the outreach mailings that will happen in all participating clinics (once at study launch in clinics in the control condition and quarterly in clinics in the experimental condition). The justification for this waiver of informed consent for this FDA-regulated study is as follows (using criteria outlined in CHECKLIST HRP-410):

- The investigation involves **no more than minimal risk** to subjects as the primary study activities include receiving written and oral information about readily available standard treatments for quitting smoking (and optional communication or readily available treatment activities to which patients would consent before participating in them). The risk is minimal due to the informational nature of the study procedures and the fact that only standard care and FDA-approved over-the-counter medications and publicly sponsored psychosocial treatments for smoking (e.g., through the Wisconsin Tobacco Quit Line and Smokfree.gov) will be promoted in the study.
- Waiving informed consent for proactive outreach **will not adversely affect the rights and welfare of subjects** because subjects will be informed in writing of their right to opt out at study initiation; any and all requests to opt out of proactive outreach mailings and letters will be honored; subjects may choose to decline or dispose of letters or decline to take calls, without any penalty, punishment, or alteration in their treatment in their host health system.
- The clinical investigation **could not practicably be carried out without this waiver** of consent because only including patients who proactively volunteer or agree to receive information about their smoking treatment options would bias the sample toward patients with the greatest interest in smoking treatment. Results of such a study would not address the critical gaps in the research literature on ways to better engage patients who smoke in EBST, and would not provide clear guidance to health systems about how best to reach the patients who are not initially or intrinsically interested in smoking treatment.
- **Subjects will be provided with additional pertinent information during or after participation.** In the initial launch letter, patients will be provided basic information about the study (who is leading the study, why the patient was included, why the study is being done and what it entails, how long the study will last, what data will be collected about participants, and what alternatives are available). In addition, the

launch letter will direct patients to a health system employee (a TCM) who can provide additional information, answer any questions patients may have, address any concerns raised by patients (in consultation with the study team and/or DSMC or IRB, as needed), and can honor any patient requests to cease smoking treatment outreach activities. Oral versions of the same information will be available to all letter recipients, either via the web or via phone call to a TCM.

We also seek an **alteration of consent and waiver of documentation of signed consent for substudy activities** that participants may opt into in the Enhanced Care condition. The justification for this request is as follows (using CHECKLISTS HRP-410 and 411 as guides):

- The communication and self-guided treatment substudies involve **no more than minimal risk** to subjects. Opting into e-mail and/or text communication with TCMs regarding smoking treatment options poses minimal risks to participants and these will be disclosed prior to enrollment in the communication substudy. Similarly, initiating a Smokefree.gov texting program to change smoking or trying FDA-approved, over-the-counter nicotine patches, gum, or mini-lozenges poses minimal risks to adult patients who smoke cigarettes, particularly when screening protocols for any safety concerns are in place, as they are for the treatment substudy.
- Waiving informed consent for proactive outreach **will not adversely affect the rights and welfare of subjects** because subjects will be informed of the risks, benefits, and alternatives (in oral and or written format on the web) prior to providing oral or web survey consent to join the communication and/or treatment sub-study.
- The clinical investigation **could not practicably be carried out without this waiver** of consent because requiring written documentation of consent would bias the sample toward those with the most stable motivation to change, greatest literacy, greatest digital literacy, and/or most sustained access to digital technology. Because the aim of the proposed research is to identify strategies that health systems can use to increase the reach of existing EBST among all their patients who smoke, biasing the sample toward those with the greatest motivation, education, or socioeconomic status would negatively affect the impact of the substudies.
- **Subjects will be provided with additional pertinent information during or after participation.** After subjects provide oral or online consent for a sub-study, a detailed study information sheet containing all required elements of consent and HIPAA authorization will be mailed to them (with audio versions also available online). Mailing these ahead of time to all patients in the Enhanced Care clinics would adversely affect the study manipulation of outreach programs. Sending 17 pages of written study information sheets to patients in the Enhanced Care condition clinics, but not the Standard Care condition

clinics, would lead to an imbalance in the study conditions that would complicate interpretation of results. This would also reduce the real-world relevance of the enhanced care communication and treatment options, in which 7-10-page documents would not be required to offer additional communication modalities or self-guided treatment options to patients. Given these concerns, we believe the study will have greater value if we offer detailed information in writing to participants during and after their requests to enter the communication and treatment substudies, rather than before they express initial interest in these options. Despite this, essential information about risks and benefits of text and/or e-mail and about Smokefree.gov texting programs and nicotine replacement therapies will be provided in the initial and quarterly outreach letters sent to patients in the Enhanced Care clinics.

- We request a waiver of written documentation of consent for substudy participation because **the research involves no procedures for which written consent is normally required outside of the research consent**. Written consent is not typically required to consent to over-the-counter medication, referral to the Wisconsin Tobacco QuitLine, enrollment in a Smokefree.gov texting program, or consent to receive text or e-mail communications. Outside the research context, oral or online responses are sufficient to indicate consent for these activities.
- We also request a waiver of written documentation of consent for substudy participation because **written information describing the research will be provided to the subject** after oral or online consent for the substudies (as described in greater detail above).

We also seek a waiver of HIPAA authorization for the medical record review and proactive (mailed and telephone) outreach for recruitment and conduct of study, and an alteration of HIPAA authorization for the communication and treatment substudies (as signatures will not be required and not all elements of HIPAA authorization will be covered during the oral or online consent process). All required HIPAA authorization information will be included in mailed information sheets that will be sent to participants who consent to a substudy, however. The justification for this request is as follows (using CHECKLISTS HRP-441 as a guide):

- The PHI needed for **recruitment and for study conduct** is described in the protocol and is **limited to information needed** to mail outreach letters and for TCMs to make outreach calls to adult patients who smoke and meet eligibility requirements for the study. Data collected about patients prior to consent will include: MRN, name, DOB, date visited a participating clinic, care team members who treat the patient (at the most recent clinic and for primary care), address, phone numbers, preferred language, preferred communication modality, tobacco use status, insurance, and demographics), and whether a power of attorney for health care or

legally authorized representative is active at the time the patient is due for TCM phone outreach or substudy participation request.

- The use or disclosure of PHI involves **no more than minimal risk** to privacy because there are thorough plans in place to: protect identifiers from improper use and disclosure (e.g., secure data transfer and storage practices; tight access controls, with access limited to TCMs and those who maintain the databases or oversee TCM outreach; logging of record access); destroy identifiers at the earliest opportunity after achievement of the study aims; prevent reuse or disclosure of PHI (except as required by law or authorized oversight bodies).
- The **research is not practicable without a waiver and alteration** of HIPAA authorization due to the sampling bias and reduced generalizability that would result.
- The research **could not practicably be conducted without access to PHI** because outreach letters must be mailed to eligible patients, TCMs must have access to phone numbers to call patients and must have access to the EHR to verify eligibility and to update records to reflect smoking treatments used by the patient.

Non-English Speaking Participants

- We do not plan to enroll participants whose preferred language is not English. Having a language other than English listed as the preferred language in the EHR is an exclusion criterion. To enhance understanding for people who may have limited English literacy, we will provide audio recorded versions of written documents regarding the study initiation letter that describes the opt-out process and regarding optional sub-study components (e.g., treatment initiation, e-mail or text communication).

Participants who are not yet adults (infants, children, teenagers) will not be included in the proposed study.

Adults with Impaired Decision-Making Capacity will not be included in the proposed study.

- Our partners at the healthcare systems have advised us that decision-making capacity fluctuates often within patients (e.g., around the time of a major medical procedure), and that exclusion for impaired decision-making process should occur at the time of treatment request or opting into the e-mail and text substudy, rather than at study launch. Patients who have an activated durable power of attorney for health care or who have a legal guardian identified in their EHR will be excluded from substudies and will not be able to consent to treatment outside of care from their regular health care team. In other words,

adults with impaired decision-making capacity may be included in the medical records review portion of the study and in mailed outreach (if they, their activated power of attorney, or legally authorized representative do not opt them out of the study), but they will not be able to consent to initiating external treatment (WTQL, Smokfree.gov texting programs, or nicotine samples) or text or e-mail communication with the TCMs. In addition, TCMs will not place outreach calls to people with an activated power of attorney or legally authorized representative at the time the patient is due for outreach (i.e., this is an exclusion criterion for telephone outreach).

Adults Unable to Consent will not be included in the proposed study.

- In addition to the protections described above for those with impaired decision-making, understanding of oral consent will be assessed prior to consent completion to prevent those who do not understand the consent materials from consenting to treatment or e-mail or text communication (online or by phone).

9.0 Process to Document Consent in Writing

9.1 Consent for study participation will not be documented for all participants in the parent medical records review study or for the mailed and TCM telephone outreach components of the study because we will be using an opt-out approach to study enrollment. Consent for optional sub-study components including treatment initiation and e-mail and/or text communication will not be documented in writing by the participant, apart from electronic documentation that a participant viewed or listened to a consent form before progressing to treatment request or e-mail or texting consent via either phone contact with a TCM or a Qualtrics or REDCap survey. This will be supplemented by documentation in REDCap that a TCM verified that neither an activated power of attorney for healthcare nor a legally authorized representative was documented as active in the EHR at the time of consent. Documentation of informed consent via other means (wet signature or e-consent) would be impracticable due to the bias that would result in the sub-study samples if in-person contact or access to e-consent computing resources were required to request treatment or to opt into text messaging. Although those who prefer e-mail communication may have computing resources for e-consent processes, such processes are more involved than simply sending and receiving e-mails and may not be equally accessible among all members of the target population. As such, we would like to offer an oral consent process as an alternative to an e-consent process for e-mail communication as well as text messaging and treatment requests. The consent scripts and online consent content are uploaded with the application.

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

10.0 Setting

10.1 The proposed research will be conducted at the University of Wisconsin Center for Tobacco Research and Intervention and Advocate Aurora Health Care.

- It will involve collection of deidentified EHR data from adult primary care clinics receiving care from 5 clinic sites at Advocate Aurora Health and 5 clinic sites at UW Health. Data on treatment requests, screening, and initiation and e-mail and text-message communication between health system TCMs and participants who opt in to sub-studies offering these opportunities will also be collected with altered consent processes.
- No compensation will be offered to patients in the proposed study.
- No community advisory board will be involved.
- The Advocate Aurora Health Care IRB will complete the RELIANT process and cede to the UW IRB as the IRB of record for this study.

11.0 Study Intervention

11.1 *Description:* The intervention to be evaluated in this cluster-randomized controlled trial is a package of outreach strategies and menu of smoking treatment options for adult primary care patients who smoke. The experimental reach-focused intervention package will comprise quarterly outreach via letter and applicable patient-preferred modalities (including EHR patient portal (if this is activated in the EHR), e-mail (if participant consents to e-mail communication with the TCM), text messages (if participant consents to text message communication with the TCM), and calls from TCMs 1-30 days after qualifying primary care visits (as already approved in IRB protocols 2019-0054 and 2019-0939) and prior to 2/23/24 at the close of IRB protocol 2019-0054 study recruitment

All of the outreach efforts in the experimental arm of this trial will promote access to the following treatment options:

- Nicotine sampling (patients can request 2 weeks starter kits of any 2 of the following nicotine replacement therapies (patch, gum in any available flavor, mini-lozenge in any available flavor), even if they are not ready to set a quit date

- Facilitated enrollment in an NCI-sponsored text messaging program: SmokefreeTXT (if ready to set a quit date in the next 14 days), Practice Quit (if ready to practice quitting 1-5 days but not ready to quit permanently), or Daily Challenges (if not ready to quit, but willing to make some changes)
- Referral to the WTQL
- Referral back to the PCP
- *Screening/enrollment in IRB protocol 2019-0054. Note: Cessation trial #2019-0054 will be removed as a treatment option as of 2/23/24 because recruitment for that study has closed.*

This experimental reach-focused intervention package will be compared against an active comparator comprising one-time outreach via mailed letter at study initiation outlining available treatment options and ways to contact the TCM by phone to either opt of the study or request treatment, and telephone outreach by TCMs 1-30 days after a recent visit to a participating primary care clinic (and prior to 2/23/24 at the close of IRB protocol 2019-0054 study recruitment) to offer smoking treatment options including 3 cessation-focused treatments:

- Referral to the WTQL (if ready to set a quit date in the next 30 days)
- Referral back to the PCP
- *Screening/enrollment in IRB protocol 2019-0054. Note: Cessation trial #2019-0054 will be removed as a treatment option as of 2/23/24 because recruitment for that study has closed.*

11.2 Drug/Device Handling: Nicotine replacement therapies will be received, stored, and disseminated as follows

- Study medications (nicotine patches, gum, and mini-lozenges) will be received at the Center for Tobacco Research and Intervention by Kari Giacalone or her designees in the Madison office.
- Nicotine patches will arrive in commercially packaged boxes of 14 patches each (two weeks of 21mg, 14mg, or 7 mg patches).
- Nicotine mini-lozenges will arrive in boxes of 81 (standard commercial packaging sizes).
- Nicotine gum will arrive in boxes of 100-110 pieces (standard commercial packaging sizes)
- Study medications will be stored in designated locked drug cabinets in Madison until processed for dispensing.
- Dissemination mailings containing processed study medication will be labeled with Study ID and subject initials and stored in secure, locked cabinets, closets, or rooms in Madison.
- Medication will be mailed to participants. Due to potential changes in medication, and availability of multiple flavors of gum and mini-lozenges, medication mailings will be assembled to order rather than preassembled.
- Medications returned by mail will NOT be recirculated.

- 11.3 No investigational drugs will be used. All nicotine replacement agents to be distributed to patients are currently FDA approved for use to treat smoking and are available over the counter. This use of nicotine replacement agents is considered IND exempt under category 1 (21 CFH 312.2(b)(1)),

12.0 Study Timelines

12.1 Timeline:

- An individual participant will be in the study for 18 months. The start date and duration of participation will be noted in the initial study launch letter mailed to participants at the start of the study.
- All participants will be enrolled within 6 months, as we will make efforts to prepare and launch study initiation letters (with opt out instructions) at nearly the same time in all 10 clinic sites.
- The estimated date for completion of primary analyses is April 30, 2025.

13.0 Procedures Involved

13.1 **Enrollment.** A cohort of up to 13,000 adult primary care patients whose EHR data indicates they currently smoke cigarettes will receive a mailed letter (and QR code to take them to an audio version of the letter) notifying them of study initiation and of the opportunity to opt out. Letters will be prepared for each clinic separately based on their panel of patients treated in the past year. All 10 sites will prepare mailings to eligible patients within the first 6 months of the study. Patients sent the study initiation letter (or their activated power of attorney or legally authorized representative noted in the EHR) will have the opportunity to opt out over the next 18 months.

E-mail, web-based Qualtrics survey, and texting communication sub-study. Participants in the parent, opt-out medical records review study who are in clinics randomized to the enhanced reach intervention arm and who elect to opt-in to additional forms of communication for the purposes of study participation and treatment initiation will need to provide altered, remote, informed consent for these forms of communication before they can communicate with TCMs in these ways. Patients in the enhanced intervention clinics who consent to such communications can use these modalities to request information about their treatment options (in addition to mailed letters or EHR patient portal messages and possibly also calls from TCMs after clinic encounters) and to request treatment without having to engage in synchronous phone contact. Participants who enroll in this communication substudy will be mailed a welcome letter and a study information sheet this details about the study after they enroll (see uploaded materials).

Treatment sub-study. Participants in the parent, opt-out study who elect to pursue smoking treatment through the study will complete an active consent process (i.e., will have to opt in) to request treatments that are not currently the standard of care in their clinics (i.e., any treatments other than WTQL referral and referral back to their PCP). In order to access the treatments offered in IRB protocol 2019-0054, participants in this study would have to complete the IRB-approved oral screening, consent, and medication approval processes that are part of that protocol. In order to access nicotine samples or Smokfree.gov texting programs, participants in the experimental arm of the proposed trial will need to provide informed consent to screen for and initiate these treatments (see uploaded document). A welcome letter and detailed study information sheet will be mailed to those who consent to this treatment sub-study (see uploaded materials). The treatment options available to participants include:

- Referral to the WTQL that offers all residents in Wisconsin aged 13 and older free phone, web, and/or texting coaching in quitting and medically eligible patients a free 2-week supply of one nicotine replacement therapy (either nicotine patch, gum, or lozenge). When a patient is referred to the WTQL by their health system, the WTQL makes up to 5 attempts to reach the patient at the phone numbers provided in the referral. Patients are also able to call the WTQL 24 hours a day, 7 days a week, or to use text or a web form to enroll. When the WTQL connects with a patient, the patient must complete a registration process by phone. Those who are willing to set a quit date within 30 days of registration are offered one free proactive coaching call from a WTQL quit coach, unlimited ad hoc calls initiated by the WTQL client, a text-to-quit program, and web coaching resources. Those who meet medical eligibility according to standing WTQL protocols for medication are allowed to choose one medication that they can receive by mail once per year. This is standard care for the WTQL.
- Referral back to the PCP entails advising patients that their PCP can offer counseling and help with smoking cessation medications and instructing them to contact their clinic to schedule an appointment if they would like to discuss smoking treatment with their PCP. Patients will be informed that they and their insurance may be charged for such appointments and for medications prescribed by their PCPs. This is standard care in both participating health systems.
- Requesting nicotine samples (2-week starter kits of up to 2 of the following medications per quarter:
 - Nicotine patch
 - 21 mg dose for those who smoke 10 or more cigarettes per day,

- 14 mg dose for those who smoke 5-9 cigarettes per day or for those smoking 1-4 cigarettes per day and requesting only patches (without gum or mini-lozenge).
 - 7 mg for those who smoke 1-4 cigarettes per day and request either gum or mini-lozenge in addition to patches. This is more conservative than the package insert guidance for patch dosing, which suggests the 14 mg dose for all those who smoke fewer than 10 cigarettes per day; we are taking this more conservative approach for participants who request nicotine gum or lozenge to prevent side effects that may occur combination therapy at a higher dose of nicotine patch in those who smoke fewer than 5 cigarettes per day.
- Nicotine gum in flavor of participant's choice (mint, spearmint, ice mint, cinnamon, fruit)
 - 2 mg dose for those who wait at least 30 minutes after waking to smoke
 - 4 mg for those who smoke within 30 minutes of waking)
- Nicotine mini-lozenge in flavor of participant's choice (mint or ice mint coated)
 - 2 mg dose for those who wait at least 30 minutes after waking to smoke
 - 4 mg for those who smoke within 30 minutes of waking).
- Smokefree.gov texting programs are free of charge and available throughout the US and US territories.
 - SmokefreeTXT is a program that sends up to 5 text messages per day (programmed to occur during typical waking hours) for up to 2 weeks before a target quit date and 6 weeks after a target quit date, with less frequent follow-up messages up to 1 year post-quit-date. SmokefreeTXT also instructs enrollees to text keywords if they want tips about how to deal with cravings, negative moods, or lapses, or if they want to stop receiving texts.
 - The Practice Quit program offers guidance in practicing quitting 1, 3, or 5 days (with no limit on repeating the program) and on-demand support, help with cravings, or help with negative moods.

- Daily Challenges is an alternative 7-day program for those who want to develop some skills before trying to quit. It offers information about craving management, help in identifying triggers for smoking, and inspiration and support. It is also repeatable.

To enroll in any of these programs, people must provide a text-capable phone number, zip code (to help identify the correct time zone for message scheduling), demographics (gender, race, ethnicity, for message tailoring), smoking frequency and tailoring (for message tailoring), and phone internet capability (to send links to external content to those with internet capable phones). To start SmokefreeTXT, people must also provide a quit day within the next 14 days. To start Practice Quit, people need to indicate if they want to practice 1, 3, or 5 times. Participants who consent to the treatment sub-study of the proposed study will be asked to share this information with the TCM so the TCM can facilitate their enrollment in the text program, if this is a treatment option they select. The TCM will also review the terms of the text services and their privacy practices with participants prior to enrollment. Participants will also be asked for their name and address so information sheets and print copies of the SmokefreeTXT Terms and Use and Privacy Policy can be mailed to enrollees.

- **Assessment.** Data collected for the study will come primarily from the EHR and not directly from participants. Patient study status will be recorded in the EHR by the TCMs to identify those who were: identified; declined (i.e., opted out); deemed ineligible (e.g., because their smoking status was wrong in the EHR and they received a study initiation letter in error); enrolled (did not opt out); or withdrawn (i.e., actively engaged in treatment seeking or opt-in communication and then withdrew) in the parent study. For those who initiate treatment, TCMs will also record this in the EHR, in accordance with standard clinical practice.

Part of requesting and consenting to treatment that exceeds standard care through the TCM in either 2019-0054 or the Enhanced Care intervention arm in the proposed study will involve consent to share information with the research team. Similarly, part of consenting to forms of communication with TCMs other than mail and phone will involve agreeing to share information about such communication with the research team. As such, the research team will not interact directly with participants to collect data in the proposed research, but TCMs will gather information that will be shared with the research team. Data to be shared with the research team will be deidentified wherever possible (with the main exception being for preparation and mailing of nicotine samples and Smokefree.gov texting program information, where it is necessary for the medication handling and mailing team to have patient names and addresses to dispense these medications and documents by mail). Because TCMs will handle all other

aspects of treatment coordination and communication with participants, identifying information for most study participants will not be needed by the research team. The data that TCMs collect in the course of treatment coordination and communication with participants will be tracked in a REDCap database to which access is limited to TCMs (with access limited to the health system that employs the TCM), and those involved in maintaining the REDCap database, Qualtrics survey, Twilio instruments for outbound communication, and university-owned email account and cell phones used for inbound/2-way communication and coordination who are covered by a Business Associate Agreement with the partnering health systems).

Information to be extracted from EHRs in a deidentified manner for participants in the cohort include tobacco use status; smoking treatment procedure codes, billing codes, and medication ordering; broader healthcare utilization data (for cost analyses); and demographics (age, sex, identified gender, race, ethnicity) and insurance type and study status. See uploaded list for data elements to be collected.

13.2 Schedule of procedures

SCHEDULE OF STUDY PROCEDURES

	Month						
	1-3	4-6	7-9	10-12	13-15	16-18	19
Enrollment via opt-out	X						
Outreach regarding treatment options in Standard Outreach clinics	X						
Outreach regarding treatment options in Enhanced Outreach clinics	X	X	X	X	X	X	
Access to TCM and standard smoking treatment (WTQL referral, PCP referral, smoking cessation trial IRB protocol 2019-0054)	XXX	XXX	XXX	XXX	XXX	XXX	
Access to additional smoking treatment options and expanded communication modalities with TCMs (e-mail, text messaging, Qualtrics) in the Enhanced Outreach clinics (nicotine sampling, text message programs)	XXX	XXX	XXX	XXX	XXX	XXX	
TCM collection of treatment utilization and communication modality consent and utilization data and TCM documentation of treatment delivery in the EHR	XXX	XXX	XXX	XXX	XXX	XXX	
Extraction of EHR data					X		X

13.3 In this pragmatic cluster-randomized controlled trial, few procedures will be just for research purposes. Smoking treatment coordination will be provided by TCMs employed by patients' healthcare systems. Although the frequency of outreach, the array of treatment options available, and the means by which patients can request smoking treatment will be manipulated across clinics in this trial, TCMs will provide standard smoking treatment coordination and phone outreach to all patients who smoke and are seen at the participating clinics, not just patients included in the proposed trial cohort based on medical records review. Likewise, TCMs and primary care teams will document smoking treatment in the EHR as they normally do as a part of clinical practice. The only procedures that are just for the purposes of the proposed study are the sub-study consent, communication via e-mail and/or text message, and enhanced treatment options (Smokefree.gov text message programs, nicotine replacement therapy sampling).

- Participants will not be routinely monitored for safety because the study focuses on outreach interventions designed to enhance the reach of extant EBST, rather than to evaluate the effectiveness of novel treatments, and because this is a pragmatic population health study in which data are collected primarily via medical records review (with optional substudies that involve direct contact between patients and TCMs).
- To reduce the probability or magnitude of risks of participation, patients whose preferred language is not English or who have diminished decision-making capacity will not be eligible for the substudies requiring consent, and those who do not smoke cigarettes, and those who do not meet medical eligibility criteria for nicotine replacement therapy at the time they request treatment will not be eligible to receive nicotine samples.
- No biospecimens will be collected from participants.
- The only drugs to be used in the proposed research are FDA-approved over-the-counter nicotine replacement therapies (nicotine patch, nicotine mini-lozenge, or nicotine gum) approved for the indication of treating cigarette smoking. These drugs will be used to increase the reach of EBST in a sub-study in which participants who meet eligibility criteria for and consent to receiving nicotine patch, gum, and/or mini-lozenge starter kits are mailed these medications along with instructions for their use.

13.4 Data collection

- List of data elements (see list of data elements to be extracted from the EHR uploaded in the ARROW application).
- Questionnaires, structured interviews, or other assessments. (See uploaded surveys and scripts in the ARROW application.)
- Source records that will be used to collect data about participants.

- ☒ UW Health medical or billing records via ICTR's Clinical Research Data Service (CRDS)
- ☒ UW Health HealthLink Records (study team will directly access; Tobacco Care Managers (TCMs) employed by UW Health will be the only study team members with access to HealthLink Records and will access these records only for the purposes of outreach to patients who smoke to offer smoking cessation treatments, and to update records of patients who were identified, declined, ineligible, enrolled, withdrawn, or who completed the study and received smoking treatment through the study).
- ☐ Data from departmental QA or QI database
- ☐ Data from UW Health Enterprise Data Warehouse (EDW)
- ☐ Data from PACS (Picture Archiving and Communication System);
- ☐ Data from Center for Medicare/Medicaid Services
- ☐ Data from publicly available datasets (e.g., U.S. census data)
- ☒ Data from outside institutions or organizations (specify: AdvocateAurora Health; Tobacco Care Managers (TCMs) at AdvocateAurora Health will play a role similar to that of the UW Health TCMs and similar data will be extracted from Clarity for EHR data analysis purposes)
- ☐ Other (specify: _____)

13.5 All available EHR data regarding healthcare utilization data, tobacco treatment utilization data, study status data, and tobacco use status data available during the study period (from study initiation in the first clinic to 18 months after the launch of the last clinic to launch, approximately 24 months total) will be collected from the EHR.

13.6 Only over-the-counter nicotine patches, nicotine gum, and nicotine mini-lozenges will be used in the nicotine replacement sampling sub-study; all these medications will be used for the FDA-approved indication of treatment of combustible cigarette smoking.

14.0 Comparison of usual care and study procedures

14.1 All of the smoking treatments to be offered in this study are readily available outside of the study. Participants can purchase nicotine replacement therapy on their own, request pharmacotherapy from their healthcare providers, access nicotine replacement therapy and coaching free of charge through the WTQL, and enroll in Smokefree.gov texting programs on their own. Patients in all participating clinics will be notified of at least some of these existing treatment options at least once during the study. All patients will be encouraged to use treatment to quit smoking. TCMs will call all eligible patients to let them know about standard care options (the WTQL, working with their provider), as well as a smoking treatment study enrollment opportunity (IRB protocol # 2019-0054) until 2/23/24 when recruitment

for trial #2019-0054 has closed. Patients at some clinics will be randomly assigned to have access to some additional outreach efforts, optional means of communication with TCMs, and optional treatments (nicotine samples, Smokefree.gov texting programs).

- 14.2 The existing standard of care recommended at UW Health is electronic referral to the WTQL, and/or care delivered by UW Health clinicians. The reach of these standard treatments is low currently, however. The proposed study is designed to enhance the reach of these and other EBST and help more people to quit smoking in both arms of the study. Advocate Aurora Health uses fax referral to the WTQL and care delivered by clinicians as the current standard of care.
- 14.3 Most of the treatment options available and most of data collection efforts will follow existing standards of care (WTQL referral, primary-care-provider referral, documentation of smoking cessation counseling and pharmacotherapy in the EHR). The only exceptions will be TCM documentation of communication preferences of and exchanges with patients who consent to e-mail, or texting communication modalities, nicotine sampling distribution, and facilitation of enrollment in SmokfreeTXT, Practice Quitting, or Daily Challenges texting programs. No assessments of smoking status that would not be conducted as part of routine care will be conducted.
- 14.4 Being enrolled in this study will not limit or delay access to standard care in any way. Standard care (WTQL and PCP referral) will be offered to every patient who smokes.

15.0 Withdrawal of Participants

- 15.1 Participants will be withdrawn from the study without their consent if they are found to have diminished capacity to consent (or to opt out) during the study, or if, in the judgment of the lead investigators, continued participation would not be in the best interest of the participant (i.e., if participation is causing distress or dysregulation in the participant). This is highly unlikely given the nature of the proposed study.
- 15.2 For patients in the parent medical records review study, termination will simply entail excluding records from withdrawn participants in data pulls and/or outreach efforts. For patients who opt in and consent to optional sub-studies with additional communication modalities and treatment options, termination will be accomplished by cessation of all proactive outbound communications to the participant and by not fulfilling medication or treatment requests that are deemed not in the patient's best interests (e.g., if a patient has developed a contraindication to a nicotine replacement therapy).
- 15.3 Participants who withdraw partially (e.g., removing consent for some forms of communication or treatment) from optional sub-studies will have this status change noted in the REDCap project that TCMs used to guide communication and treatment activities in the enhanced care clinics. For

participants who withdraw fully from the parent study (asking to be removed from the study panel, not receive additional outreach, and withdraw their data from EHR reports), they will be noted as having declined (if at the outset of the study) or withdrawn (if they engaged in some study activities with the TCM before withdrawing) in the study research record in the EHR and will be excluded from further outreach and data collection and analyses. Previously collected data from people who later request to withdraw from the medical records review portion of the study will be retained in study datasets, in keeping with HRP-314 criteria for approval for FDA-regulated research. Removal will not be possible once deidentification has occurred; it will not be possible to identify and delete records for specific participants. Participants who are incarcerated during the study or who request temporary suspensions of outreach, treatment, or communication will be given a temporary suspension status until they are able to resume participation because their incarceration has ended (e.g., they have been released or transitioned to parole or probation).

16.0 Data Management and Confidentiality

- 16.1* Both an internal quality improvement team and an external Data Safety and Monitoring Committee will help to monitor and ensure data quality. The project will follow a thorough Data and Safety Monitoring Plan (DSMP). Under this DSMP, the Lead Researcher will develop and implement protocols for assuring UW-CTRI data collection accuracy and protocol compliance, with the support of the UW-CTRI staff including the Director of Information Technology (IT) and our Regulatory and Compliance Coordinator, among others (e.g., our database and implementation teams and TCMs). Study protocols will include data verification and protocol compliance checks. The Lead Researcher will also be responsible for ensuring that the data for the project are securely transferred from 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. In addition, the Department of Medicine employs extensive data backup and server redundancy procedures and performs full backups weekly of all servers, along with incremental and daily backups to prevent loss of data.
- 16.2* As specified in the DSMP, the Lead Researcher 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 viruses. A complete virus scan of all workstations also takes place once a week. Server system log files are scanned for unusual activity, which is immediately investigated. Network and server administration staff members apply critical and non-critical patches as needed. In addition, UW-CTRI and UWSMPH Department of Medicine also have multiple mechanisms for preserving confidentiality of research participants and providing data security in the transfer of data from participant machines to the SFTP server. The Department of Medicine web servers use Secure Socket Layer (SSL or https) technology to encrypt data exchanged between the client and the server. In addition, all online and offline components of data systems will be accessible only through a login and password unique to each user. The security access levels for these login accounts are tiered and the features and privileges given to each staff member will be determined by the PI and UW-CTRI Director of Information Technology (IT). To further protect confidentiality, only the UW-CTRI Director of IT will be permitted to transmit data to the SFTP server. Additional measures include:

- ☒ Data will be coded, and the “key” linking identities to codes will be kept separately from the data.
- ☐ Data will be coded, and the “key” linking identities to codes will be kept on paper only. The study data will be stored electronically and labeled only with codes.
- ☒ Only those listed as key personnel will have access to the “key.”
- ☐ Access to the “key” will be limited to the following person (e.g., Database Administrator): _____
- ☒ This study is funded by the National Institutes of Health and is covered by a Certificate of Confidentiality.
- ☐ This study is NOT funded by the National Institutes of Health but because it will collect sensitive information, the research team will apply for a Certificate of Confidentiality to protect data from being requested without the subject’s consent as part of a legal proceeding.
- ☒ Other: Most data will be deidentified and extracted EHR data will only be linked to an encrypted medical record number that no one on the research team will be able to decode (no one on the research team will have access to the key created by health system report writers). The only exception will be for patients who provide consent to participate in a sub-study component involving additional forms of communication or treatment. For these patients who choose to participate in additional forms of outreach or treatment, data will be keyed and will contain identifiers (e.g., e-mail addresses or mobile phone numbers; names and addresses for medication and information sheet mailings). Even among those participants who consent to additional forms of

communication or treatment, only the team members involved in such communications, treatment facilitation, or supervision or quality assurance of such activities will have access to identifying data and all data access will be logged and timestamped in REDCap.

16.3 Describe how and where data and/or specimens will be stored and maintained. The following list is provided for convenience but is not an exhaustive list. Select all that apply:

- ☐ Online Collaborative Research Environment (OnCore) Biospecimen Management
- ☒ Research Electronic Data Capture (REDCap) Instances: UW-CTRI (for outreach prompting, generation, and tracking, and treatment facilitation) and ICTR (for inbound, patient-initiated communication)
- ☒ Other software option that will be stored on departmental server. Department: Qualtrics (Division of Information Technology)
- ☐ Locked filing cabinet or drawer inside a locked room. Specify the building: _____
- ☐ Other (describe): _____
- ☐ Data will not be stored or accessed on portable devices.
- ☐ Portable devices will be used to access secure web-based data collection sites such as ICTR's REDCap. No data will be stored locally on the device.
- ☐ Data stored on portable devices will be coded with the key stored separately. No identifiers will be stored on portable devices.
- ☐ Data stored on portable devices and therefore only encrypted devices will be used.

16.4 Management of Identifiers: Limited identifiers will be collected from participants who consent to sub-studies involving additional forms of communication or treatment facilitation, for the purposes of ensuring that they receive the outreach and/or treatment facilitation to which they consented. Data from the parent study (all extracted from the EHR) will not contain identifiers beyond an encrypted medical record number that no one on the research team will have a key to decrypt. This key will be used solely by the health system report writing teams that prepare the EHR data reports for the research team.

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

16.5 Describe any planned sharing of data and/or specimens outside the study team / institution.

- Any data to be shared will be completely deidentified prior to sharing. Such sharing is required under the resource sharing policy of the funder, NIH.
- Data sharing will occur under approved and executed data use agreements, in accordance with University policy, and with permission of the healthcare systems who are sharing EHR data for the project.
- Data to be shared will include data on smoking cessation outreach activities, smoking cessation treatment initiation and utilization, smoking status, patient demographics (in broad categories to prevent identification), and healthcare utilization data (for cost analyses).
- Data transfers will occur via secure means (e.g., SFTP).

17.0 Provisions to Protect the Privacy Interests of Participants

17.1 To protect against violations of privacy, patients will have the option to opt out of the program at study launch. Those who opt out will not receive outreach and will not be included in EHR data reports prepared by health system personnel. In addition:

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

17.2 Sensitive data will not be collected in this study.

17.3 To help participants feel at ease, the initial study outreach letter will describe what the study entails and provide accessible instructions about how to opt out of the parent study. Likewise, consent scripts for the optional sub-studies will clearly describe what the sub-study involves and that participation is completely voluntary, and that only information needed to communicate in participants' preferred modalities or to access participants' preferred treatments will be collected.

17.4 We will work with both UW Health and Advocate Aurora Health to ensure that data sharing complies fully with regulations and is duly authorized and allowed by the legal record holders.

18.0 Sharing of Results

18.1 Study results will be collected from the EHR. Treatment utilization data among those who consent to the sub-study involving treatment facilitation by the Tobacco Care Manager will be recorded in both REDCap databases and participants' health records.

Select study results will be shared with participants. Specifically, results of screenings for treatment eligibility in the treatment substudy will be shared immediately after screening is complete, and participants will be directed to

any and all treatments for which they qualify. Participants who endorse past-year suicidal ideation during treatment study screening (or at any other contact with study team members) will be directed to appropriate resources (the suicide prevention hotline, a licensed clinical psychologist on the study team, their primary care provider, an emergency room or the police, as needed and appropriate).

- 18.2 Study results will be shared with the public in aggregate, deidentified form via presentations, publications (e.g., in peer-reviewed journals), newsletters, web pages, and possibly also press releases and media coverage.

19.0 Data and Specimen Banking

- 19.1 No specimens will be collected for this project. Data from the project will not be banked for future use beyond the purposes described in the opt-out study notification or consent scripts for the optional sub-studies. Fully deidentified/anonymized data will be stored for 7 years in case replication, follow-up, or sensitivity analyses are necessary.
- 19.2 Data to be stored for additional analyses consistent with the original study purpose described to participants will be fully deidentified and anonymized and will include EHR-derived data on smoking status, demographics (in broad categories), healthcare utilization, and EHR and REDCap data on smoking cessation treatment communication and utilization.
- 19.3 Data will only be shared under the auspices of an approved and executed Data Use Agreement, in accordance with University regulations, and with approval from the health systems who provided EHR data.
- 19.4 Participants may withdraw their data up until study closure, at which time data will be fully anonymized and it will no longer be possible to withdraw data from a particular individual due to the lack of identifiers in the data.

20.0 Study Analysis

- 20.1 We will test the following hypotheses in the proposed study:
1. A higher proportion of patients in clinics randomly assigned to Enhanced Care (enhanced smoking cessation outreach and treatment options) will initiate any form of evidence-based smoking treatment (primary outcome) over 12 months of study participation than in clinics randomly assigned to Standard Care (superiority comparison).
 2. A higher proportion of patients in clinics randomly assigned to Enhanced Care will initiate smoking treatment (primary outcome) over 18 months of study participation than in clinics randomly assigned to Standard Care (superiority comparison).
 3. Patients in clinics randomly assigned to Enhanced Care will convert from current smoking to former smoking (secondary outcome) at a higher rate over 12 and 18 months of study participation than will patients in clinics randomly assigned to Standard Care (superiority comparison).

4. Increases in smoking treatment use will mediate increases in conversion to former smoking status among participants over 18 months in the Enhanced Care clinics, relative to the Standard Care clinics (mediation hypothesis).
5. Enhanced Care will be highly cost-effective over 18 months relative to Standard Care and historical data on other preventive interventions, as indicated by incremental cost-effectiveness ratios per each additional assisted quit attempt and per each additional conversion to former smoking status.
6. Enhanced Care (vs. Standard Care) will have stronger effects on smoking treatment use and conversion to former smoking over 18 months among historically undertreated groups, including African-American and Medicaid-eligible patients who smoke.
7. Sensitivity analyses will be conducted to examine rates of entry into specific forms of treatment, and to see if the rate of treatment entry changes after an experimental treatment trial (protocol 2019-0054) is closed to recruitment and no longer offered as an option for treatment to participants in this study. It is important to note, however, that all enrolled participants have had the opportunity to screen for and (if eligible) enroll in protocol 2019-0054 and have been sent at least 2 mailings offering this option.

20.2 Sample Size Justification: Although randomization will occur at the clinic level, the outcomes of interest (smoking treatment initiation and conversion to former smoking status) will be at the patient level, with patients nested within clinics. We seek to include all patients who meet eligibility criteria and do not opt out of participation after receiving the initial study notification (roughly 11,160 patients out of approximately 13,000 eligible). A sample of only 1,700 would be sufficiently large to detect 8% increments in the key outcomes of having at least one smoking treatment episode and of converting to former smoking with power $>.80$ at $\alpha=.05$ and at base rates ranging from a low of 5% to a high of 30%. As such, we are confident that we will have sufficient power to detect hypothesized effects on the primary outcome even if a much higher proportion of patients than expected opt out of the study.

20.3 Participant Population(s) for Analysis: Primary analyses will adopt an intent-to-treat framework in which all participants who do not opt out will be included in analyses, with missing data coded as untreated (for analyses of treatment initiation) and continuing smoking (for analyses of conversion to former smoking). That is, analyses will use all participants who do not opt out of the parent study.

20.4 Statistical Methods: Multilevel models in which patients are nested within clinics will be used to assess the effects of randomly assigned clinic care condition (Enhanced vs. Standard) on treatment initiation (hypotheses 1-2) and abstinence (converting from current to former smoking; hypothesis 3) using Bernoulli models (due to the binary outcomes). To test hypothesis 4, we will conduct formal mediation analyses with asymmetric bootstrapped confidence intervals of the mediated effect (the product of the effect of randomly assigned care condition on treatment initiation and the relation between treatment initiation and conversion to

former smoking status, both of which are hypothesized to be positive). To test hypothesis 5 regarding cost-effectiveness, total costs of Enhance Care and Standard Care will be computed, converted to a common year with 3% inflation adjustment, and then used to compute incremental cost-effectiveness ratios (additional costs for each additional treatment episode and each additional conversion to former smoking in Enhanced vs. Standard Care). To test hypothesis 6, care condition will be added as a moderator of patient-level relations between demographic variables such as race and insurance type and outcomes (e.g., treatment initiation and conversion to former smoking) in the multilevel Bernoulli models described above. This will assess the degrees to which randomly assigned care condition reduces disparities in treatment initiation and abstinence.

20.5 Planned Interim Analysis: To accelerate progress in the project, interim data will be collected approximately 13 months after launch of the last clinic to launch to enable initiation of analyses to address aim 1 and hypothesis 1. It is unlikely that the results of these interim analyses would suggest a need to halt the study, as it is possible that cumulative effects over 18 months may differ from those observed at the 12-month time-point. If interim analyses suggested that the two arms differ significantly and substantially in terms of treatment initiation, the DSMC will be asked to review results unblinded to clinic care condition/arm and to advise the team if the Enhance Care condition is underperforming Standard Care and if termination of the trial should be considered.

20.4 Handling of Missing Data: The extent, type, and reasons for missing data (e.g., death, leaving the healthcare system, attending visits but not providing tobacco use data) will be explored and reported via descriptive analyses. Primary analyses will adopt an intent-to-treat framework in which all participants who do not opt out will be included in analyses, with missing data coded as untreated (for analyses of treatment initiation) and continuing smoking (for analyses of conversion to former smoking). Sensitivity analyses will be conducted to assess the robustness of results across varying assumptions regarding missing data (e.g., that 10% of those lost to follow-up were treated, that 8% of those lost to follow-up quit smoking).

21.0 Potential Benefits to Participants

21.1 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 tobacco quitline coaching). 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 (Babb et al., 2017; NAQC, 2022). 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). This benefit is of very high probability (proactive efforts will be made to send information about low-barrier treatment options to all eligible patients identified based on medical records review), of modest to moderate magnitude (some patients may already

know of their options), and long duration (most treatment options are readily available and will be available after study completion).

22.0 Risks to Participants

22.1 This project poses minimal risks to participants as its interventions include information about and access to existing FDA-approved and publicly sponsored evidence-based smoking cessation interventions that meet or exceed current standards of care (e.g., combination of counseling and pharmacotherapy, as from the WTQL). Foreseeable risks are limited to potential loss of privacy, breach of confidentiality, or minor inconvenience (having to call a TCM to opt out of the study). All of these risks are low in probability. The risk of privacy-related concerns will be mitigated by constructing outreach materials in a way that will not disclose that a patient definitely uses tobacco (materials will instead indicate that patients are receiving information because they *may* use tobacco and acknowledge that this may be inaccurate). The risk of breach of confidentiality will be reduced by ensuring that outreach will be conducted by authorized personnel with training certification in human subjects research and HIPAA. The team will also use only HIPAA-compliant technology with oversight by the Lead Researcher and a DSMC. Inconvenience will be minimized by ensuring that a single, brief call will be sufficient to opt out of participation. These risks will persist for 18 months for each participant.

For participants who consent to additional forms of communication in the sub-study, the risk of breach of confidentiality or loss of privacy will increase somewhat, and they will be informed of these additional risks prior to consenting.

For participants who consent to additional forms of treatment (e.g., nicotine sampling, enrollment in a texting program) there are low probability risks of nicotine replacement side effects (these tend to be immediate, mild to moderate in severity, and reversible) or costs for text messaging. These additional risks will be disclosed to Enhanced Care participants at the time of consent to the treatment sub-study. No other physical, psychological, social, legal, or economic risks are anticipated.

22.2 No risks are associated with participant decisions to opt out of or withdraw from either the parent medical records study or the sub-studies, as all patients will still have access to evidence-based smoking cessation care (e.g., WTQL care) even if they choose not to participate in or withdraw from the study.

22.3 None of the study procedures have currently unforeseeable risks, to our knowledge.

22.4 The only study procedure that could have risks to an embryo or fetus is distribution of nicotine replacement samples/starter kits in the optional treatment sub-study. To minimize this risk, people who are pregnant will be ineligible for nicotine samples in the sub-study. Only 2 week supplies of

medication are provided at a time to prevent likelihood that people will become pregnant between screening and medication use. Medication instructions will also indicate that participants should stop using the medication if they are trying to become pregnant or pregnant.

22.5 No risks to others who are not participants are anticipated.

22.6 To protect against violations of privacy, study initiation letters will not disclose a definite smoking status, and patients will have the option to opt out of the program. Those who opt out will not receive a call from a TCM or additional offers of smoking cessation treatment. To protect against breach of confidentiality, we will collect as few identifiers as possible to achieve the study goals and to follow-through on participants' communication and treatment requests (in the optional sub-studies). Data already in EHRs in the health systems will be used for outreach conducted by healthcare system personnel (TCMs) rather than by the research team. We will ensure that any and all research data are stored on secure, encrypted servers, and that transfers of data between health systems and the UW-CTRI research team are conducted via HIPAA-compliant means. In addition, risks of privacy loss and distress are reduced by excluding people whose preferred language is not English, and people who clarify that they do not use tobacco.

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

23.1 Describe:

- Although this is a minimal risk study, the Lead Researcher and study team will still report on participant safety to an independent DSMC twice per year. The team will also follow a DSMP that specifies what will be monitored, who has responsibility for such monitoring, and how unanticipated problems, adverse events and serious adverse events will be assessed, documented in REDCap and the EHR, reviewed (by a study physician) and reported. The AE/SAE assessment protocol is uploaded with the application.
- Data on participant safety will not be collected routinely in the parent medical records review study, as the only interventions applied in that study are outreach efforts to inform patients about their treatment options and provide referrals to existing treatment options.
- In the treatment sub-study in Enhanced Care, additional risks are associated with nicotine sampling (side effects) and texting programs (possible costs if a person has limited minutes/data), and slightly increased risk of loss of privacy or confidentiality. Participants who consent to these optional treatments will be informed of these risks prior to consent. Those who receive nicotine samples will be encouraged to call the study team and their healthcare team if they experience side effects. Because no other direct interactions with

participants are proposed, additional data on participants safety will not be collected.

- The research team will follow a protocol for assessing, documenting, and reviewing any adverse events reported by participants in a timely manner, and for reporting these to the IRB, FDA, sponsor, and primary care team via the EHR, as needed.
- Any adverse, study-related events that come to light during the study will be assessed fully and reported (see uploaded AE/SAE assessment protocol and form). 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) they 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) they are possibly related to study participation. Any SAE will be queried and reported if it meets the definition of unanticipated problem.
- Adverse event assessment, recording in REDCap, reporting, and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by the study team.
- The IRB will receive an annual report of all SAEs and AEs meeting the criteria listed above
- Given the minimal risk of the proposed interventions and the lack of standardized assessments of safety, statistical tests of safety data are not planned. Instead, descriptive data regarding the nature, severity, and frequency of adverse events will be prepared at the end of the study.
- Conditions that may trigger suspension of the trial would be evidence of greater than anticipated risks of loss of privacy or confidentiality or participant distress, or significantly and substantially lower rates of EBST initiation in Enhanced Care clinics than Standard Care in interim analyses. 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 will develop a plan for continuation of the study and discuss this plan with the NIH grant program director in a reasonable time frame.
- Any reportable events that are unexpected, immediately life-threatening or severely debilitating, probably caused by study

medication (nicotine samples) will be reported within 1 business day. If new information about study medication risks that was not previously known to investigators or participants is discovered, investigators will prepare a change of protocol with revised study documents or withdraw affected drugs from the protocol within 14 business days. Likewise, the research team will report to the IRB within 14 business days any of the following: failures to obtain informed consent for the optional sub-studies; acting on consents collected from people with an activated power of attorney for healthcare or a legally authorized representative at the time of consent; dosing errors in medication dispensing; unexpected harms to participants or others that are probably related to the study procedures; noncompliance that could affect participants' rights, welfare, or safety; reportable audit findings; breach of confidentiality; failure to suspend study activities during a participant's known incarceration; and unresolved participant complaints. Breaches of confidentiality of PHI will also be reported to the HIPAA privacy officer.

24.0 Economic Burden to Participants

24.1 The only costs related to study participation that participants may incur are co-pays for care provided or medications ordered by their PCP (participants will be advised about this ahead of PCP referral) and possible costs of cell phone minutes or data use charges if they use a phone with limited minutes or data for WTQL calls, communication with the TCM, or any of the texting programs. These are standard costs associated with these existing treatment options. Participants will be advised about these costs before making treatment decisions. There will be no costs associated with research procedures.

25.0 Resources Available

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

- The proposed research will involve patients, primary care teams, and TCMs at both UW Health and Advocate Aurora Health.
- 10 different clinic sites will participate (5 in each system) and historical data suggest that roughly 13,000 individual patients who

smoke will meet initial criteria for the proposed medical records review parent study. Given this, and the proposed opt-out approach, it is highly feasible to recruit enough participants to achieve the study aims in the study period.

- Our partner health systems already employ the TCMs who will facilitate outreach and communicate with patients regarding their desire to opt out, enter a sub-study, or request treatment assistance.
- Roughly 24 months of data collection will occur (6 months of launching each clinic and then 18 months of study participation at each clinic).
- The research will be conducted at the University of Wisconsin Center for Tobacco Research and Intervention which has the human, physical, communication, and technological resources needed to achieve the study aims in the study period, including the ability to receive, store, and analyze EHR data in a HIPAA-compliant manner.
- All study participants will have existing relationships with a partner health system (as recent receipt of care there is a criterion for inclusion). Patients will be directed to their existing primary care team in cases of care needs in consequence of participation in the research.
- Study teams meet no less than monthly, with some teams meeting weekly, to ensure that all persons assisting with the research are adequately informed throughout the study about the currently approved protocol, the research procedures, and their duties and functions. Study staff are trained to mastery of protocols prior to implementing them with participants and ongoing monitoring of performance with feedback are provided to team members. A dedicated quality improvement team provides additional feedback.

26.0 Multi-Site Research

26.1 UW will be the lead research site and Aurora (AdvocateAurora) Health will be an additional site that will cede to the UW-IRB. We work closely with the PI at Aurora (Dr. Lisa Sullivan-Vedder) and the study coordinating team there (led by Jessica Kram, and including the Aurora TCMs). Members of our team meet with Aurora Health TCMs and the Coordinator no less than weekly (and sometimes more). We also stay in frequent communication by email and phone. We at UW, as lead researchers, will ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization throughout the study. We will send updated IRB-approved materials to the Aurora Coordinator by email.
- All required approvals (initial, continuing review and modifications) are obtained at each site (including approval by the site's IRB of record). We work directly with the PI and Coordinator to draft, review, and revise IRB application materials at Aurora, and ensure

that the Aurora team has the current UW IRB application and approval notice.

- All modifications are communicated to sites and approved (including approval by the site's IRB of record) before the modification is implemented. We do not implement changes until they have been approved by the IRB of record.
- All engaged participating sites safeguard data, including secure transmission of data, as required by local information security policies. We have completed security reviews of data transmission and storage procedures in collaboration with Aurora Health.
- All local site researchers conduct the study in accordance with applicable federal regulations and local laws.
- All non-compliance with the study protocol or applicable requirements is reported in accordance with local policy.

26.2 We will communicate with the Aurora PI and Coordinator in the case reportable events or other unanticipated problems occur:

- Problems (inclusive of reportable events) will be reported promptly and any action plans or protocol changes needed in light of these problems will be discussed with the Aurora PI and Coordinator.
- Interim analyses are not planned for the project, but any interim results that are generated (e.g., high opt-out rates) during the course of the study will be shared and discussed with the Aurora study team.

Any plans to close the study ahead of schedule will be discussed with the Aurora study team prior to implementation.

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28.0 Appendices

Provide any additional information relevant to management of the study, such as instructions for specialized procedures, charts or workflow diagrams.