

**PROTOCOL**

“Breaking Addiction to Tobacco for Health (BREATHE) Study”

PI: Michael Fiore, MD, MPH, MBA; UW-CTRI Center Grant: 1P01CA180945-01.

**PROTOCOL****UW HS-IRB # 2014-1041**

“Breaking Addiction to Tobacco for Health (BREATHE) Study”

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Coordinating Center: UW-Center for Tobacco Research and Intervention (UW-CTRI)

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

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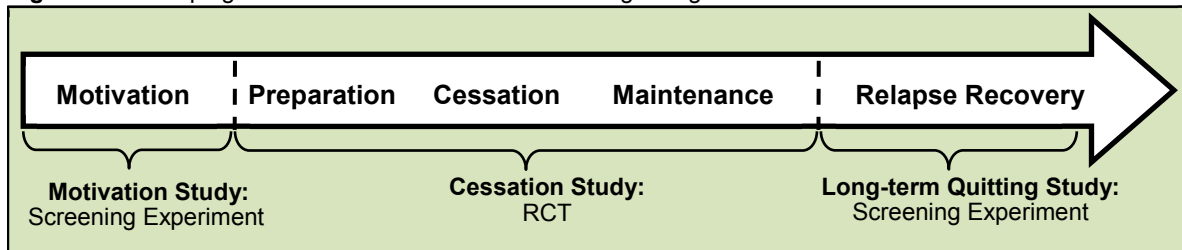
## Study Overview

The ultimate goal of this research is to develop a chronic care treatment package for smokers that will address the challenges and opportunities of each phase of the cessation process – motivation, preparation, cessation, maintenance, and relapse recovery. That is, to develop treatments for smokers not yet ready to quit, those who are preparing to quit, those actively engaged in the quitting process and those who have tried to quit but relapsed.

To achieve this goal, this research comprises three distinct research studies, each of which represent a phase in a comprehensive chronic care treatment model for clinical intervention with smokers in the primary care setting: the Motivation Study, the Cessation Study, and the Long-term Quitting (LTQ) Study (see Figure 1). The goal of each study is to test and identify effective intervention components for distinct phases of the smoking cessation process. These components will then be combined for future research on the effectiveness of this chronic care treatment package. While the three studies are distinct, they are conceptually integrated, rely on the same recruitment mechanism, have similar inclusion/exclusion criteria and use similar assessments and treatment. For that reason, we have submitted this as a single protocol for IRB review.

In sum, these three studies will allow us to identify experimentally validated intervention components that constitute a menu of highly effective interventions for every phase of smoking cessation and that can be combined to constitute a comprehensive chronic care treatment for smoking.

**Figure 1.** Developing Chronic Care Treatment for Smoking Using the Phase-Based Model



In addition to the three clinical (human subjects) research projects, this research includes a randomized control trial testing the use of the EHR as a way to initiate smoking cessation intervention as compared to current standard of care. This is a clinic comparison (not human subjects) trial. The electronic health record (EHR) has the potential to enhance the efficiency, consistency, and ascertainment of the delivery of smoking treatment in primary care. The main goal of clinic comparison research project is to develop and test new, comprehensive EHR enhancements and associated healthcare practices that efficiently guide smoker identification, referral to, and engagement in the chronic care treatments for smokers developed in the three treatment projects. The EHR enhancements will include: 1) smoker identification and documentation aids; 2) a 1-click system to refer primary care patients to the chronic care smoking treatments developed in Projects 2-4; 3) a function to provide EHR feedback to clinicians on the outcome of those referrals; and 4) communications resources to reach out to smokers in the health system (via a query of existing smokers within each clinic), informing them of the chronic care smoking treatment options available as part of this Program Project.

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The impacts of the EHR-based enhancements along with the integrated chronic care smoking treatment will be evaluated in a randomized clinical trial (RCT) involving up to 28 primary care clinics in two healthcare systems in Wisconsin that will serve as recruitment sites for the clinical studies. The methodology, data collection and analysis plans for this clinic comparison trial are presented at the end of each section of the narrative regarding the treatment studies.

**Recruitment & Study Entry**

Up to 2600 participants will be recruited to participate in this research: 512 in the Motivation Study, 600 in the Cessation Study and 1000 in the Long-term Quitting Study and an estimated 188 additional participants. These additional participants are necessary in order to keep both a quitting and motivational project open enough time to allow full recruitment in all of the studies. However, to get a proper balance of participants across the three studies, we may need to recruit as many as 2600. Participants will be patients in approximately 18 primary care clinics from within 2 Wisconsin clinic systems (Aurora Health Care and Dean Clinic) that serve diverse populations. Smokers who express interest in quitting smoking or cutting down during the electronic health record (EHR)-guided assessments will have their willingness (verbal consent) to share their contact information and be contacted by the study documented in their EHR and their contact information electronically sent to the study office. Alternatively, smokers at participating clinics who do not have a scheduled clinic visit will receive direct recruitment information via mailings and EHR-specific messaging to other smokers from each clinic who do not have scheduled clinic visits. The direct recruitment messages will encourage smokers to learn more about the study by contacting the UW-CTRI research office directly. Research personnel will call all referred patients, whether they were self-referred or referred via the EHR, and assess interest and eligibility.

In either entry method, patients interested in quitting smoking will be eligible for either the Cessation Study or the Long-term Quitting Study, and they will be randomized to one of these two studies. The amount and level of randomization of those interested in quitting to these two projects will be adjusted in order to meet study recruitment goals. This adjustment may include assigning subjects to only one of the two quitting studies if necessary to achieve the necessary balance and overall recruitment required for the primary analyses. Smokers expressing an interest in cutting down on their smoking will be eligible for the Motivation Study. Patients who pass the phone screen will be invited to attend a study session at their referring clinic (where all treatment visits will occur), where they will learn more about the study, have eligibility confirmed, and provide written informed consent. Records collected in this research will allow us to determine the overall reach of the intervention within the clinic (e.g. percentages and demographic characteristics of patients who complete each recruitment step) and will allow us to complete a full CONSORT diagram.

Communication that includes essential PHI between each participating health system clinic and UW-CTRI research staff takes place for two purposes. First, following verbal consent, the clinic communicates information about their patients interested in hearing about the study to UW-CTRI. This information will include patient name, contact information (phone, address) available and responsible clinic provider and MR number (all necessary to contact patients and to fully match referred patients and complete the data analysis at the end of the study). (Note: Second, UW-CTRI must communicate back specific information about those patients consented. This information communicated after written consent is obtained and includes the name of the enrolled patient and over-the-counter (OTC) medication (dosage and duration) provided by the

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study to the patient. As described below, these communications will take place without any UW-CTRI staff having access to any additional patient medical record information and without health system staff having access to any additional research information.

At no time will UW-CTRI research staff be able to access any patient information contained in the health system EHR. However, in order to expedite communication between the health system and research personnel, we will take advantage of either Epiccare Link, which is a secure method of data transmission supported by the health care clinic’s Epic electronic health record (EHR), or some comparable secure, HIPAA-compliant email transmission of the essential contact information. This secure transmission method will be used to transmit information from patients who verbally consent to supply their information to study personnel. The contact information will be retrieved by specific UW-CTRI study staff (i.e., among those who are part of the IRB-approved study team) who are granted access by each health system who will then enter the contact information into the UW-CTRI research study database. As per health system requirements, these specific UW-CTRI staff will complete necessary user confidentiality/security information. When a patient is enrolled, the same authorized UW-CTRI staff will create a return communication using the same secure transmission system to send the enrollment information and medication dosage and duration to the responsible clinic provider to update the provider’s clinical record (EHR). Only clinic staff authorized by the clinic to view and handle PHI will be given access to these return communications. Similarly, the health system will not be provided within any non-clinical information from the research study, since clinics and their staff are not engaged in research.

At the present time, we are seeking IRB approval to recruit and enroll participants contingent upon our submission of confirmation from each health system IRB that they agree that their health system is “not engaged in research,” as defined in the UW Human Research Protection Program and OHRP 45 CFR part 46. Their activities do not include any study intervention and are limited to letting potentially eligible patients know about the study, obtaining prospective participants’ permission for investigators to contact them, allowing their facilities to be used by study staff to provide intervention, providing other de-identified data necessary for the study to ascertain rates of recruitment from the overall pool of smokers, and receiving clinical information such as medication being given as part of the study in order to provide proper clinical care.

***Additional Data Related to Recruitment and the CONSORT Diagram***

In order to evaluate the reach of the treatments in this study among the general and smoking populations in each clinic, and to report the necessary CONSORT information, we will collect additional aggregate data from the EHR of each clinic in which we are recruited participants. These data will allow us to clearly report patient flow through the clinic (e.g., number of patients seen in the clinic, number of patients who are smokers) as well as the proportion of smokers who participated in the study and any differences in basic demographic characteristics of those who participated and those who did not (See Appendix 1: Sample Representativeness/Study Recruitment Aggregate Data Plan for details). No individual data will be collected. The data will be aggregated by group depending on the response to the smoking identification and study invitation within the EHR. Comparable data will be collected from the set of individuals who did not come in for a study visit during the time frame of study recruitment but received outreach from the clinic via a letter or myChart message to determine the level of response and the demographics of smokers who responded to these forms of recruitment. In

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sum, this aggregate data collected from clinic EHRs will allow us to determine percentages of patients who completed each recruitment step and will allow us to complete a full CONSORT diagram (See Appendix 2: Consort Diagram)

**Inclusion/Exclusion**

Inclusion criteria for all 3 studies will be: age (18 years or older); smoking >4 cigarettes/day for the previous 6 months; able to read, write, and speak English; have reliable phone access and agree to respond to Interactive Voice Response (IVR) phone prompts; a patient at a clinic currently recruiting in the study; not currently taking bupropion; if currently using nicotine replacement therapy (NRT) or varenicline, agreeing to use only study medication for the duration of the study; free of medical contraindications to using NRT; no history of stroke, mini-stroke, heart attack, TIA (Transient Ischemic Attack) nor an abnormal electrocardiogram in the past 4 weeks; no hospitalizations for diabetes or congestive heart failure in the past 4 weeks; no diagnosis of or treatment for schizophrenia, a psychotic disorder or bipolar disorder in the last 10 years; and, if the participant is a woman of childbearing potential, using an approved method of birth control during treatment. We will not exclude participants based on their prior use of cessation medication or if they use multiple tobacco products in order to enhance real-world generalization (these will be statistically controlled in analyses). However, we will encourage participants to discontinue use of all tobacco products on their target quit date.

Additional inclusion criteria for the individual studies include:

- Motivation Study: not currently attempting to quit smoking; not intending to quit smoking (defined as no plans to quit in the next month); and planning to remain in the area for at least 12 months.
- Cessation Study: reporting being motivated to quit; and planning to remain in the area for at least 12 months.
- Long-term Quitting Study: reporting being motivated to quit; and planning to remain in the area for at least 2 years and 2 months.

Incarcerated individuals will not be enrolled in this study. However, given the longitudinal nature of the research, participants could be incarcerated for periods during their participation. If study staff learn that a participant is incarcerated at a time point subsequent to enrollment, the participant will not be withdrawn unless that incarceration will take them beyond the study period. Staff will not contact the participant while incarcerated and will not provide any treatment (counseling or medication) nor conduct any assessments during that incarceration. Services and assessments will be re-initiated if the participant is released at a later study time point.

Even though we screen out participants who are pregnant, plan to become pregnant, nursing, or are unwilling to take steps to avoid pregnancy, there is a chance that a participant previously eligible could become pregnant. She would then be considered part of a vulnerable group. Given the longitudinal nature of the research, a participant who becomes pregnant after enrolling may remain in the study for counseling and other assessments. However, she will be advised to immediately stop using study medications and to return any unused medications. No further medications will be given to this study participant while in the study.

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**Study Design**

This research utilizes innovative engineering principles and designs. The Motivation and Relapse Recovery Studies are screening studies utilizing factorial designs that will allow us to evaluate different treatment components and how well they work when combined. The Cessation Study is a randomized controlled trial of treatment components that were identified as optimal in a previous screening study that used a factorial experimental design.

***Motivation Study***

This study is a 2x2x2x2 factorial design (see Table 1). Participants will be randomized to one of two levels on four different factors: 1) Nicotine Mini-Lozenge vs. No Mini-Lozenge, 2) Behavioral Reduction Counseling vs. No Behavioral Reduction Counseling, 3) 5Rs Motivation Counseling vs. No 5Rs Motivation Counseling, and 4) Behavioral Activation Counseling vs. No Behavioral Activation Counseling. These components have strong theoretical and empirical support, but their relative, additive, and interactive effects are unknown.

**Table 1. Motivation Study Treatment Conditions**

Conditions	Medication Type (Mini-Lozenge)	Behavioral Reduction (BR) Counseling	5Rs Motivation Counseling	Behavioral Activation (BA) Counseling
1	Mini-Lozenge	BR	5Rs	BA
2	Mini-Lozenge	BR	5Rs	No BA
3	Mini-Lozenge	BR	No 5Rs	BA
4	Mini-Lozenge	BR	No 5Rs	No BA
5	Mini-Lozenge	No BR	5Rs	BA
6	Mini-Lozenge	No BR	5Rs	No BA
7	Mini-Lozenge	No BR	No 5Rs	BA
8	Mini-Lozenge	No BR	No 5Rs	No BA
9	No Mini-Lozenge	BR	5Rs	BA
10	No Mini-Lozenge	BR	5Rs	No BA
11	No Mini-Lozenge	BR	No 5Rs	BA
12	No Mini-Lozenge	BR	No 5Rs	No BA
13	No Mini-Lozenge	No BR	5Rs	BA
14	No Mini-Lozenge	No BR	5Rs	No BA
15	No Mini-Lozenge	No BR	No 5Rs	BA
16	No Mini-Lozenge	No BR	No 5Rs	No BA

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\*Note. In factorial designs each main effect is tested; within each column, the shaded vs. non-shaded rows are compared.

### Cessation Study

This study is a 2-arm randomized clinical trial (RCT). Participants motivated to quit smoking will be randomized to one of two treatments: 1) a Modern Usual Care (M-UC) vs. 2) Abstinence-Optimized Cessation Treatment (AOCT). The components for the optimized treatment have strong theoretical and empirical support from our previous screening studies.

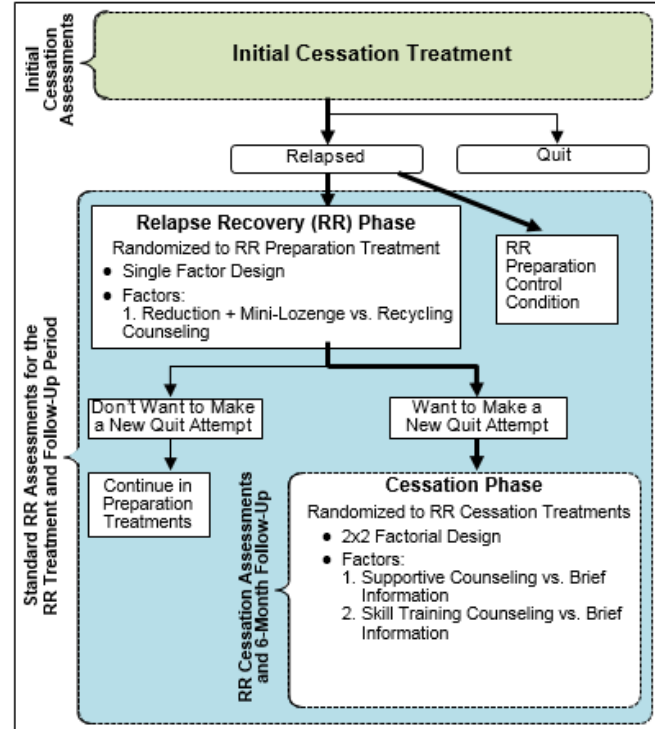
### Long-term Quitting Study

This study utilizes a sequential, multiple assignment, randomized trial (SMART) design—an innovative approach aimed at optimizing adaptive treatments. In a SMART design, randomization occurs at more than one stage, with randomization at a later stage based on response to treatment at an earlier stage.

This experiment will test adaptive

intervention components that are applied at two stages: 1) when a smoker relapses, and 2) when a smoker decides to make a new quit attempt (See Figure 2 and Figure 2a). Participants will initially receive a Usual Care cessation treatment. If they relapse (smoke for 7 consecutive days prior to 6 months after the quit day), they will be randomized to one of three Relapse Recovery (RR) Preparation conditions: 1) Preparation Control, 2) Behavioral Reduction Counseling + Nicotine Replacement Therapy (NRT with the nicotine mini-lozenge), or 3) Recycling Counseling. If they are randomized to the Preparation Control condition, the participant will continue to receive the Initial Cessation usual care treatment, but will also be told that they can receive additional treatment from the Wisconsin Tobacco Quitline (WTQL). Thus participants randomized to the Preparation Control condition will receive at least a usual care cessation treatment and will be told how to get more free treatment, but they will not receive any further study treatment. If participants are randomized to one of the two active RR Preparation conditions, they will be seamlessly transitioned into either Behavioral Reduction Counseling + Nicotine Replacement Therapy (NRT with the nicotine mini-lozenge) or Recycling Counseling. If participants in either of these active RR Preparation conditions (the “Behavioral Reduction” or the “Recycling” conditions) choose to make a new aided quit attempt, they will be randomly assigned—stratified for prior type of RR Preparation treatment and gender—to one of two levels of each of the 2 RR Cessation treatment factors in a 2x2 factorial design: 1) Supportive Counseling & Maintenance vs. Brief Information, and 2) Skill Training Counseling and Maintenance vs. Brief Information (See Figure 2, Figure 2a, and Table 2.)

Figure 2. Participant Flow, Assessments, and the Relapse Recovery Factors Tested



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Figure 2a. Long-Term Quitting Study Design.

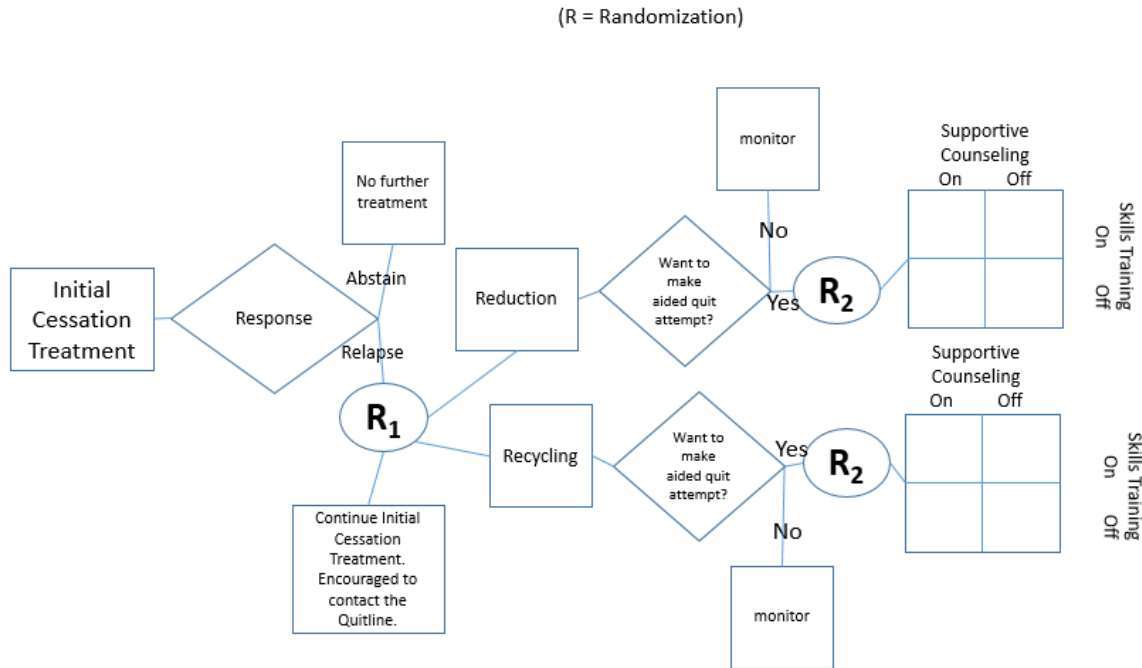


Table 2. Long-term Quitting Relapse Recovery Cessation Treatment Conditions.

Condition	Supportive Counseling Intervention	Skill Training Counseling Intervention
1	Supportive	Skill Training
2	Supportive	Brief Info
3	Brief Info	Skill Training
4	Brief Info	Brief Info

\*Note. In factorial designs each main effect is tested; within each column, the shaded vs. non-shaded rows are compared.

**Clinic Randomized Control Trial**

A set of EHR modifications (described in detail below) will be presented sequentially to groups of clinics within both healthcare systems as per an RCT design (RCT). Over 36 months, and across the two healthcare systems, the EHR enhancements will be introduced into up to 18 “experimental” clinics. During this time 10 control clinics will also be inducted into the study. It is possible that fewer experimental clinics will be used in this design if recruitment for Projects 2-4 is so successful that not all 18 clinics are required. The experimental clinics will each participate in the study for at least 16 months (albeit, unforeseen events could cause us to terminate participation earlier in some clinics: e.g., clinic closure, dramatic change in clinic size or structure). Experimental clinics will be yoked to a control clinic for the purpose of fixing the duration of participation. A variation of the Multiattribute Utility Measurement Matching strategy will be used to allocate experimental and control clinics so that they are matched with regard to key baseline variables and timing of study induction.



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The following will serve as dependent variables: 1) rate of smoking status documentation among adult patients visiting the primary care clinic; 2) rate of referral of smokers to smoking treatment; and 3) rate of engagement in smoking treatment (the primary outcome).

A set of standard EHR modifications will be implemented in (up to) 18 experimental clinics as part of the RCT. Importantly, these 18 clinics will also serve as recruitment sites for participants for Projects 2, 3, and 4, consistent with the integration of all projects across the P01. The ultimate, specific N for the experimental group may comprise 10–18 clinics depending on recruitment rates; we project good power across this range of sample size. The clinics participating in the study will be selected based on the following criteria: 1) *Size*: clinics will be fairly large, including at least 3-6 clinicians, to ensure adequate recruitment for the three clinical research projects. 2) *Location*: clinics will be concentrated in Southcentral and Southeastern Wisconsin so that case managers from UW-CTRI Madison and Milwaukee research sites can provide services at multiple clinics. 3) *Diversity*: clinics from both of the health systems will include both urban and rural location and a range of SES (based on rates of Medicaid and uninsured patients). 4) *Independence*: we will ensure that clinics with high levels of clinic integration (e.g., sharing significant numbers of staff) do not participate (i.e., only one of such highly linked clinics can participate). And, 5) all clinics will have to have, or be willing to adopt, the control or experimental smoker identification and referral routines (either fax referral or the enhanced EHR strategies) and be willing and able to collect necessary data.

The key new EHR functions that will be implemented and tested are: 1) a modified “**screen for smoking status**” to enhance the identification and documentation of all smokers visiting targeted primary care clinics; 2) an outreach to smokers, (direct-to-consumer communications) about the study availability in their clinic; 3) a **1-click referral system** to evidence-based smoking treatment with UW-CTRI case managers; 4) a **closed-loop feedback feature to communicate to the clinician the fate of a referral**, documenting receipt of the referral and treatment engagement; and 5) **EHR-based communication options** to inform smokers of treatment resources.

After pre-testing in each healthcare system, the enhanced EHR functionalities will be implemented in experimental clinics as they become available for induction into the study starting with the two pilot experimental clinics that are identified by the health systems. During the 6-month period when the enhanced EHR resources are being developed (anticipated completion 1/10/15), candidate clinics will be screened for participation criteria as noted above.

**Assignment to conditions.** Clinics will be assigned in sets or groupings using a multistage or captive assignment procedure. These sets can vary in size, and not all members of a set must be available for assignment at the same time. We propose that assignment may start when there are at least 3-6 clinics available for assignment. The clinics in each set will be randomly assigned until the set is exhausted, and then clinics within the next set will be assigned. Within each set of clinics, a subset will be assigned to the control condition and a subset will be assigned to the experimental condition to ensure that assignment to condition is not correlated with time and secular events (as the sets will be started at different times as additional clinics become available). Finally, we will use an approximation to the MultiAttribute Utility Measurement (MAUM) strategy using principal components (PC's) to stratify clinics with regards to possible biasing features: size, mix of Medicaid patients, healthcare system, and

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rural-urban setting, baseline rate of WTQL referral, and smoker prevalence. These criteria can be altered depending upon their pre-assignment availability. Thus, the approach involves: 1) Conducting a PC analysis in the pool of *potentially* available clinics (combined across the 2 healthcare systems) to identify a small number of uncorrelated PC's. 2) Integrating the PC's in a way that reflects the hypothesized direction of their impact on outcomes (inflating vs. reducing treatment engagement). 3) Locating all clinics available for randomization on a single dimension that reflects the hypothesized net impact of the PC's. 4) Forming two groupings of high and low clinics that are set using a cut-score imposed on the dimension composite. 5) The clinics are randomly assigned within and across sets in a manner that ensures that approximately an equal number of high and low ranking clinics are assigned within each condition. Thus, if a set of 6 clinics is being used for captive assignment, and this entails assigning 2 of the 6 to the control condition, one of the high scoring clinics and one of the low-scoring clinics will be randomly assigned to the control condition. Conversely, 2 of the high scoring and 2 of the low-scoring clinics must be assigned to the experimental condition (to complete an assignment set), exhausting this particular set. Thus, randomization to condition is nested within the high and low PC-score groupings. We will assign clinics to the two conditions on a 50/50 basis during early recruitment when the ultimate N (and mix of experimental and control clinics is unknown). Note that if the set of clinics is quite small (due to limited availability at a given point in time), it might be the case that only one clinic can be assigned to a particular condition in that set (e.g., to the control condition). In that case, in the next set the clinic assigned to the control condition must come from the other end of the PC risk dimension. In this way, the approach is flexible but nevertheless increases the likelihood that clinics are assigned to the two conditions at a similar rate over time, and that the two conditions are similarly balanced on factors thought to affect the dependent variables.

### **Study Procedures, including Visits and Phone Contacts**

All participants will attend an initial in-person baseline visit at their primary care clinic where they will provide written informed consent, receive information on assigned intervention components, complete assessments, provide a breath sample for carbon monoxide (CO) assessment, and receive initial treatment based on their treatment condition. After the initial visit, study participation will include phone calls and/or additional in-person visits to provide interventions and collect data.

#### ***Motivation Study***

This study has two phases: Motivation and Cessation. While all participants will receive Motivation treatment, participation in the Cessation phase of the research depends on whether participants decide they would like to quit smoking during the Motivation phase.

**Motivation Phase.** After the in-person baseline session, all participants in the Motivation Study will receive assessment calls at Weeks 12, 26, 39 and 52. They will also receive 11 IVR calls over the course of 52 weeks. Participants receiving Behavioral Reduction (BR) Counseling and Behavioral Activation (BA) Counseling will receive 1 in-person session at Week 0 followed by 9 phone sessions (Table 3). Participants receiving 5Rs Motivation Counseling will receive 1 in-person session at Week 0 followed by 3 phone sessions (Table 3). Participants who are randomized to receive Nicotine Mini-Lozenge will receive 15 weeks of medication at Week 0. Participants who are still using the medication will receive more medication following the 12, 26,

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and 38-week assessment calls. Medication use and AE assessments will occur either during the Week 3 and 5 counseling calls, or alone if the participant is not randomized to receive any counseling.

**Table 3. Motivation Study Schedule of Study Contacts**

Week	0	1	2	3	4	5	6	9	12	15	18	22	26	30	34	38	39	43	47	52
Visit	X																			
Assessment Call				X*		X*			X				X				X			X
IVR Calls			X		X		X	X		X	X	X		X	X			X	X	
BR counseling	X	X		X		X		X		X		X		X		X			X	
BA Counseling	X	X		X		X		X		X		X		X		X			X	
5Rs Counseling	X									X				X					X	
Mini-Lozenge	X								X				X			X				

\*Medication use and AE Assessments only

**Cessation Phase.** Participants who decide to quit during the first 9 months of the Motivation Phase treatment period will receive a cessation treatment. The cessation treatment includes in-person counseling sessions at Days -7, 7 and 14, and a counseling phone call on the target quit day (TQD). Participants will receive 8 weeks of medication at Day -7 (see Table 4). Two follow up assessments will occur at 28 and 56 days post TQD to assess for medication use and symptoms for the full duration of the medication schedule. *Participants who chose to receive the cessation treatment will still receive all Motivation Phase phone and IVR assessments to permit standardized assessments for all Motivation Phase participants.*

**Table 4. Motivation Study Schedule of Treatment Contacts for Participants who Choose to Quit Smoking**

Day	-7	TQD	7	14	28	56
In-Person Counseling	X		X	X		
Phone Counseling		X				
Medication	X					
Assessment					X	X

**Cessation Study**

After the in-person baseline session, participants assigned to the Modern Usual Care (M-UC) will have no other treatment visits or calls, other than the single call from the Wisconsin Tobacco Quit Line. However, participants in this condition will receive the 6 assessment calls at Weeks 4, 8, 16, 26, 39 and 52.

Participants in the Abstinence-Optimized Cessation Treatment (AOCT) will attend three additional visits at 1 week pre-quit, on the Target Quit day (TQD), and 1 week post-quit, during which they will receive the in-person counseling (see Table 5). In addition, AOCT participants will receive 8 counseling calls at Weeks 3, 4, 6, 8, 10, 14, 18, and 22 as well as 7 or 11 automated calls that encourage medication adherence at Days 1, 3, 10, 17, 24, 31 and 45 (those who are still smoking at Week 8 will receive 4 additional automated adherence calls to encourage medication use at Days 73, 101, 126 and 154). Participants in AOCT will receive 3 weeks of pre-quit nicotine mini-lozenges at Visit 1 and will receive nicotine mini-lozenges and

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nicotine patches 1 week before their quit day. Participants who are still using the medication will receive more medication following the 8-week and 16-week assessment calls.

**Table 5. Cessation Study Schedule of Treatment Contacts for AOCT Participants.**

Day	-21	-7	TQD	1	3	7	10	17	24	28	31	45	56	73	101	112	126	154
Week	-3	-1	0	1	1	1	2	3	4	4	5	6	8	10	14	16	18	22
Visit	1	2	3			4												
Medication	X	X				X							X			X		
In-Person Counseling		X	X			X												
Maintenance Calls								X		X		X	X	X	X		X	X
Automated Calls*				X	X		X	X	X		X	X		x	x		x	x
IVR Calls**		X	X	X	X	X	X											
Assessment Calls†										X			X			X		

\*Automated calls will be discontinued after Week 6 for those who report abstinence at their Week 8 assessment call

\*\*IVR calls will be daily from 1 week pre-quit through 2 weeks post-quit.

†Additional assessment calls will occur at Weeks 26, 39 and 52. Further, participants reporting abstinence at 26 weeks will be invited to come to the clinic to provide a breath sample for biochemical confirmation of abstinence.

**Long-term Quitting Study**

This study has three potential phases: Initial Cessation (also called the “Quit Phase”), Relapse Recovery (RR) Preparation (also called the “Preparation Phase”), and RR Cessation (also called the “New Quit Phase”). While all participants will receive the same Initial Cessation Treatment, participation in the subsequent phases of the research depends on participant response to the prior phase and on what RR Preparation condition they are randomized to.

**Initial Cessation Phase.** All participants will receive the same Initial Cessation Treatment, and includes an in-person counseling session at Day -7 and counseling phone calls on Day 7, and Day 14 (see Table 6). There will also be assessment calls from research staff (see Table 6). *Initial Cessation Assessments will stop once a participant is randomized to the RR Preparation treatment or Control conditions.*

**Table 6. Long-Term Quitting Study Initial Cessation Phase Schedule of Treatment Contacts\***

Day	-7	-1	1	3	7	14	28	56	84	112	140	168
Week	-1				1	2	4	8	12	16	20	26
Visit	X											
Medication	X											
In-Person Counseling	X											
Phone Counseling					X	X						
IVR Calls		X	X	X								
Assessment Calls					X†	X†	X	X	X	X	X	X

\*All treatment and assessments will be discontinued for those who relapse between the quit date and 6 months postquit. (Relapse criteria can first be met at 6 days after the target quit day.) †These assessment calls will be combined with the counseling calls.

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**RR Preparation Phase.** Participants may enter the Relapse Recovery (RR) Preparation phase if relapse is detected during the initial cessation treatment for up to 6 months after the quit day via either counseling calls or assessment calls. If relapse is detected, the health counselor or student assessor will randomize the participant to one of the 3 RR Preparation intervention conditions via a dynamic real-time database. If the participant does not relapse or chooses not to enter the preparation phase during this 6 month period, they will not be eligible for the RR preparation phase.

If participants are assigned to the Preparation Control condition, they will be encouraged to continue the Initial Cessation treatment (if counseling sessions and/or medication remain) and to continue taking the study medication, but to contact the WTQL or talk to their referring clinician for additional treatment. Participants in the Preparation Control condition will be given WTQL contact information only the first time they report relapse. The RR Preparation Control participants will complete their RR Preparation baseline assessments at their first Standard Assessment Staff call at Week 1. They will also be asked to attend a visit at the 14 month mark to provide a CO sample if they claim abstinence at that time (abstinence demonstrated by a CO  $\leq 5$  ppm).

Participants assigned to an “active” RR Preparation condition (either Reduction or Recycling) will schedule a visit. At the visit, participants will complete RR baseline assessments, the nature of that treatment will be explained, future contacts will be described and scheduled, and treatment will be provided (Behavioral Reduction Counseling + nicotine mini-lozenges or Recycling Counseling); see Table 7. This first contact, where RR Preparation treatment begins for those in non-control conditions, is designated Preparation Day 0. Subsequent treatment contacts will be scheduled for such participants for Week 2 and Months 1, 3, 6, 9, & 11 post-Preparation Day 0. The contacts at Week 0 and Months 1 & 6 will be in-person visits; all other RR Preparation contacts will be by phone. However, if a participant cannot attend an in-person visit, a phone visit will be conducted instead.

All participants assigned to the non-control (active) RR Preparation conditions will receive Standard Assessment Staff calls (at Week 1 and Months 2, 4, 7, & 10) in addition to assessments that occur at RR Preparation treatment contacts (at Day 0, Week 2, and Months 1, 3, 6, 9, & 11). The phone assessments occurring at RR Preparation treatment contacts other than the Day 0 and Week 2 contacts will be brief, collecting primarily data on smoking since the last treatment contact. Finally, all RR Preparation participants (including those in the control condition) will participate in follow-up calls at Month 14; at Month 14 they will be asked to make a visit to provide a CO sample should they claim abstinence (see Table 7).

Table 7. Long-Term Quitting Study RR Preparation Phase Schedule of Treatment Contacts*																
Preparation Week	Preparation Day 0 (Day 0)	1	2	4	8	10	12	16	24	28	32	36	40	41	43	56
Month	0			1	2		3	4	6	7	8	9	10		11	14
Visit	X			X					X							X†
Reduction or Recycling Counseling	X		X	X			X		X			X			X	

# PROTOCOL

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Quitting Help Letter					X					X			X		
Assessment at Prep Phase treatment contacts (controls do not get this)	X		X	X		X		X			X			X	
Standard Assessment Staff Calls		X***			X		X		X			X			X

† A visit to biochemically confirm abstinence will follow the Month 14 call for those who claim abstinence.

\*All Preparation medication and treatment content will be discontinued for those who transition to the Cessation Phase. Participants in the Cessation Phase will, however, continue to complete the Standard Assessment Staff Calls. All participants (including RR Preparation Control participants) will complete the Standard Assessment Staff Calls and the 14 month assessments listed above.

\*\*Medication is only for participants in Reduction Counseling.

\*\*\*Preparation Control participants get the Standard Assessment Staff Call at Week 0 instead of at Week 1.

Note. RR Preparation Control participants will get only the Standard Assessment Staff calls and not other treatment elements, assessments, or visits.

**RR Cessation Phase.** Participants enter the RR Cessation Phase when they are in the active Preparation Phase conditions and indicate they are ready to make a new cessation attempt. Participants assigned to the RR Reduction condition will be encouraged to delay their new quit attempt (for at least one month or longer) until they have had some experience reducing their smoking and building their quitting skills. However, if participants in Reduction Counseling strongly wish to quit before 1 month has passed, they will be transitioned into the RR Cessation Phase earlier. In both the RR Reduction and Recycling conditions, as soon as participants enter RR Cessation treatment (via either a Staff Assessment call, an RR Preparation therapy call or visit, or by proactively contacting their counselor/research program), they will be randomly assigned to one of the 4 RR Cessation conditions.

All RR Preparation participants (both control and non-control) will complete Standard Assessment Staff Calls regardless of entry into RR Cessation treatment. However, once a participant has entered RR Cessation treatment, all RR Preparation treatment contacts will end. Thus, for those in RR Cessation treatment, all RR *Preparation* medication and treatment content will be discontinued.

The first contact in RR Cessation treatment will be a visit (RR Cessation Day -7). That visit will be scheduled during the RR Preparation contact when the participant reports wanting to try to quit. If the RR Preparation contact at which the participant decides to enter RR Cessation is an in-person contact, it is possible that the Day -7 Cessation treatment contact will be initiated at that Preparation visit.

Participants assigned to Brief Information only will have 1 RR Cessation visit on Day -7 when they receive their medication and basic, brief (“generic”) cessation counseling. They will also receive 2 brief phone counseling contacts at the TQD and at Week 1. If a participant is assigned to Skill Training or Supportive Counseling or both, they will receive 2 visits (at Day -7 and Day +7) and 7 brief phone calls on Day -2, the TQD, and at Weeks 2, 3, 6, 8.5 and 14 (see

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Table 8).

In addition to the RR Preparation Standard Assessment Staff Calls and 14-month follow-up call that continue from the RR Preparation phase, participants in the New Quit Phase will complete assessment on the first RR Cessation treatment visit, automated assessment calls (IVR calls) -4, -1, +1, +3 after initiation of RR Cessation treatment, and RR Cessation Follow-up Calls at Days +7, +14, Months 1, 2, 4, and 6 after initiation of RR Cessation treatment.

<b>Table 8. Long-Term Quitting Study RR Cessation Phase Schedule of Treatment Contacts</b>													
Day	-7	-2	TQD	7	14	21	28	42	60	70	98	112	182
Week	-1		0	1	2	3	4	6	8.5	10	14	16	26
Month			0				1			2.5		4	6
Visit with assessments	X			X**									
Medication	X												
Brief Information	X		X	X									
Supportive and/or Skills Counseling	X	X	X	X	X	X		X	X		X		
IVR Calls	Days -4, -1, 1, and 3												
Assessment				~X	~X		X			X		X	X
** This visit at Week 1 is only for participants randomized to Supportive Counseling, Skills Counseling, or both. ~The assessment occurs during the treatment call wherever possible.													

### The Intervention Components

All 3 studies will use as their primary interventions nicotine replacement therapy for treating smokers and one or more specific types of counseling. They will also employ the same research staff (referred to as health counselors) with each health counselor trained to provide all types of counseling. The research will use specific quality/fidelity assurance strategies that include: intensive case manager training in counseling and ethical conduct, mock sessions, review of audiotapes, and meetings to discuss safety, confidentiality, and treatment fidelity. Health counselors will meet every other week for clinical supervision with a clinical psychologist investigator to review the study protocol and address treatment issues. A common database provides guidance on the counseling content, medication and assessments to be provided at each contact. Such procedures have produced excellent treatment delivery fidelity in our recent work. The distinct intervention components are detailed below.

### Motivation Study

Participants in the Motivation Study may receive treatment during 2 phases: Motivation and Cessation. While all participants will receive Motivation treatment, participation in the Cessation phase of the research depends on whether participants decide they would like to quit smoking during the Motivation phase.

**Motivation Phase.** All participants will start the study in the Motivation Phase.

**Nicotine Replacement Therapy (NRT).** Participants randomly assigned to the Mini-Lozenge condition will use either the 2- or 4-mg doses (smoke within 30 min of waking = 4mg; smoke more than 30 min after waking = 2mg—as per package insert). Starting Spring 2018 we started to screen individuals who would be prescribed mini-lozenges for soy allergens prior to

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dissemination to prevent allergic reaction AEs - per the ML new package insert. Participants will be instructed to use the product for 12 months and to use it in a scheduled manner consistent with the 2008 PHS Guideline; they will be instructed to use one Mini-Lozenge every 1-2 hours and up to 12 daily, with a goal of using at least 5 daily. Participants will receive 12-weeks of medication at Visit 1 and will be sent additional medication after the assessment calls at Weeks 12, 26, and 39. The case manager will provide use instructions, teach participants to detect symptoms of nicotine toxicity, and encourage them to reduce smoking and/or NRT use to avoid these symptoms. All participants will be given an information sheet that conveys all medication instructions as well as a phone number to call if they have concerning side effects or other questions about their medication. All participants will be told to promptly report any difficulty, side effects or allergic reactions, and we will consult with participants as per good clinical practice to address any problems they have with NRT use. In some cases we may counsel participants to stop using NRT if they develop significant side effects (e.g., vomiting). The case manager will refer the patient to their primary care physician should the patient require medical consultation.

Behavioral Reduction Counseling (BR). We will deliver BR in 10 (10-15 minute) sessions over a 52-week period, with an in-person session at Visit 1 followed by nine phone counseling sessions (see Table 3). Sessions are front-loaded to enhance acquisition of new behaviors. BR Counseling will emphasize the development of smoking control skills via feasible, specific, and graded assignments of smoking reduction activities that will be tracked over time. BR will also emphasize competence and self-efficacy, both which will be directly linked to the *practice of smoking reduction skills and success in smoking control*. The health counselor will provide rationales for the reduction intervention, why reduction (e.g., eliminating smoking contexts) should help the smoker, and provide the participant with specific exercises and goals. The health counselor will explicitly address pragmatic issues such as work contexts, smoking policies, and habits that interfere with smoking reduction efforts. The health counselor will suggest the strategic use of medication to help achieve reduction goals (as appropriate with NRT treatment assignment). The health counselor will not pressure the smoker to quit. Smoking reduction will be presented as an important and worthwhile goal, and participants will be told that they are in the best position to decide when they are ready to make a quit attempt.

Behavioral Activation (BA). The BA treatment will be delivered in 10 (10-15 minute) sessions over a 52-week period starting with Visit 1 followed by nine phone counseling sessions (see Table 3). This BA treatment will be modeled after Behavioral Activation for quitting smoking, but made relevant for smoking reduction. Treatment goals focus on helping participants engage in positively reinforcing activities while not smoking. The treatment includes: 1) a rationale for the BA exercises as they relate to smoking (e.g., engaging in non-smoking reinforcers will provide other sources of pleasure and assist with cutting down); 2) assessment of the participant's goals, values, and reinforcing value of current nonsmoking activities; 3) training in self-monitoring using an activity log; 4) ongoing assignments of activities that should significantly increase the participant's nonsmoking reinforcement and create broader lifestyle and cue exposure changes; and 5) problem-solving to address obstacles to goal attainment. BA fosters a collaborative, problem-solving relationship between the health counselor and participant, and will be front-loaded (a dense schedule of sessions early in treatment) since BA activity assignments depend on the early assessment of the participant's reinforcing activities and feedback on success in assignment completion.



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**5Rs Motivation Counseling.** The 5Rs Motivation Counseling will be delivered in four (10-15 min) sessions over a 52-week period starting at Visit 1 and followed by three phone counseling sessions (see Table 3). Participants in the “on” condition will receive three brief phone sessions over the year to prompt processing of motives for smoking reduction or cessation. This light schedule of sessions is a reasonable burden even when paired with the other counseling conditions. The same health counselor will conduct these sessions and any other counseling interventions components (e.g., BR Counseling) with the participant. 5Rs Motivation Counseling will be similar to that described in the 2008 PHS Guideline. The health counselor and smoker will discuss: 1) Relevance of smoking to the individual; 2) Risks of continued heavy smoking; 3) Rewards of quitting and significant reduction; and 4) Roadblocks to success; and will do so on a 5) Repeated basis. The discussion will follow the general principles of MI: counselors will use strategies that are nonauthoritarian, nonconfrontational, supportive, and use open-ended questions. At the 2<sup>nd</sup>-4<sup>th</sup> sessions, the health counselor will first ask the patient to discuss his/her current feelings about smoking and then will review the patient’s thoughts and attitudes shared in previous sessions. The participant will be asked to discuss any changes that have occurred over time and their relevance to making a behavior change—towards both smoking reduction and cessation goals. If a participant has stopped smoking, the call will be directed at reinforcing cessation.

**Cessation Phase.** Motivation Phase participants who decide to quit smoking during the 9 months of the intervention period will receive a smoking cessation treatment, delivered by their same health counselor with whom they have been working. This cessation treatment will involve 2 in-person counseling sessions and 2 phone counseling sessions (see Table 4). Participants will also receive 8 weeks of the Nicotine Patch and Nicotine Mini-Lozenge.

**Medication.** Participants will receive 8 weeks of nicotine patch (participants who smoke >10 cigs/day: 4 weeks of 21 mg, 2 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches; participants who smoke ≤10 cigs/day: 6 weeks of 14 mg and 2 weeks of 7 mg nicotine patches) at the Day -7 counseling session (see Table 4) and will be instructed to begin using the patch on the TQD. Participants will also receive 8 weeks of the Mini-Lozenge, and use either the 2- or 4-mg doses (smoke within 30 min of waking = 4mg; smoke more than 30 min after waking = 2mg—as per package insert). Starting Spring 2018 we started to screen individuals who would be prescribed mini-lozenges for soy allergens prior to dissemination to prevent allergic reaction AEs - per the ML new package insert. Participants will be instructed to use it in a scheduled manner consistent with the 2008 PHS Guideline; they will be instructed to use one Mini-Lozenge every 1-2 hours and up to 12 daily, with a goal of using at least 5 daily. All participants will be given complete instructions on proper patch and Mini-Lozenge use, including an information sheet and contact information if they want to ask questions regarding their medication, and/or symptoms they experience. We will recommend dosage/use alterations as per good clinical practice if the participant experiences any medication side effects. The case manager will refer participants to their primary care physician should they require medical consultation. Participants will be asked to take the medication for the full 8 weeks, regardless of whether they return to smoking.

**Counseling.** Participants who decide to quit smoking will receive a 20 minute in-person counseling session at Day -7 that will involve preparing for the TQD (e.g., reinforce motivation, remove cigarettes and smoking paraphernalia from the environment, plan for the quit day), develop techniques to cope with withdrawal symptoms and smoking triggers, including negative

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affect and withdrawal, and provide support (see Table 4). A 20-minute phone counseling session will occur on the TQD, followed by 2, 20-minute in-person counseling sessions on Days 7 and 14. These sessions will focus on maintaining abstinence, coping with withdrawal symptoms and smoking triggers, encouraging quitting following a lapse, and providing support (see Table 4 for counseling schedule).

**Cessation Study**

Modern Usual Care (M-UC). We developed the Modern Usual Care (M-UC) to serve as a control condition to demonstrate that the abstinence-optimized cessation treatment would result in improved cessation compared to what would typically happen in a primary care practice. However, we wanted a control condition that was sufficiently effective to serve as a reasonable control condition. Therefore, while “usual care” in primary care may not extend beyond advice to quit smoking, participants assigned to the M-UC will receive 8 weeks of nicotine patch, a single brief, in-person counseling session, a faxed referral to the Wisconsin Tobacco Quit Line (WTQL), and will be signed up for either the QUITNOW app or the Web Coach (both provided by Alere Wellbeing, the vendor that provides the WTQL services).

*Medication.* M-UC participants will receive 8 weeks of nicotine patch (participants who smoke >10 cigs/day: 4 weeks of 21 mg, 2 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches; participants who smoke ≤10 cigs/day: 6 weeks of 14 mg and 2 weeks of 7 mg nicotine patches) at their first clinic visit and will be instructed to begin using the patch on the TQD. All participants will be given complete instructions on proper patch use, including an information sheet and contact information if they want to ask questions regarding their medication, and/or symptoms they experience. We will recommend dosage/use alterations as per good clinical practice if the participant experiences any medication side effects. The case manager will refer participants to their primary care physician should they require medical consultation. Participants will be asked to take the medication for the full 8 weeks, regardless of whether they return to smoking.

*Counseling and Technology.* Participants in the M-UC condition will receive a brief (10 minute) counseling session that will involve setting a quit date, identifying motivation for quitting and preparing for the quit date. Participants will then complete a fax-to-quit referral form for the WTQL, which will be faxed to the WTQL and result in the WTQL calling the participant to provide cessation counseling at the time of the participant’s choosing. Finally, the health counselor and the participant will review a handout that educates the participant about the QUITNOW app and the Web Coach feature from the WTQL. The handout will review how the app will provide access to evidence-based tools to help the smoker quit and for the first 2 weeks post-quit will provide active support and how to complete the 3 set-up screens for the app: 1) entering the quit date; 2) entering the number of cigs/day they smoke and the cost/pack; and 3) entering the reasons for quitting. The handout will also remind participants to mention their interest in the Web Coach feature to the Quit Line caller, who will then send them the link and password so that they can access the Web Coach after their Quit Line call. The handout will also provide the link to a brief 4-minute video about the Web Coach site, which will illustrate how they can enter their quit date and medication into their quit plan and access the different tools and support from the website through quit coaches or other quitters in the web community.

Abstinence-Optimized Cessation Treatment (AOCT). In our prior research using the Phase-Based Model and MOST, we conducted two screening experiments and experimentally

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evaluated 19 different intervention components delivered during the Preparation, Cessation, or Maintenance Phases. Based on the results, we identified 5 particularly effective intervention components to include in the AOCT package: 1) Preparation Nicotine Mini-Lozenges; 2) 26-week postquit Combination NRT (nicotine patch + nicotine mini-lozenges); 3) Intensive In-Person Cessation Counseling; 4) Extended Maintenance Counseling Calls; and 5) Automated Adherence Calls. Earlier research supports the individual intervention components identified by our screening experiments but no research has evaluated how well these components work together as an integrated treatment package, one assembled based upon experimental evidence that these components exert additive and synergistic effects when used together (as per MOST). Because our earlier screening experiments show that each of these components produces especially great benefit at the phase of smoking intervention at which it is used, we hypothesize that these components will constitute a particularly effective treatment package. Moreover, because the screening experiments occurred in real-world healthcare settings, and the intervention components were designed for this context, we believe that they will easily translate to real-world use.

*Medication.* The 3 weeks of Preparation nicotine mini-lozenge use will begin the day after Visit 1 (Week -3), during which most participants will likely continue to smoke regularly, albeit at a reduced rate. Participants will use 2- or 4-mg mini-lozenges, depending on how soon they smoke after waking, as per package insert (smoke within 30 min of waking = 4mg; smoke more than 30 min after waking = 2mg). Starting Spring 2018 we started to screen individuals who would be prescribed mini-lozenges for soy allergens prior to dissemination to prevent allergic reaction AEs - per the ML new package insert. Participants will be instructed to use the product in a scheduled manner consistent with the 2008 PHS Guideline; they will be instructed to use one Mini-Lozenge every 1-2 hours and up to 12 daily, with a goal of using at least 5 daily. Participants will be advised to try to cut down on their smoking, stop smoking in different places, and substitute mini-lozenges for cigarettes in preparation for quitting. Preparation use of NRT is safe and accepted by the FDA.

Starting on the TQD, participants will be instructed to use both the nicotine patch and the nicotine mini-lozenges. Patch dosing and mini-lozenge dosing will be consistent with the 2008 PHS Guideline and package inserts (smoke within 30 min of waking = 4-mg mini-lozenge; smoke more than 30 min after waking = 2-mg mini-lozenge; smoke >10 cigs/day = 22 weeks of 21-mg, 2 weeks of 14-mg, and 2 weeks of 7-mg nicotine patches; smoke ≤10 cigs/day = 24 weeks of 14-mg and 2 weeks of 7-mg nicotine patches). Participants will be told to try to use a mini-lozenge every 1-2 hours until 2 weeks before treatment termination at which time participants should cut down until they are down to no mini-lozenge use by the end of 26 weeks. Participants will also be told that they may not be able to take a full, recommended dose of mini-lozenges given their conjoint use of the patch. Participants will be urged to use an average of 9 mini-lozenges/day, unless this amount of use produces negative (toxic) effects—instructions which have been shown to be effective in prior research; it reduces the potential for side effects, and research shows that very few people use ≥9 pieces of oral NRT, whether alone or in combination with other NRT, regardless of instructions. All participants will be given complete instructions on proper NRT use, including an information sheet and contact information if they want to ask questions regarding their medication, and/or symptoms they experience. We will recommend dosage/use alterations as per good clinical practice if the participant experiences symptoms of nicotine toxicity or other side effects. The case manager will refer participants to their primary care physician should they require medical consultation. Participants will be asked

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to take the medication for the full 26 weeks, regardless of whether they return to regular smoking. Additional medication will be mailed to those still using the medication, following the assessment calls at Weeks 8 and 16.

*Counseling and Automated Calls.* Participants in the AOCT will receive In-Person Cessation Counseling which will be supportive and focus on skill development and problem-solving, as recommended by the 2008 PHS Guideline. The goals of Cessation-phase counseling are to prepare for the TQD (e.g., reinforce motivation, remove cigarettes and smoking paraphernalia from the environment, plan for the quit day), develop techniques to cope with withdrawal symptoms and smoking triggers, including negative affect and withdrawal, and provide support. There will be three 20-min In-person Cessation Counseling sessions (Week -1, TQD, Week 1). The timing and counseling content of the three sessions is consistent with the 2008 PHS Guideline recommendations. AOCT participants will also receive 8 Maintenance-phase smoking cessation counseling sessions. These 15-minute calls emphasize content similar to that provided in the In-Person counseling, namely support and problem-solving.

Finally, participants will receive 11 brief, automated calls reminding them to use their medications properly at Days 1, 3, 10, 17, 24, 31, 45, 73, 101, 129, and 157. However, if participants report that they are not smoking during the Week 8 assessment call, they will not receive any further automated adherence messages (i.e., they would get 7 automated calls during the first 6 weeks of their quit attempt). This decision was based on data from our prior study that suggested that smokers who were able to achieve abstinence early in the quit attempt, appeared to have less long-term cessation success if they got the automated adherence calls.

### ***Long-term Quitting Study***

Initial Cessation Treatment. The Initial Cessation Treatment, which meets the standard of care, will include 3 counseling contacts: one 10-minute in-person counseling session 1 week prior to the quit day, and 5 min counseling calls 1 and 2 weeks post-quit. The counseling content will be supportive and will include some skill development as recommended by the 2008 PHS Guideline (Fiore et al., 2008). The counseling will include encouragement and will also emphasize the importance of taking the medication and how to use it, and provide information about side effects/safety and what to do in case of problems. Participants will receive 8 weeks of nicotine patch (participants who smoke >10 cigs/day: 4 weeks of 21 mg, 2 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches; participants who smoke ≤10 cigs/day: 6 weeks of 14 mg and 2 weeks of 7 mg nicotine patches). Participants will receive their medication at Visit 1 (i.e., 1 week before the quit day).

Relapse Recovery Phase. If participants relapse within 6 months of their Initial Cessation treatment quit day, they will be eligible to receive RR Preparation treatment unless they have been randomized to the RR Preparation Control condition. Relapse will be defined as 7 consecutive days of smoking at any point after the quit day. Relapse will be detected via counseling calls and Initial Cessation phase assessment calls (see Table 6). Participants will

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also be asked to call the program office if they return to daily smoking. Participants in the Relapse Recovery Preparation Phase (and not in the RR Preparation Control condition) will be randomized to one of two treatments: Behavioral Reduction Counseling + Nicotine Replacement Therapy (NRT with the nicotine mini-lozenge) or Recycling Counseling.

**Table 9. Counseling contacts for the Relapse Recovery Preparation Phase Components.**

	Wk 0	Wk 2	Mo 1	Mo 3	Mo 6	Mo 9	Mo 11
<b>RR Reduction Counseling</b> (All calls 15 min; 30 min Visit 1; 20 min at Visit 2 and 3)	V1	C1	V2	C2	V3	C3	C4
<b>RR Recycling Counseling</b> (20 min at V1; 15 min at V2, 10 min at V3; all others are 5-10 min)	V1	C1	V2	C2	V3	C3	C4

Note: C = Calls V = Visits *RR Reduction Counseling and Nicotine Replacement Therapy.*

Participants randomized to this treatment will receive manual-based counseling calls and visits over the course of 11 months (see Table 9). The ultimate goal will be smoking that is reduced in amount and location. Case managers and participants will collaboratively identify a set of steps to progressively reduce smoking (e.g., make the house smoke-free). The primary vehicles for change are to encourage substitution of the nicotine mini-lozenge for cigarettes and to reduce the contexts in which smoking occurs (including making the home smoke free). Counseling will counter post-lapse demoralization by emphasizing participants' progress, the value of smoking *reduction* as a transitional goal, and the critical value of ongoing treatment engagement. Evidence of progress in reduction of smoking, and smoking contexts will be used to build self-efficacy. Case managers will monitor the outcomes of these tasks, provide feedback to patients on their status over time and help participants attribute their success to their own efforts.

Participants will also receive up to 11 months of mini-lozenges as part of this treatment (dosing based on their nicotine dependence as measured when they started the study: 4 mg if they smoked within 30 minutes of waking and 2 mg if they smoked more than 30 minutes after waking, as per the package insert), along with instructions for use. Starting Spring 2018 we started to screen individuals who would be prescribed mini-lozenges for soy allergens prior to dissemination to prevent allergic reaction AEs - per the ML new package insert. Participants will receive 2 months of mini-lozenges at the Week 0 visit, 2 months of mini-lozenges at the Month 1 visit, 3 months of mini-lozenges following the counseling call at Month 3, and the last 4 months of mini-lozenges at the Month 6 visit. *If participants don't attend the RR Reduction Counseling V1, V2, or V3 but they indicate that they want mini-lozenges, we will mail the mini-lozenges to them.* Participants will be able to switch to a lower dose of mini-lozenges over the course of Reduction Therapy if the Medication Safety Assessment suggests this could be helpful. Participants will be encouraged to use around 9 lozenges/day for the duration of time they are in Reduction therapy. If adherence data suggest low usage, the health counselor will work with the participant to identify barriers to use. Participants will also be asked about the occurrence of side effects. Participants will be told that if they are using the mini-lozenge regularly and are smoking in only a limited number of contexts, they are building success for their quit attempt. The intent is *to convey a realistic and positive appraisal of participants' increasing ability to control their smoking.*

After 1 month of treatment, at every RR Reduction Counseling contact case managers will offer participants the option of beginning RR Cessation treatment. However, care will be taken

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to ensure that participants do not feel pressured to make a quit attempt before they are ready.

**RR Recycling Counseling.** Participants assigned to this treatment condition will also have 7 treatment contacts (see Table 9) and will be encouraged to commit to a quit date as soon as they feel ready. As in prior recycling efforts, participants will be encouraged to discuss reasons for quitting, concerns and barriers, and to view abstinence as the primary treatment goal.

To ensure all participants remember they can make a quit attempt with study help at any time, participants in both the RR Reduction and Recycling Conditions will receive letters, emails, or text messages (depending on the preferred delivery route they selected at the start of the study and depending on what is feasible) at Weeks 10, 32, and 41 encouraging them to make a quit attempt and providing information on how to contact study staff to receive RR Cessation treatment.

**RR Cessation or “New Quit” Phase.** When participants opt to make a new quit attempt within 11 months of entering the RR Preparation Phase, they will be transitioned to RR Cessation treatment. RR Cessation Phase participants will be randomized to one of 4 treatment conditions (a 2x2 factorial design) comprising 2 active intervention components: 1) Skill-Based Training vs. Brief Information; and 2) Supportive Counseling vs. Brief Information. Each form of counseling is designed to boost cessation success through the incorporation of medication adherence content: i.e., the importance of using medication despite lapsing, inculcating positive beliefs about medication, and so on. Participants will receive skill-based, supportive counseling or both prior to and after discontinuation of study medication, including supportive maintenance phone calls. Elements of this counseling will be designed to ease the transition off medication.

The delivery of *each active* counseling component (i.e., Skill-Based Training or Supportive Counseling) will take 15-20 minutes at Visit 1, 15 minutes at Visit 2 and 10-15 minutes/call. The RR Cessation Brief Information intervention will take about 5 minutes/contact and occur at Visit 1 and 2 and the Target Quit Day. When a participant receives both of the active components the net delivery time will be 35-45 minutes for each visit and 20-25 min/call to ensure that the Brief Information content is also covered (see Table 10).

**Table 10. Long-Term Quitting Study RR Cessation (“New Quit”) Phase Counseling**

Week	-1	Day -2	0 (TQD)	1	2	3	6	8.5	14	Total Contact Time
Visit or Call	V	C	C	V*	C	C	C	C	C	
# Minutes Brief Info Only	5		5	5						15
# Minutes Support or Skill Training + Brief Info	20-25	10-15	15	20	10	10	10	10	10	115-125
# Minutes Support + Skill Training + Brief Info	35-45	20-25	25	35	20	20	20	20	20	215-230

\*This is a call for the Brief Info Only Group. TQD = Target Quit Day

**Brief Information.** All participants will receive brief (generic) information about the importance of taking the medication and how to use it, information about side effects/safety and what to do in case of problems, and will also be given encouragement.

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*Skill Training Therapy.* Skill training therapy will: 1) carefully assess smoking cue contexts and opportunities to smoke, concentrating especially on problems encountered in the participant’s prior quit attempt; 2) develop specific plans for avoiding such contexts and skills for coping with them; 3) help participants develop plans for negotiating with critical others who smoke (e.g., housemates, co-workers); 4) develop lifestyle changes to reduce future smoking opportunities and contexts; and 5) assign homework and assess execution of assigned skills. Participants will also receive coping menus that the counselor fills out with the patient that provide personalized coping/avoidance options and “coping reports” that assess coping execution over time and troublesome contexts and cues around which counseling will be focused. These will be handed to participants after sessions or emailed or mailed to participants (based on the participant’s preference) after some calls. While the emphasis will clearly be on skill acquisition and execution, the targeting of skills for individual participants will be done in a collaborative manner. There will be praise for any progress and a collaborative determination of barriers to skill execution. Thus, coping and avoidance plans will be: 1) collaboratively developed, 2) given/ sent to patients immediately after any contact where plans are developed, and 3) reviewed carefully at future contacts to refine coping plans. The key elements of this counseling will be specific, individualized coping plans, monitoring of plan execution and effects, and on-going modification of plans.

*Supportive Therapy.* This intervention will comprise elements and content consistent with the characterization of intra-treatment support as contained in the PHS Clinical Practice Guideline (Fiore et al., 2008). Thus, it will involve encouragement (e.g., information that previous failure to quit is often positively related to subsequent success), a focus on short-term goals (e.g., go without smoking for 2 hours, communication of belief in the participant’s ability to quit), discussion of participant values (what the participant feels would be good and healthy for them in the long run) and how these values are congruent with cessation, emphasis on the patient and the counselor being a team, encouragement for the participant to generate a quitting strategy with the message that smokers often have a good sense of what will work for them (a client centered approach), and prompts for the participant to explore his/her feelings about quitting and feelings of optimism and concern; i.e., to use the counselor as a sounding board. Therefore, the Skill Training approach emphasizes explicit training while the Supportive intervention does not. Because these two forms of therapy may co-occur, counseling manuals will be carefully prepared so as to permit their effective integration. For instance, while the Skill Training intervention will recommend coping skills for the participant, when the participant also receives Supportive counseling s/he will be encouraged to discuss his/her feelings about the quit plan and reflect on its “fit” for his/her life.

*Medication.* All participants will receive 8-weeks of combination NRT (nicotine patch + nicotine mini-lozenge). Nicotine patch dosing will be based on current cigarettes smoked per day, per package insert: for those who currently smoke >10 cigs/day=4 weeks of 21 mg, 2 weeks of 14 mg, and 2 weeks of 7 mg nicotine patches, along with nicotine mini-lozenges; for those who currently smoke ≤10 cigs/day=6 weeks of 14 mg and 2 weeks of 7 mg nicotine patches along with mini-lozenges. Mini-lozenge dosing will be based on how soon participants currently smoke after waking before their initial quit attempt and will be consistent with the package insert (4 mg for participants who smoke within 30 minutes of waking and 2 mg for participants smoke more than 30 minutes after waking).

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**Clinic Randomized Control Trial**

**Implementation.** The clinics assigned to the experimental condition will have the EHR enhancements introduced by methods we have used previously to introduce healthcare upgrades into clinics (including EHR enhancements). These procedures include staff training visits, follow-up calls, and feedback on EHR use and treatment referral. Importantly, clinic training will be standardized across clinics. The great majority of the clinics assigned to the control condition will already be participating in the Fax-to-Quit (F2Q) program. However, all clinics (including those already using the F2Q program) will be given implementation training to ensure that all clinics start with similar implementation support. The minimum implementation training will be one initial staff meeting and a second meeting at six months to provide feedback, encouragement, and promote problem solving). Also, as per good clinical practice, if notable problems are observed in smoker identification and referral data coming from a clinic, ad hoc problem solving via phone calls or meetings will be undertaken with the clinic to resolve obstacles. Such ad hoc problem solving will occur with clinics in both conditions and will be recorded so as to permit comparison of needed implementation support.

Certain additional procedures will be used in the active (non-control) clinics. Prior to the EHR modifications and initiation of participant recruitment in a given clinic, an in-service training will take place, attended by UW-CTRI research staff, clinic physicians, and other clinical and support staff. These trainings will be scheduled during one of the clinic's existing staff meetings. Trainings will include a description of the study protocol relevant to clinic staff and an overview of the goals of the project and the role of the clinic personnel in achieving these goals. Past experience has demonstrated the importance of both Dr. Fiore (as study PI) and the clinic Medical Director attending these launch training meetings for each clinic (i.e., 18 meetings in the proposed Program Project). Their joint attendance at the meetings increases staff attendance and highlights how important the project is to the clinic and healthcare system. These launch meetings will include a walk-through of the new EHR functions (including EHR screen-shots), emphasizing their ease of execution and how they will enhance patient care. The training will also clearly describe the roles of clinic personnel in the research/treatment project and explain how their activities benefit the patient and the project. We will then answer any questions and address concerns. Because the roomers will play a pivotal role in using the enhanced EHR functions (e.g., smoking documentation, referral), we will arrange additional meetings with these key clinic staff members to continue training, answer questions and enhance their commitment. These additional trainings with roomers often involve a lunchtime meeting where the UW-CTRI research staff brings lunch. UW-CTRI staff will conduct the research interventions for the clinical projects at the clinic sites and therefore will be available throughout the study, providing refresher training once every other month and regular quality/progress reports to the clinic.

About a week after this introduction and launch of the EHR enhancements in each clinic, UW-CTRI research staff assigned to the clinic will follow-up with the clinic manager to address questions, problem solve, provide early performance feedback on smoker identification and recruitment, and reinforce proper EHR use. Over the next 3 weeks, UW-CTRI research staff will work with each clinic manager, as well as healthcare system database personnel, to examine de-identified data to ensure that clinic staff are using the new EHR resources properly. We will record all instances where we intervene and train with clinics in order to identify and document best practices training recommendations. When problems come to light, we will work



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collaboratively with the clinic manager and roomers (and occasionally the Medical Director and other medical staff) to support proper EHR use and smoker referral. These training and feedback systems have been used successfully by UW-CTRI research staff in more than a dozen prior NIH studies and by UW-CTRI staff who have trained over 10,000 clinicians across Wisconsin in tobacco intervention as part of the Center’s statewide outreach mission.

***Smoker identification and referral in clinics.*** Therefore, in control clinics, clinic personnel will use methods consistent with good clinical practice, and that very similar to those currently in use in such clinics, to identify smokers, document their smoking status, and refer them to the WTQL (and possibly to other resources such as the patient’s primary care physician). These methods include using existing EHR resources to identify smokers (e.g., the expanded vital signs) and to document their smoking status, and then use the standard paper fax-to-quit methods to refer patients to the WTQL. As is typical of current practice (and distinct from a chronic care approach) *only those patients who are interested in cessation will be referred to the WTQL* (not those interested in reducing their smoking). These methods will be compared with the EHR methods that will be used in the experimental clinics and that are described above, with both the F2Q and EHR methods having comparable levels of implementation support.

**Data Collection: Questionnaire, Interview, and Behavioral Assessments for the Clinical Studies and Data Collection for the Clinic Randomized Control Trial**

Part of the synergy of this research arises from the use of consistent assessments across all three research studies. This consistency will allow us to compare participants and events across all three samples – including allowing us to compare smokers who are and are not motivated to quit and smokers who do and do not relapse. Assessments, which have good to excellent psychometric characteristics, will include: 1) individual difference variables related to outcome; 2) potential mediators of intervention component effects; and 3) proximal and distal outcomes. At Visit 1 participants in all 3 studies will complete a standard baseline assessment that includes: tobacco use history, demographic assessments, exhaled carbon monoxide assessment, height and weight assessment, tobacco dependence assessed via the Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM-34) and the Fagerström Test of Nicotine Dependence (FTND), affect assessed using the well-validated Positive and Negative Affect Scale (PANAS), withdrawal assessed using the Wisconsin Smoking Withdrawal Scale (WSWS), and motivation and self-efficacy assessed using Likert scale items used in previous research. Participants will also evaluate the treatment provided in terms of burden and acceptability as well as their perceptions of the healthcare system for providing such treatment, using measures developed for this study based on previous research on patient satisfaction assessments. Specifically, we will assess constructs such as satisfaction with study staff, clinic staff for referring the smoker to the study, and the healthcare system for providing the treatment. Consistent mediators assessed across the 3 projects include motivation, self-efficacy, and withdrawal. There will also be study-specific baseline and follow-up assessments, as described below.

***Motivation Study***

At Visit 1 participants will complete the standard baseline assessment (see above). Participants will also complete the 15-item Snaith-Hamilton Pleasure Scale and confidence assessments using Likert scale items used in previous research. Participants will also complete

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a Decisional Balance Questionnaire about smoking, assessments about whether they have been encouraged to quit, and assessments of recent quit attempts and plans for future quitting. Participants will complete 4 assessment calls at Weeks 12, 26, 39 and 52 (see Table 11). Only selected items from the above scales will be used for the subsequent assessment calls. Medication usage and side effects will be assessed at every study contact for participants using Nicotine Mini-Lozenge. NRT use and smoking will be assessed at each contact using the timeline follow back procedures.

**Intensive Longitudinal Data (ILD).** Participants will receive 11 brief, automated assessment calls over 52 weeks after Visit 1 (see Table 3 for schedule). The assessment schedule will continue even if a participant receives the cessation treatment to permit standardized assessments for all participants. The 3-4 min calls will occur shortly before bedtime, based on participants’ self-reported sleep times. This has resulted in acceptable call times in our previous research. The calls will assess: withdrawal symptoms (selected items from the Wisconsin Smoking Withdrawal Scale, including craving); positive and negative affect assessed via items from the PANAS; time to first cigarette in the morning; any smoking and use during the day of the call and during the preceding 7 day period; alcohol use, quit attempts and plans for quitting; pleasure from events; medication use; intrinsic motivation to quit or reduce smoking; and self-efficacy. Missed or deferred calls will be reinitiated in 15-minute intervals. Eligible participants must have access to a phone (either cell or land line). This assessment burden is much less than has been used successfully in many other studies, and research has shown that ILD/ecological momentary assessment produces modest assessment reactivity. Our prior experience shows that IVR systems yield high quality information with response rates exceeding 80%, even among primary care patients.

**Table 11. Schedule of Motivation Study Assessments**

Assessments	V1	Call Wk 12	Call Wk 26	Call Wk 39	Call Wk 52
Sign informed consent and HIPAA	X				
Demographics	X				
Tobacco use history	X				
Tobacco dependence	X				
Medication beliefs	X				
Height, weight	X				
Carbon Monoxide	X				
Tobacco dependence	X	X	X	X	X
Current tobacco use	X	X	X	X	X
Current alcohol use	X	X	X	X	X
Motivation, self-efficacy, and confidence	X	X	X	X	X
Dual Use		X	X	X	X

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Smoking Environment	X	X	X	X	X
Withdrawal	X	X	X	X	X
Quit attempts, Plans for quitting	X	X	X	X	X
Affect and pleasure	X	X	X	X	X
Stress	X	X	X	X	X
Decisional Balance	X	X	X	X	X
Self-report of medication adherence		X	X	X	X
Safety assessment		X	X	X	X
Healthcare system evaluation	X	X		X	
Treatment acceptability					X
IVR*		X	X	X	X

\* Participants will receive 11 IVR calls over the course of 52 weeks (see Table 3).

### Cessation Study

At Visit 1 participants will complete the standard baseline assessment (see Table 12). It should be noted that we will assess use of all tobacco and nicotine products (e.g., electronic cigarettes, smokeless tobacco), but the primary outcome for this study is abstinence from all combustible tobacco products. Participants will complete 6 assessment calls at Weeks 4, 8, 16, 26, 39 and 52 (see Table 12). Only selected items from the above scales will be used for the subsequent assessment calls. In addition, participants will complete assessments of cessation fatigue and confidence in quitting. Medication usage and side effects will be assessed at all appropriate assessment calls. NRT use and smoking will be assessed at each contact using the timeline follow back procedures. We will ask participants reporting abstinence at Week 26 to come to their primary care clinic to provide a breath sample for carbon monoxide biochemical confirmation of abstinence. The timeline follow back smoking assessment will allow us to determine the key clinical outcomes: 1) initial cessation; 2) latency to lapse (smoking their first postquit cigarette) and relapse (the first day of smoking on 7 consecutive days); and 3) consistent with the recommendations of the Society for Research on Nicotine and Tobacco (SRNT) Workgroup on Biochemical Confirmation, 6- and 12-month continuous abstinence (no smoking or other tobacco use between the quit day and a specified follow-up time-point). This selection of outcomes is consistent with the Phase-Based Model’s recommendation that researchers use outcomes appropriate for the smoking cessation phase being studied.

Intensive Longitudinal Data. The Cessation Study will collect intensive longitudinal data (ILD) to examine the impact of the two treatment packages on potential treatment mediators and outcomes. ILD will be collected via automated calls and will assess constructs posited to mediate treatment effects and/or influence cessation success. Participants will complete daily ILD assessments for a 3-week period (1 week prequit and 2 weeks postquit). The 3-4 min calls will occur shortly before bedtime, based on participants’ self-reported sleep times. This has resulted in acceptable call times in our previous research. The calls will assess: withdrawal symptoms (selected items from the Wisconsin Smoking Withdrawal Scale, including craving); positive affect assessed via items from the PANAS; stressors; any smoking during the day; temptation events; urges; pleasure from events; medication use; cessation fatigue; and self-efficacy over the day. Missed or deferred calls will be reinitiated in 15-minute intervals. Eligible participants must have access to a phone (either cell or land line). The brief assessment items—tailored for ILD collection—have been shown to sensitively reflect treatment effects,

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predict relapse, and reveal treatment mediation. This assessment burden is much less than has been used successfully in many other studies, and research has shown that ILD/ecological momentary assessment produces modest assessment reactivity. Our prior experience shows that IVR systems yield high quality information with response rates exceeding 80%, even among primary care patients.

**Table 12. Schedule of Cessation Study Assessments**

Assessments	V1	TQD <sup>†</sup>	Call Wk 4	Call Wk 8	Call Wk 16	Call Wk 26	Call Wk 39	Call Wk 52
Sign informed consent and HIPAA	X							
Demographics	X							
Tobacco use history	X							
Tobacco dependence	X							
Medication beliefs	X		X	X				
Height, weight	X					X <sup>**</sup>		X <sup>**</sup>
Carbon monoxide	X					X <sup>*</sup>		
Current tobacco use	X		X	X	X	X	X	X
Motivation, self-efficacy and confidence	X		X	X	X	X	X	X
Withdrawal	X		X	X	X	X	X	X
Affect and pleasure	X		X	X	X	X	X	X
Self-report of medication adherence			X	X	X	X		
Safety assessment		X	X	X	X	X		
IVR assessment	X	X						

\*Participants who report abstinence at the 26-week call will be asked to come to the clinic to provide a breath sample to biochemically verify abstinence.

\*\*Participants will self-report weight at Weeks 26 and 52.

**Long-term Quitting Study**

Assessments will be gathered during the three phases of the proposed research: 1) Initial Cessation, 2) RR Preparation, and 3) RR Cessation (see Figure 2). The Initial Cessation assessments will be gathered at baseline and during the 6-month Initial Cessation treatment (see Table 13). Participants who relapse from Initial Cessation treatment and who are randomized to the active RR Preparation treatment conditions (Reduction and Recycling Counseling), will complete assessments during the Standard RR Assessment Staff Calls across the RR treatment (at Week 1 and Months 2, 4, 7, & 10), at the treatment contacts at RR Preparation Day 0, Week 2, and Months 1, 3, 6, 9, & 11, and at the 14-month RR follow-up period contact (which *may* include a *visit* at 14 months if the participant claims abstinence at that time). Participants who enter RR Cessation treatment will continue to receive the Standard RR Assessment Staff Calls but RR Preparation treatment and associated contacts will be discontinued. The RR Preparation Control subjects will complete the RR Preparation Standard Staff Assessment calls (at Week 1 and Months 2, 4, 7 & 10) and will also provide assessment information at the Month 14 follow-up call/visit.

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**Initial Cessation Phase.** Participants will complete core baseline assessments at Visit 1 (Week -1). Participants will also complete assessments during phone calls using selected items from the baseline scales (see Table 13) and 4 brief evening automated IVR assessments (Days -4, -1, 1, and 3). These staff assessment calls will assess medication use, reasons for nonadherence, exposure to contextual risk factors, withdrawal symptomatology, and smoking over the past week (to detect relapse). The IVR calls will assess: withdrawal symptoms (selected items from the Wisconsin Smoking Withdrawal Scale, including craving); positive affect assessed via items from the PANAS; stressors; any smoking during the day; temptation events; urges; use of coping skills; pleasure from events; medication use; cessation fatigue; and self-efficacy over the day. *Initial Cessation Phase assessments will stop once a participant is randomized to RR Preparation treatment.*

**Table 13. Schedule of Long-Term Quitting Study Quit Phase (Initial Cessation) Assessments**

Day	-7	-1	1	3	7	14	28	56	84	112	140	182
Week	-1				1	2	4	8	12	16	20	26
Contact	V	I	I	I	C	C	C	C	C	C	C	C
Assessments												
Sign informed consent and HIPAA	X											
Demographics	X											
Tobacco use history	X											
Tobacco dependence	X											
Health, mental health, and health behaviors	X											
Height, weight	X											
Carbon monoxide	X											
Current tobacco use		X	X	X	X	X	X	X	X	X	X	X
Other tobacco and medication use	X						X					X
Motivation, self-efficacy, and fatigue	X	X	X	X	X		X		X			X
Demoralization	X	X	X	X	X		X		X			X
Withdrawal	X	X	X	X	X		X					X
Pleasure	X	X	X	X	X							X
Coping skills	X				X							
Smoking context	X	X	X	X	X		X					
Positive Affect	X	X	X	X	X		X					X
Stressors	X						X					
Medication adherence and beliefs		X	X	X	X	X	X	X				
Medication safety assessment					X	X	X	X				
Adherence Factors question												

## **PROTOCOL**

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V = Visit; I = IVR assessment; C = Call

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**Relapse Recovery Phase.** All participants who relapse and are randomized to RR Preparation treatment (both control and non-control participants) will complete Standard RR Assessment Staff Calls during the 11-month RR Preparation period (see Table 14). In addition, the non-control participants will complete assessments at each RR Preparation treatment contact (i.e., at Day 0, Week 2, and Months 1, 3, 6, 9, and 11). Both control and non-control participants will complete the 14 Month Follow-up (and an associated visit if the participant claims abstinence at that time). These calls will assess smoking status, self-efficacy at controlling smoking, and exposure to smoking cues and contexts. Participants will also be queried about NRT/medication use, “intentional” quit attempts (conscious attempts to quit regardless of success/length of abstinence), number of “meaningful” quit attempts (that led to more than one day of abstinence), use of other cessation aids/treatments, and estimated amount of smoking/day for the past 7 days. We will assess use of all tobacco and nicotine products (e.g., electronic cigarettes, chew), but the primary outcome will be abstinence from combustible tobacco products. Finally, we will assess desire to enter an RR Cessation Phase treatment (the latter only for non-control RR Preparation participants). All participants will complete the Standard RR Assessment Staff Calls, regardless of entry into RR Cessation treatment.

**Table 14. Long-Term Quitting Study RR Preparation Phase Assessments**

Month	Baseline	Wk 1	Wk 2	Wk 4	2	3	4	6	7	9	10	11	14
Visit or Call	V (C for Control)	C	C	V	C	C	C	V	C	C	C	C	C
Reduction motivation and self-efficacy	X		X	X	X			X			X	X	
Cessation motivation and self-efficacy	X		X	X	X			X	X		X	X	X
Time to first cigarette	X			X			X	X			X	X	X
FTND	++							X					X
Withdrawal	X		X	X	X		X	X			X	X	X
Coping skills				X				X					
Smoking context	X			X				X				X	X
Current smoking	X	++	X	X	X	X	X	X	X	X	X	X	X
Smoking status and quit attempts	X	++			X		X		X		X	X	X
Dual use	X			X			X	X				X	X
Plans to quit							X						X
Demoralization, fatigue	X			X	X			X				X	X
Positive Affect	++			X				X					
Self-compassion	X			X				X				X	
Medication safety assessment		+++	+++	+++		+++		+++		+++		+++	
Mini-lozenge use		+++	+++	+++		+++		+++		+++		+++	
Adherence factors form				+++				+++					
Carbon monoxide	++			X				X					X**
Use of other cessation treatments					X		X		X		X		X
Ask if want to switch to New Quit Phase	+		+	++		++		++		++		++	

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Note. Grey columns are for active RR Preparation participants only. + = for Recycling participants only; ++ = for Reduction and Recycling participants; +++ Reduction participants only. \*\*All participants claiming abstinence at the Month 14 Follow-up will be asked to take a CO test to confirm their self-report.

**RR Cessation Phase.** When participants decide to make a new quit attempt and are randomized to RR Cessation treatment, they will also receive RR Cessation Phase assessments (see Table 15). The RR Cessation Assessments will involve assessment on the first RR Cessation treatment visit, IVR calls -4, -1, +1, and +3 days after initiation of RR Cessation treatment, and RR Cessation Follow-up Calls at Days +7, +14, Months 1, 2, 4, and 6 months after initiation of RR Cessation treatment

The RR Cessation Assessments will typically elicit information on smoking heaviness and potential mechanisms (e.g., demoralization, pleasurable activities, exposure to smoking cues, self-efficacy, coping execution, medication use, medication side-effects, perceived treatment support, smoking heaviness, and craving; see Table 15). Participants will also complete a smoking calendar for the duration of the RR Cessation treatment to establish time to lapse and time to relapse.

**Table 15. Schedule of Long-Term Quitting Study New Quit Phase (RR Cessation Phase) Assessments**

Day	-7	-4	-1	1	3	7	14	28	70	112	182	
Week	-1					1	2	4	10	16	26	
Contact	V	I	I	I	I	V/C	C	C	C	C	C	
Time to first cigarette	X					X					X	
Tobacco dependence	X											
Carbon monoxide	X					X**						
Current tobacco use	X	X	X	X	X	X	X	X	X	X	X	
Number of alcoholic drinks		X	X	X	X	X	X	X				
Relapse context questionnaire as needed						X	X	X	X	X	X	
Mental health and alcohol use	X											
Non-study med use						X					X	
Dual use	X					X					X	
Motivation, self-efficacy, and fatigue	X	X	X	X	X	X	X	X	X			
Demoralization	X	X	X	X	X	X	X	X	X			
Withdrawal	X	X	X	X	X	X	X	X	X			
Stressors	X	X	X	X	X	X	X	X				
Pleasure	X	X	X	X	X	X		X				
Coping skills	X	X	X	X	X	X	X	X				
Positive affect	X	X	X	X	X	X		X				
Medication adherence and beliefs				X	X	X	X	X	X			
Self-Compassion	X					X						



# PROTOCOL

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Day	-7	-4	-1	1	3	7	14	28	70	112	182	
Week	-1					1	2	4	10	16	26	
Contact	V	I	I	I	I	V/C	C	C	C	C	C	
Questionnaire												
Avoidance and Inflexibility Questionnaire	X					X		X				
Medication safety	X					X	X	X				
Smoking context	X	X	X	X	X	X	X	X				

V = Visit; I = IVR assessment; C = Call;

\* = This visit is only for participants claiming abstinence.

### **Data Collection for the Clinic Randomized Control Trial**

**Baseline data.** Baseline data will be used for assigning clinics to the experimental conditions: e.g., using WTQL referral rates and smoker prevalence data as matching criteria in the MAUM method. Second, baseline data will be used as pretreatment covariates in outcome analyses. Again, WTQL referral and smoker documentation data would be useful for this purpose. We anticipate being able to derive the smoker documentation rates from the clinic’s EHR records. Documentation of smoking status per visit will be assessed by determining the percentage of time that known smokers at a clinic are asked about their smoking status. The denominator (“known” smoking status) will be determined by search of the EHR smoking relevant ID fields. We will query the WTQL records to obtain baseline rates of WTQL referral for the various control and experimental clinics.

**Post-intervention data.** Post-intervention data (i.e., once training and implementation have occurred in a clinic) will be gathered from the control clinics using the same methods as were used in the baseline period. In the experimental clinics, **smoker documentation** will be assessed via the same method as used during baseline (i.e., comparing per visit smoker documentation with EHR smoker identification fields). However, in the experimental condition clinics, **treatment referral** will be ascertained not only from the EHR records but also from records from the chronic care research program. The clinic’s EHR records should reveal referral to the research program and the research program’s records will reveal receipt of clinic referral to it, and also referral from the research program to the WTQL. The latter will occur because the research program will refer the patient to the WTQL if the patient is not interested in the research program, is screened out from that program, or decides that s/he prefers WTQL referral. The EHR records will be cross checked with both the research program records of referral and with WTQL records to examine agreement. **Treatment engagement** for the experimental clinics will be derived from the research program records and from WTQL records. Treatment engagement will be defined as receipt of any clinical contact with either the WTQL or the chronic care research program: e.g., a counseling phone call, medication receipt, use of the WTQL website or text messaging service (if available on a cost-effective basis). Further, for both control and experimental clinics there will be an attempt to gather data on clinician billing for smoking cessation counseling, and prescription issuance for a smoking cessation medication (with a special focus on varenicline and nicotine replacement therapy, given that bupropion is also used in treating depression). These latter two measures will not be included in the primary

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treatment engagement dependent variable because of their expected low rate of occurrence and because the EHR changes do not target these outcomes. They will be used merely to ascertain whether the experimental and control conditions differ in rates of referral to auxiliary treatment resources. In this way the design can reflect increases in the three identified dependent variables due to the EHR enhancements and chronic care treatment availability. In addition, the WTQL, e-prescriptions for smoking medications, and clinician counseling are the only documentable smoking treatment options currently available in both healthcare systems (e.g., there are no in-house or other cessation programs). Therefore, the list of measures for smoking treatment referral and engagement are exhaustive; they should capture all clinic-based smoking-related intervention during the baseline period.

It is important to note that other outcome measures will be collected during the post-intervention period. For example, we will also track: the rate at which patients referred to chronic care treatment complete treatment and quit smoking successfully. These are not dependent variables, however, since data on these outcome classes will not be available from control clinics. In addition, we will determine the number of calls to the dedicated smoking treatment information call-line that follow Smoker Registry communications to seek smoking treatment information. (Note: Within Epic, the Registry function allows patients with similar diagnosis or other characteristics to be readily identified. Typically, the function is used for health maintenance or health promotion. Smoker Registry in this document refers to the use of that functionality to allow Dean Clinic staff to identify adult smokers connected with a particular clinic to perform these recruitment functions.) Finally, quality assurance methods will be used to examine the consistency of EHR functions: e.g., 1) the percentage of patients referred to treatment for whom closed loop feedback is entered into their EHR's (based on WTQL or research treatment referral or the healthcare pharmacy database); and 2) the proportion of smokers in the Smoker Registry who are identified as smokers or recent quitters on an index clinic visit.

### **Promoting Continued Experimental Participation**

We will utilize participant retention strategies that were effective in our prior research, including strategies such as scheduling flexibility, calling participants' cell phones if they request that, continued interaction with the same health counselor, and providing medication contingent upon visit attendance/call completion. If participants appear to have dropped out of the study (they miss appointments and do not reschedule, or they do not answer our phone calls, but they have not formally withdrawn from the study), we may write them (via standard mail or email) to encourage their renewed participation.

### ***Motivation Study***

For the Motivation Study, participants will be reimbursed \$25 each for completing Visit 1. They will receive \$10 for completing each of the assessment calls at Weeks 12, 26, 39, and 52. Participants will also be reimbursed \$25 for completing at least 75% of their IVR calls. Thus, participants will be compensated up to \$90 for assessments but not for therapy participation.

### ***Cessation Study***

For the Cessation Study, participants will be reimbursed \$20 for completing Visit1, \$20 for completing at least 75% of their IVR calls, and \$10 for completing each of the assessment calls at Weeks 4, 8, 16, 26, 39, and 52. Participants who report 7-day point-prevalence abstinence at 26 weeks and attend a visit to provide CO-confirmation of abstinence will be

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reimbursed \$25. Participants will not be compensated for participating in treatment visits. The maximum compensation would be \$125. Participants will be paid after the Week 4 call, after the Week 16 call, and then after the 26, 39 and 52 week calls.

**Long-term Quitting Study**

For the Long-term Quitting Study, participants will be reimbursed \$10 for completing the Initial Cessation Phase Visit 1 assessments plus \$5/call for the 6 Initial Cessation Follow-up assessment calls that do not include phone counseling (\$30) plus \$5 if they complete the 3 scheduled IVR calls for a maximum of \$45 for the Initial Cessation Phase.

If participants relapse and are randomized to one of the active RR Preparation conditions, they will be paid \$25 for attending the initial RR Preparation visit at Day 0, \$5/call for the 5 Standard RR Assessment Staff Calls (\$25), \$10 for completing the Month 14 Follow-up Call, and \$40 for attending the Month 14 Visit if they claim abstinence for a maximum of \$100. Participants randomized to the RR Preparation Control condition will receive \$25 for the first Standard Assessment Staff Call and \$5/call for the next four (\$20), \$10 for the Month 14 Follow-up Call and \$40 for attending the Month 14 Follow-up Visit if needed for a total potential compensation of \$95.

Participants who choose to make a new quit attempt and are randomized to the RR Cessation conditions will be paid \$10 for completing the New Quit Phase baseline assessment, and \$5/call for the 5 RR Cessation assessment calls (\$25) plus \$10 for completing the Month 6 Follow-up Call and \$5 for completing at least 3 of the 4 IVR scheduled calls for a maximum compensation of \$50.

In sum, participants who complete all assigned study activities could be reimbursed \$45 if they never move beyond the Initial Cessation Phase. Those who relapse could receive \$140 if they relapse and are randomized to the RR Preparation Control group or \$145 if they are randomized to an active RR Preparation condition. Then for those who go on to the New Quit Phase, they could earn \$195.

**Analytic Plans**

Each study has a distinct analytic plan to address the unique specific aims of that study.

**Motivation Study**

*Primary Aim 1: Determining the main and interactive effects of the intervention components on primary outcomes.* Our primary outcomes, assessed at both 6 months (end of treatment) and 12 months, are: 1) making a serious quit attempt (defined as  $\geq 48$  hours of nonsmoking as part of an intentional effort to quit); and 2) cessation success (defined as 7-day point-prevalence abstinence (PPA)—self-reported abstinence from smoking, even a single puff). With each of the components, we hypothesize that the “on” condition will produce higher quit attempts and cessation success than the “off” condition. Data for these aims come from phone assessments over the 12 months. We will model abstinence longitudinally via a mixed-effects logistic regression model including the main effects of treatment<sup>106</sup>. Longitudinal models will include the effects of time, condition, and a random subject effect to account for the correlation of repeated assessments within subjects. We will also identify any interaction effects that emerge from the combinations of intervention components. For example, we will examine whether the combination of the BR and 5Rs has a larger or smaller effect than their additive

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effects would predict. Although we will examine all possible interactions of the intervention components, we do not anticipate significant effects beyond 2-way interactions. *In sum, the proposed analyses will determine whether the tested intervention components, either via main or interaction effects, increase meaningful quit attempts and long-term abstinence rates.* In addition, we will use logistic regression analyses with effects-coding to examine the effect of each intervention component on the occurrence of the binary outcomes of quit attempt occurrence and PPA at different follow-up points. Models will include only main effects and two-way interactions; no higher-order interactions are expected. Following the intent-to-treat principle, all 512 participants randomized to treatment will be included; missingness will be investigated in other analysis

*Secondary Aim 1: Determining the main and interactive effects on secondary outcomes.* We will use generalized linear mixed models to test main and interactive effects of components on smoking reduction. Entry into Cost-Optimized cessation treatment will be analyzed via logistic regression models that include main effects and two-way interactions. Cost for each treatment component will be tracked and used to identify optimal intervention components for further study and to aid decision making.

*Secondary Aim 2: Mediation analyses.* We will use a Bayesian multi-mediator approach, with the longitudinal data collected during the automated phone assessments to examine whether quit attempts and cessation success are predicted by treatment effects on key putative mediators: craving, self-efficacy, number of cigarettes smoked per day, tobacco dependence, intrinsic motivation, anhedonia, medication use, and contextual restrictions of smoking. Multi-mediator models will comprise mediators that are significant in univariate mediation analyses and allow us to address questions such as whether BR Counseling, relative to no BR, increases strength of participants’ self-efficacy, their use of reduction skills, or their magnitude of smoking reduction, and whether these increases result in increased quit attempts, and/or cessation rates. Or, does assignment to the Nicotine Mini-Lozenge condition, relative to assignment to No Nicotine Mini-Lozenge, increase participants’ self-efficacy, or decrease their craving, or amount of smoking reduction, and do these changes result in increased quit attempts, and/or cessation rates?

*Secondary Aim 3: Moderation analyses.* Potential moderators (e.g., age, gender, dependence) will be tested in moderated logistic regression models. These models will include main effects for all treatments and the moderator (e.g., gender) as well as two-way interactions of each treatment effect and the moderator.

### **Cessation Study**

*Primary Aim 1:* A primary aim of Project 3 is to compare Abstinence-Optimized Cessation Treatment (AOCT) with Modern Usual Care (M-UC) on 7-day point-prevalence abstinence evaluated at 8, 16, 26, 39 and 52 weeks postquit. We will use GLMM implemented via SAS PROC GLIMMIX (SAS Institute Inc., Cary, North Carolina) to test the group effects in longitudinal models. Specifically, we hypothesize that participants receiving AOCT will have higher cessation rates at each timepoint than those receiving M-UC. We will also analyze other clinical outcomes because they provide complementary information about outcome (e.g., initial cessation, 6- and 12- month point-prevalence abstinence, latency to lapse and relapse, and treatment engagement and adherence) as recommended by SRNT Workgroup and others. We will evaluate initial cessation (did or did not establish 24 hours of abstinence in the first 2 weeks

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following the quit day) and 6- and 12-month abstinence rates using logistic regression and latency to lapse and relapse using Cox proportional-hazards regression. We will also examine cessation outcomes controlling for treatment adherence in secondary analyses. The distributions of the adherence data (percentage of days using nicotine replacement; number of mini-lozenges used per day; percentage of counseling sessions completed) will be examined to inform decisions about transformation and analysis options.

*Primary Aim 2:* Another primary aim is to compare AOCT and M-UC on outcomes important to healthcare systems: net monetary benefit (NMB), incremental cost-effectiveness ratio (ICER), cost per long-term quit, and patient ratings of treatment and healthcare system quality. All of these will inform decision-making with regard to the efficient allocation of healthcare resources. Specifically, we hypothesize that, relative to M-UC, AOCT will produce an NMB higher than zero. Net monetary benefit analyses will convert the long-term relapse rates to Quality-Adjusted Life Years added (QALYs) and then monetize the QALYs added using a range of willingness to pay values. NMB analyses will allow us to compute confidence intervals and report whether these confidence intervals overlap for the AOCT relative to M-UC. For the ICER analyses, we will compare the additional cost of the AOCT to M-UC costs. Participants' quality ratings will be analyzed using ANOVAs. We will examine the role of cessation success in satisfaction ratings and control for cessation success as needed.

*Secondary Aim:* The secondary aim is to understand better the underlying treatment mechanisms of the Abstinence-Optimized Cessation and Modern Usual Care treatments and to determine which effects mediate cessation success. We will use mediational models similar to those used in our previous research to estimate the extent to which treatment-related change in the mediator (e.g., change in self-efficacy, craving, negative affect, or perceived support) leads to improved outcomes (initial cessation, latency to relapse). The EMA data on daily urges, smoking, treatment-related support, withdrawal, cue exposure, coping, etc. will be combined with the other phone assessments and studied using latent growth curve models. For example, we will examine whether AOCT's use of a Combination NRT component results in greater withdrawal suppression and thereby reduced likelihood of relapse, relative to the M-UC treatment and whether the counseling in the optimized treatment produces greater intratreatment social support and coping skills and thereby reduces the likelihood of relapse relative to M-UC treatment. We will use procedures from our prior work to reduce error and ensure temporal ordering of causal modeling. Parameters of the growth models (e.g., intercept and trajectory parameters) will be studied as mediators of short-term outcomes such as initial cessation and lapse or relapse. We will also examine orthogonal mediation paths via multiple mediator analyses. Mediational analyses will be conducted using Mplus, which offers flexibility in the handling of outcome variables (e.g., continuous, categorical counts, censoring).

We will also conduct exploratory analyses to determine whether individual difference variables such as gender, race, educational attainment, and baseline nicotine dependence moderate treatment effects using chi-square analyses and by modeling interaction effects in Cox Regression. We will also examine moderated mediation to determine whether any of these individual difference variables moderate specific treatment effects.

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***Long-term Quitting Study***

The analytic plan reflects that the treatments will be delivered in sequence (i.e., analyses will accommodate the transition of participants across the RR Preparation and RR Cessation treatments) as is recommended for SMART designs.

*Primary Aim.* To determine the effects of the RR Preparation treatment on abstinence at the Month 14 Preparation assessment time point amongst participants randomized to RR Preparation treatment (“active” and “control”). This analysis will be conducted using generalized linear models (GLM) with point-prevalence abstinence data as the outcome variable. Potential covariates will include: race, gender, tobacco dependence (e.g., before initial cessation treatment) and duration of abstinence in the initial cessation attempt. The main model will not control for RR Cessation factors; rather it will focus on the question of whether long-term differences in abstinence rates emerge from the RR Preparation treatment. These analyses will be done in several ways: 1) by comparing each active RR Preparation component with the Preparation Control condition, and 2) by conducting a GLM analysis comprising only the RR Reduction vs. Recycling Preparation participants. The former will address the issue of whether the active Preparation components, and any consequential access to RR Cessation treatment, affects the long-term smoking outcomes of participants. Results will be examined to determine the extent to which differences are related to the use of RR Cessation treatments. The second type of analysis will focus on the active RR Preparation components, when participants in each component have an equal chance of being assigned to any of the RR Cessation intervention components. RR Cessation factors will be used as covariates in supplementary analyses of the active components and the interactions of these factors with Preparation treatment condition will be examined. Marginal frequencies will be examined to determine the rate at which participants elect to be randomized to RR Cessation treatment.

*Secondary Aim 1.* We hypothesize that RR Reduction Counseling will lead to a greater likelihood of *meaningful* quit attempts and that these will occur at shorter latencies than RR Recycling Counseling. Even though Reduction participants will be encouraged to delay their quit attempts for 1 month of treatment, we predict they will be more successful than Recycling participants in sustaining early abstinence. All participants randomized to the non-control, active RR Preparation factors will be included in the following two analyses. First, we will use logistic regression to test for differences, due to Preparation factor, in the probability of a meaningful quit attempt during the 12 months after they enter RR Preparation treatment. Second, to examine latency to a new meaningful quit attempt, Cox Proportional Hazard models will be used to determine the hazard rate, with those not making a meaningful quit attempt treated as censored observations. Potential covariates will include: race, gender, tobacco dependence (e.g., before initial cessation treatment) and duration of abstinence in the initial cessation attempt (in subsequent analyses the type of RR Cessation treatment used will also be modeled as a covariate). These analyses will reflect Preparation effects comprehensively because they will reflect meaningful quit attempts that occur both with and without use of RR Cessation treatments. Then, only Preparation participants using RR Cessation interventions will be included in analyses of relations between RR Preparation and RR Cessation components as they influence meaningful quit attempts. This analysis will focus on whether type of RR Preparation treatment affects initial success (more than 1 day of abstinence at the start of the quit attempt) in an aided quit attempt, and whether this effect depends on type of RR Cessation treatment. We hypothesize that RR Reduction Counseling will produce stronger effects than

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RR Recycling Counseling with regard to both the probability and latency of meaningful quit attempts, and we hypothesize that these effects will not interact with the RR Cessation factors.

*Secondary Aim 2.* To determine the main and interactive effects of the 2 RR Cessation factors on smoking abstinence following a quit attempt, and to determine whether these effects differ as a function of the RR Preparation factor. One analytic strategy will involve a 2x2 factorial analysis via a longitudinal generalized linear mixed-effects model (GLMM) with the 2 RR Cessation factors as independent variables, and RR Preparation factor as a covariate. Several outcomes will be analyzed. One outcome will be longitudinal abstinence across the 4 RR Cessation Follow-up time points ( Weeks 4, 10, 16, 26). A second will focus on survival analyses after the start of the participants’ course of RR Cessation treatment. Finally, a logistic regression analysis will be used to analyze abstinence reports at 26 Weeks post-RR Cessation treatment initiation. Only those who choose to make an aided quit attempt and are randomized to the RR Cessation factors will be included in these analyses, and all tests will be two-sided with  $p=.05$ . Additional potential covariates in the longitudinal models will include race, gender, and time since the initiation of the RR Preparation treatment (for the analysis examining long-term effects of RR Cessation treatment). We predict significant main effects for the enhanced level of each RR Cessation factor, but we predict no significant interaction effects between RR Preparation and RR Cessation factors; that is, we predict the RR Cessation factors will exert similar effects across the Preparation factor but we will test these relations. Because some participants randomized to Preparation treatment will not be included in this analysis (since they will not make aided quit attempts), this analysis will not capture the comprehensive effects of the Preparation factor. We are aware that the Preparation factor may cause different numbers or types of smokers to make aided quit attempts with the RR Cessation treatments. Such effects *might* moderate effects of the Preparation factor on the RR Cessation factors. However, this is not a limitation because this would be present in the real-world clinical effects of a Preparation treatment; e.g., such treatments could influence outcomes by better preparing smokers for cessation or by sending different types of smokers to an RR Cessation treatment.

Supplemental analyses will examine correspondence between CO levels at the 6 and 14 Month Preparation Phase follow-up and abstinence self-report at those and other time points (e.g., 10 months into the Preparation Phase). Adherence analyses will use Preparation Phase data and RR Cessation treatment contact data to analyze both patch and mini-lozenge use. Adherence will be evaluated with regards to both the RR Preparation phase (amongst Reduction participants) and in the RR Cessation Phase.

*Secondary Aim 3.* We will also examine “transition rates” across the phases of treatment: 1) To what extent do participants who relapse in response to Initial Cessation treatment, enter the RR Preparation treatment? 2) To what extent do participants who enter RR Preparation treatment remain in that treatment for 11 months? and 3) To what extent do participants who enter RR Preparation treatment decide to enter RR Cessation treatment? In other words, we will examine the extent that “chronic care” treatment “works” amongst relapsers, and the extent that this is related to type of “chronic care” provided. Do relapsers transition into chronic care and use its various resources? Such pragmatic analyses will be complemented by cost analyses regarding the various treatments analyzed.

*Secondary Aim 4.* We will also identify moderators and mediators of the effects of the RR Preparation and RR Cessation treatment factors. In keeping with the secondary aims of a

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SMART trial, these moderator and mediator analyses will be useful for identifying candidate tailoring variables. For instance, a key mediator of RR Preparation Reduction treatment might be amount and persistence of smoking reduction. We will examine the relation between such reduction and success in RR Cessation treatment and also success as measured by outcome at the 7-, 10-, and 14-month Preparation phase assessment time points. Of course, smoking reduction will be analyzed as an outcome in its own right. All those assigned to RR Preparation conditions, including Control participants, can be included in such analyses, with outcomes assessed across the RR Preparation phase and at Month 14 follow-up.

For RR Cessation treatment moderation and mediation models, the outcome will be abstinence at 6 months after the RR Cessation target quit day. Mediation models (including multiple mediators) will use methods developed for use with dynamic mediator assessments (maximum likelihood estimation using hierarchical linear modeling: HLM 5.04, using RR Cessation treatment assessments and possibly data derived from Standard Assessment Staff calls) with binary outcomes (via a weighted least squares model in Mplus). Candidate mediators will include: demoralization, medication use, coping, smoking cue/trigger density, self-efficacy, craving, and smoking heaviness. Mediation effects will be tested using statistically powerful approaches (e.g., the joint significance test). Care will be taken to preserve mediator/outcome temporal priority, and the occurrence of smoking during the quit attempt will be statistically controlled when appropriate. Analysis of moderators will use both logistic regression (with model fitting techniques) and regression tree analyses to identify predictors of differential response to the RR Cessation components. Candidate moderators will include factors such as tobacco dependence and gender, and contextual factors such as household smoking.

Finally, while not a formal aim, we will also compare all possible types of “embedded adaptive treatments” on abstinence rates at the 7, 10, and 14 Month outcome time points. That is, we will compare the abstinence outcomes of groups of participants receiving the different unique combinations of RR intervention components. Logistic regression will be modified to weight for the fact that data for each participant are consistent with more than one adaptive intervention (an individual will receive multiple intervention components) and to accommodate the over/under-representation of outcomes based on the sequential randomization scheme. Embedded comparisons are typically underpowered in SMART designs but can be highly informative (viz. to check consistency with the factorial analyses).

**Clinic Randomized Control Trial**

**Primary Aim:** Using a multiple baseline design, determine the effects of a healthcare intervention package comprising a comprehensive set of EHR-based enhancements and a chronic care treatment for smoking, on rates of documentation of smoking status, referral to smoking treatment, and engagement in smoking treatment as compared to a usual care fax-to-quit referral to the Wisconsin Tobacco Quit Line.

**Power for Primary Outcomes in the three clinical studies and the clinic randomized control trial**

Power for each of the three studies was calculated based on the sample size and hypothesized effect sizes for each of the individual studies.

**Motivation Study**



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We will enroll 512 participants. We will use an intent-to-treat principle for the primary abstinence analyses. Our factorial design takes advantage of all cells and participants, allowing us to analyze the entire sample for main effects. With two levels of each factor (e.g., BR Counseling or no BR), we will have 256 participants per group for analyses. We have based our power estimates on effect sizes found in our prior studies.

For cessation success, we conducted longitudinal power analyses. We computed power for the mixed effects longitudinal analysis using a SAS macro<sup>111</sup> with the following parameters:  $N=256$  per group; smoking status assessed at 6 points (months 1, 2, 3, 4, 6, and 12); a drop-out rate of 10% at each successive time-point (higher than in Preliminary Study 1); a 10% versus 18% abstinence treatment effect modeled as a consistent effect over time; random effects variance=1; and within-subject correlation=0.6. We consider the targeted treatment effect (i.e., 8 percentage point difference: 10% vs. 18% among participants receiving an “on” intervention component) to constitute a clinically meaningful effect. Power for this scenario is 0.94 with a compound symmetry (CS) within-subject covariance structure; power is 0.99 with a first-order autocorrelation (AR(1)) within-subject covariance structure and correlation. Thus, the study is powered adequately to yield statistically significant treatment effects in the mixed effects analyses.

For quit attempts, we conducted single endpoint power analyses. We expect approximately 60% of participants to make a quit attempt on minimal treatment, as suggested by our Preliminary Study data. With a total  $N=512$ , there is adequate power (.81) to detect at least a 12 percentage point increase, a clinically meaningful increase, in quit attempts in the “on” treatment condition (72%) relative to the “off” condition (60%).

For smoking reduction, we conducted longitudinal power analyses. We calculated statistical power for a longitudinal mixed effects regression model for the smoking reduction outcome with two groups using the RMASS2 sample size program<sup>112,113</sup>. We specified the following parameters for the program:  $\alpha=.05$ , two-tailed test, 6 time-points (months 1, 2, 3, 4, 6, and 12), attrition of 10% at each successive time-point (a high rate), within-subject correlation=0.6, a mean difference of 1.5 cigarettes (consistent across time), and a standard deviation of 7 (consistent across time). With attrition of 10% at each successive time-point, the retention rate decreased to 59% by the 12 month follow-up. These specifications yielded a composite effect size of .27 adjusted for attrition. With a sample size of 256 per group and adjustment for attrition, we have power of at least .85 to detect this effect size with AR(1) within-subject covariance structure and correlation.

### **Cessation Study**

This study will enroll at least 600 participants to address the primary aims.

*Primary Aim 1:* We computed power for the GLMM longitudinal analysis of abstinence outcomes using a SAS macro developed by Dang and colleagues with the following parameters:  $N=300$  per group; 3 time-points; drop-out rate of 20%; treatment marginal rates (over time) of 30% vs 40%; random effects variance=1; and within-subject correlation=0.6. Power for this scenario is 0.91. Thus, the proposed study appears to be powered adequately to yield a statistically significant group difference in point-prevalence abstinence in the longitudinal GLMM analyses.

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Power analyses were also computed for 6-month point-prevalence abstinence using nQuery Version 7.0 (Statistical Solutions, Cork, Ireland). With sample sizes of Abstinence-Optimized Cessation Treatment=300, and Modern Usual Care=300 we examined the power to detect the primary outcome—biochemically confirmed 7-day point-prevalence abstinence at 6 months post-target quit day. A previous meta-analysis found that abstinence rates at 6 months post-quit were 23.4% of participants receiving 8 weeks of nicotine patch and 28.1% for those receiving quitline counseling and medication, as will occur in the M-UC treatment. Given that this will be an effectiveness trial with only 1 quitline call, we expect that M-UC will likely produce a lower 6-month abstinence rate of approximately 20%. With  $\alpha=.05$ , and  $n=300$  for M-UC and  $n=300$  for the AOCT, we are powered at .80 to detect a 10% difference in relapse rates of the AOCT vs. M-UC. Therefore, we are powered to detect approximately a 10% treatment effect, which we consider to be clinically meaningful.

*Primary Aim 2:* Power analyses for the main systems outcome were computed based on the approach described by Glick and implemented in STATA Version 12.1 (StataCorp, College Station, TX) programs developed by Glick (<http://www.uphs.upenn.edu/dgimhsr/stat-samps.htm>). For purposes of powering cost-effectiveness comparisons, we utilized net monetary benefit (NMB) which has benefits over the incremental cost-effectiveness ratio (ICER). In contrast to a ratio measure such as the ICER, NMB is a continuous measure with a relatively normal distribution; in addition, the variance for NMB is well-defined which permits good estimation of confidence intervals, sample size, and power. NMB is computed as the difference in effectiveness ( $\Delta Q$ ) minus the difference in costs divided by willingness to pay ( $\Delta C/W$ ). Willingness to pay ( $W$ ) is conceptualized here as the amount society would be willing to pay for a health benefit; for our purposes,  $W$  is the amount that would result in an additional quality-adjusted life year (QALY). Power was computed for two key comparisons: (1) cost-effectiveness of COT relative to UC, and (2) cost-effectiveness of AOT relative to UC. We made the following assumptions for each of these comparisons: sample size of  $n=300$  for the Abstinence-Optimized Cessation Treatment and  $n=300$  for the Modern Usual Care treatment; two-tailed test;  $\alpha=.05$ ; standard deviation (SD) for costs=250; SD for effects (i.e., abstinence rates)=.42; correlation for the difference in costs and effects=.1; and maximum willingness to pay=\$50,000. For the AOCT vs. M-UC comparison, we set the difference in abstinence effects at .1 (i.e., a 10 percentage point difference; 20% vs. 30%) and a cost difference at \$1222 reflecting a UC cost of \$128 and AOCT cost of \$1350. Power for this comparison is .60. However, we do have sufficient power (.80) to determine cost-effectiveness if there is a 12 percentage point difference in abstinence rates. This analysis requires a larger abstinence difference to establish that it is cost-effective, as well as clinically effective, because of the large cost differential.

*Secondary Aim:* Published estimates of sample sizes for mediational analyses, for various types of tests (e.g., the joint significance test and the Sobel test), provide the minimum sample size needed for detecting a mediated effect when the size of the effect of an independent variable ( $X$ ; e.g., medication effect) and the size of the mediator effect ( $M$ ; e.g., coping) are jointly considered. Based upon these values, if both the  $X$  effect and  $M$  effect are small/medium, a sample size of 196 would be needed to detect the mediated effect. Thus, we feel confident that our sample sizes of 270 per group ( $n$ 's=300 with 10% attrition) are sufficiently large to detect at least small/medium-sized (7.5% of variance) effects even in the presence of measurement error.

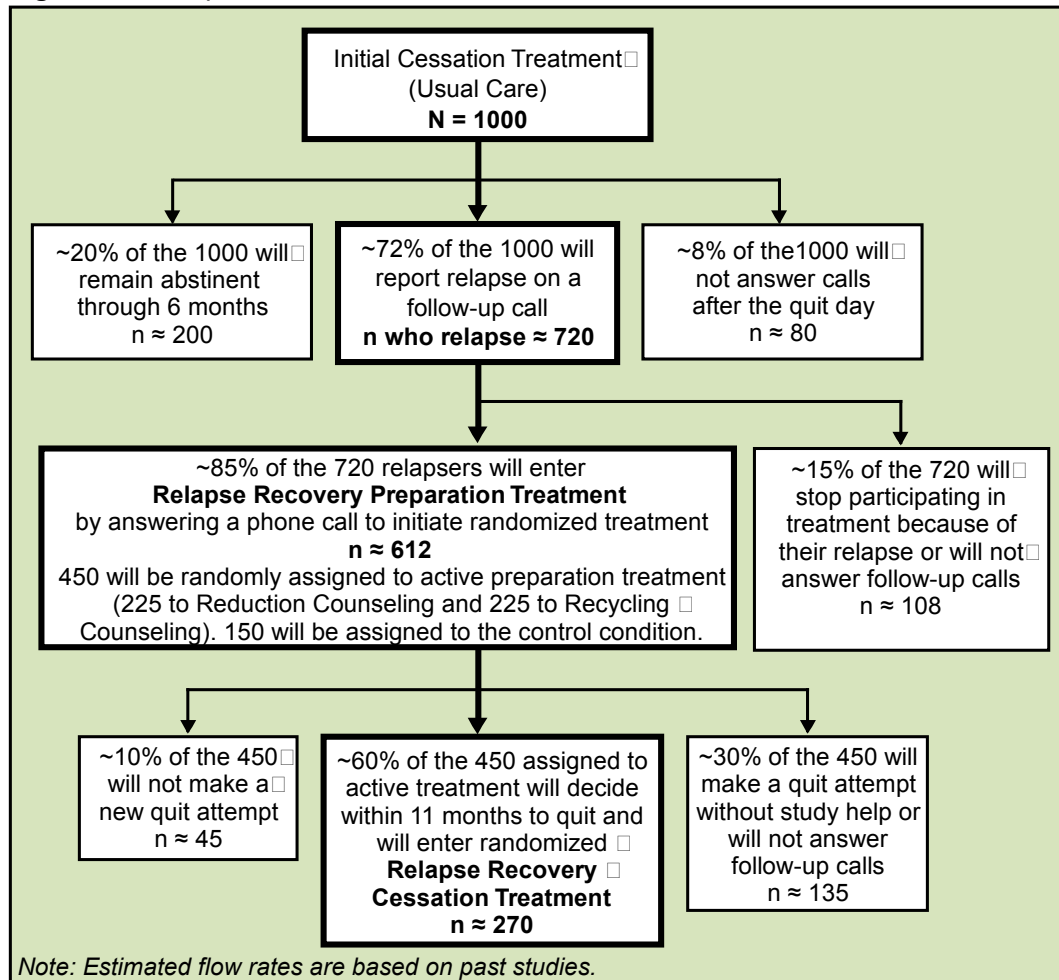
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**Long-term Quitting Study**

We have engineered a recruitment strategy that models attrition and subject loss, resulting in good power under conservative assumptions. In this project, ~1000 smokers will receive a Usual Care cessation treatment. Based on other trials, we anticipate that 72% of the  $N \approx 1000$  smokers will relapse in the first 6 months (i.e.,  $n \approx 720$ ; see Figure 3); we believe that 20% will remain abstinent and 8% will attrit. Of the 720 relapsers, we predict that 85% will enter RR Preparation treatment ( $n = 612$ ) at some point in the 6 months after their quit day, while 15% ( $n = 108$ ) will stop participating. The 612 participants who continue in treatment will be randomized to the 3 RR Preparation intervention conditions: the Low-Contact control condition ( $n \approx 150$ ), the Recycling condition ( $n \approx 225$ ) and the Reduction condition ( $n \approx 225$ ). Of 450 assigned to the Recycling and Reduction conditions, we believe that 10% ( $n \approx 45$ ) will never make a new quit attempt, another 30% ( $n \approx 135$ ) will quit on their own or attrit without entering RR Cessation treatment, leaving 60% ( $n \approx 270$ ) who will enter RR Cessation treatment, and be randomized to the 2 RR Cessation intervention factors ( $n \approx 135$ /each level of each factor).

**Figure 3.** Participant Flow with Estimated Ns



We have computed power for Primary Aim 1: to determine the effect of the RR Preparation factors on abstinence assessed at 14 months after randomization to RR

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Preparation treatment. We computed power for the GLMM longitudinal analysis using the SAS macro developed by Dang and colleagues. We used the following parameters: N=600 in the intent-to-treat comparisons involving all 3 RR Preparation conditions (Control n = 150, and n's = 225 for each active condition), and N = 450 for comparisons of the two active Preparatory conditions. Smoking status will be analyzed at 1 time point (Month 14 after randomization to RR Preparation treatment); a 10% attrition rate across follow-up; with the treatment effect modeled as consistent over time; random effects variance=1; and within-subject correlation=0.6. We hypothesize average abstinence rates to be 15% for the Control condition, 25% for the Recycling condition, and 35% for the Reduction condition. We propose that any increase in abstinence of 15% or higher would be clinically significant. For the purpose of the power analysis we will assume a 15% abstinence rate for the Control condition. Under this scenario, there would be insufficient power to detect an effect for the Recycling condition versus the Control condition (i.e., 15% vs. 25%), but power would exceed .80 if the Reduction treatment produced an abstinence rate of .28 or higher. If we assume a 10% abstinence rate for the Control condition, power would exceed .80 if either the Recycling condition or the Reduction condition produced an abstinence rate of .21 or higher. We did not power the study to demonstrate a significant difference between the two active conditions. Therefore, we anticipate that only the RR Reduction treatment will significantly increase long-term abstinence rates over those produced by the Usual Care control condition.

We also computed power for the Secondary Aim of determining the effect of the RR Preparation factor on the likelihood of a meaningful quit attempt characterized by more than one day of abstinence (that occurs at some point in the 12 months following entry into RR Preparation treatment). For power analyses we will restrict this comparison to the two active RR Preparation treatments since they yield the more conservative test. We predict that 60% of the 225 participants receiving Recycling Counseling will make a meaningful quit attempt, while 80% of the 225 participants receiving Reduction Counseling will make a meaningful quit attempt over the 12 months following entry into the RR Preparation treatment. Thus we predict a 20 percentage point difference (with 60% vs. 80% of participants making a meaningful quit attempt); we have power of > .85 to detect this effect. With a 15 percentage point difference (e.g., 60% vs. 75% or 65% vs. 80%) power remains > .80. The estimate of a 60-65% base rate of meaningful quit attempts is taken from the rate of quit attempts among smokers in general: i.e., with no preparation treatment ~40-45% of smokers a year make a quit attempt. We believe that Recycling Counseling will increase this figure by about 40-50% based upon the impact of Recycling Counseling on acceptance of pharmacotherapy when it is offered. Therefore, we assume that 60% of the Recycling participants will make a meaningful quit attempt, and we further propose that a 15-20 percentage point increase in meaningful quit attempts is a clinically worthwhile effect, given the strong relation between early quitting success and later abstinence.

We have not powered this study to detect significant effects for the other data comparisons offered as Secondary Aims (e.g., transitions across phases of chronic care treatment, the effects of RR Cessation treatments). Rather, those Aims are included in this research so that we can gather additional evidence related to the feasibility of a chronic care approach to smoking and so that we can gather additional preliminary data to guide our future research and treatment development.

**Clinic Randomized Control Trial**

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The primary outcome will be treatment engagement and we will analyze this with repeated measures analysis of variance (ANOVA) and analysis of covariance (ANCOVA). In these analyses we will contrast the experimental and control (F2Q) clinics on the basis of treatment engagement means averaged over the periods of clinic participation (which may differ somewhat across clinics) pre and post implementation. Since data on the dependent variables will be routinely collected pre-implementation, we have opportunity to determine the length of the baseline period: we will average data over 6 months to establish a baseline. The analyses will, conservatively, use the clinic as the unit of analysis. ANCOVA will use clinic location (rural vs. urban), size, SES, and baseline rates of smoker documentation and referral as covariates. We will conservatively use ANOVA to estimate power, in part, because it is unclear how much this set of covariates will affect error within the ANCOVA. Based on earlier data, we anticipate treatment engagement will be 1% for both groups at baseline (for the 6 months pre-implementation) and 10 and 2% post-implementation for experimental and control clinics, respectively. Previous research also suggests that both groups will have the same standard deviation (SD = 4). Assuming an SD = 4, and a mean difference of 8 at post-implementation (2% vs 10%), power to detect a group by time interaction  $> .998$  with  $\alpha = .05$  and  $N = 28$  (18 experimental and 10 control clinics). If we are able to recruit adequately with only 10 experimental clinics (with  $N = 20$ , comprising 10 experimental and 10 control clinics), the smallest  $N$  that we can envision, then power = .887 with a smaller prognosticated post-implementation group difference (8 vs. 2%). Thus, power appears ample for conservative tests of our primary outcome. We will use other analytic strategies to analyze these data (e.g., General Estimating Equations) that model patients as the units of analysis, with patients being nested within clinics. Only aggregated (non-identifiable) data will be used for these analyses. Such approaches should have greater power than the approach described above, which we present for purposes of clarity and simplicity. In addition, in secondary analyses we will compare subcategories of treatment engagement rates: e.g., comparing WTQL engagement rates in the control clinics with engagement rates for *cessation* treatment in the experimental clinics (i.e., removing chronic care engagement data for smokers who wanted to reduce their smoking). We will also examine treatment completion rates and 6-month abstinence rates, especially for those referred to the chronic care treatment, to determine the “yield” of treatment referral. Such data would also allow us to compute cost-effectiveness and cost-benefit analyses.

The analytic approach that we have described above will also be used for the other major outcomes (i.e., smoker documentation and treatment referral). There is adequate power for both of these outcomes.

## **Protection of Human Subjects**

### **Risks to the Subjects**

#### *Human Subjects Involvement and Characteristics.*

This protocol addresses 3 clinical research studies and a clinic-level study comparing system enhancements coming from modifications of the EHR to usual care Fax to Quit referral of smokers. The clinic level study has not human subjects. The 3 clinical research studies involve human subjects and that involvement is described below. For the clinic level study, necessary data for the intervention clinics will be obtained from the subjects in the clinical research as well as from the sample representativeness data described in Appendix 1 below. The additional data on non-study participants at the intervention clinics available through these aggregate sample representativeness data files will not include any identifiable private

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information and these individuals are they not considered human subjects. All data from the control clinics (aggregate information on clinic visits and smoker rates obtained from the health systems and summary numeric data on the number of referrals received and served reported by the Wisconsin Tobacco Quitline for all fax referral sites) will be aggregate data with no identifiable private information. The patients participating in smoking cessation treatment as a result of their fax to quit/standard of care referral from the control clinics are therefore not considered human subjects and are not discussed further in this section of the protocol. In summary, the remainder of this human subjects section focuses on the human subjects who will participate in the clinical interventions as a result of referral from an active clinic assigned to the EHR intervention condition within the clinic randomized control trial, since these are the only human subjects involved in this set of studies.

Specific eligibility requirements for all 3 clinical studies within the intervention clinics are: 1) 18 years of age or older; 2) report smoking at least 5 cigarettes per day for the previous 6 months; 4) able to read and write English; 5) have reliable phone access and agree to respond to Interactive Voice Response (IVR) phone prompts 8) free of medical contraindications to NRT; and 9), if participant is a woman of childbearing potential, using an approved method of birth control during treatment. Participants who are eliminated due to screening failure, or elect not to participate in this research medication program, will be given a list of alternative smoking cessation programs, including an opportunity to receive usual care from the clinic and a referral to the Wisconsin Tobacco Quit Line (1-877-270-STOP). For the Motivation Study, participants also have to be not currently attempting to quit smoking or intending to quit smoking (defined as no plans to quit in the next month); and planning to remain in the intervention catchment area for at least 12 months. For the Cessation Study, participants also have to be motivated to quit smoking and planning to remain in the intervention catchment area for at least 12 months. For the Long-term Quitting Study, participants also have to be motivated to quit smoking and planning to remain in the intervention catchment area for at least 2 years and 2 months.

A minimum of 2112 participants will be recruited to participate in this research: 512 in the Motivation Study, 600 in the Cessation Study and 1000 in the Long-term Quitting Study. However, to get a proper balance of participants across the three studies, we may recruit as many as 2600. No special vulnerable populations will be intentionally recruited (pregnant women will be specifically screened out due to medication safety concerns and no persons under the age of 18 will be allowed to participate because the medications we are using have not been approved by the FDA for individuals less than 18 years old). See the Inclusion/Exclusion section for protocol regarding participants previously eligible who become incarcerated or pregnant.

Eligible participants will be randomized at the point of screen passing the phone screen (stratified by gender). Those who do not enroll will be unrandomized and the treatment condition assigned to them will be reassigned to a new preparticipant.

Medication dosing will be consistent with the 2008 PHS Guideline, other recent clinical practice guidelines, and package inserts (smoke within 30 min of waking = 4-mg mini-lozenge; smoke more than 30 min after waking = 2-mg mini-lozenge; smoke >10 cigs/day = start with 21-mg patch; smoke ≤10 cigs/day = start with 14-mg patch). Starting Spring 2018 we started to screen individuals who would be prescribed mini-lozenges for soy allergens prior to dissemination to prevent allergic reaction AEs - per the ML new package insert. Research

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personnel will recommend dosage/use alterations as per good clinical practice if the participant experiences symptoms of nicotine toxicity or side effects. The health counselor will refer participants to their primary care physician should they require medical consultation. Medication is provided to participants in dosage periods defined within each protocol. It is important to note that study medication use in this research is all in accordance with FDA guidelines, including using NRT for longer than 8 weeks, before quitting, and in combinations (e.g., patch + mini-lozenge). For the Motivation and Long Term Quitting studies, if a medication is discontinued due to one or many NRT symptoms, or the patient had a CVD event in the last 4 weeks, that medication will not be prescribed at a later phase. No further medications will be given to this study participant while in the study.

The research involves collaborating sites at Penn State University and University of Illinois-Chicago. Neither of these sites will collect data. Investigators at these two sites will work with cleaned, limited analytic data sets provided by UW-CTRI through secure web access to the named investigators. The work of both sites will be overseen by their own institutional IRB's. The data sets provided by UW-CTRI will conform to the rules for a limited data set, including dates of service and an identifier that allows for analysis at the individual study participant level. The research also involves collaboration with staff of two health systems (Aurora Health Care and Dean Health). In prior research of similar scope, their involvement has been determined to be not involved in research since their role is limited to providing information about the availability of a study and sending contact information to the study staff, as well as providing other types of aggregate data. No identifiable research data from UW-CTRI are shared with the clinics.

*Sources of Materials.* Data on those expressing interest in the study within their healthcare clinic are gathered by electronic health record (EHR). This statement of interest generates an electronic transmission of the person's contact information (address and phone) to a password-protected email account accessed by specifically named study personnel. The contact information is entered into the study database.

Data collected from participants in this Program Project will primarily be used for research. Data will consist of answers to questionnaires, automated phone assessments, and interviews assessing smoking history, demographics, nicotine dependence, personality, affect, and breath samples to permit determination of carbon monoxide. Carbon monoxide assays reflect smoking status. All data are retained in the study database. The study database access is limited to those staff members and investigators directly involved in the study and under the supervision of the UW IRB.

*Potential Risks.* Risks associated with this research are judged to be minimal. Smoking withdrawal is associated with a number of unpleasant symptoms such as sleep disturbance, hunger, craving, and negative mood. Most smokers have tried to quit in the past and are familiar with these phenomena. Participants will be informed about the likely effects of smoking withdrawal.

With respect to the pharmacotherapies, participants will be made aware of the common side effects before they consent to participate in the study. It should be noted that the nicotine mini-lozenge and patch are available over the counter. The nicotine patch is generally well tolerated, but up to 50% of participants may have a local skin reaction, and rarely, individuals

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may have a more systemic allergic reaction. The most likely side effects associated with the nicotine mini-lozenge are heartburn, nausea, hiccups, and sore throat. Although most smokers have tolerance to nicotine, symptoms of acute nicotine toxicity (nausea and vomiting) are possible. The two other primary FDA approved alternative medication treatments for smoking cessation are bupropion and varenicline. Both have a considerably greater side effect profile than nicotine replacement products and require extensive medical monitoring<sup>7</sup>. Finally, individuals often attempt to stop smoking without the use of medication. As the 2008 PHS Guideline<sup>7</sup> shows, this method is considerably less likely to produce long-term cessation. Those not successful in quitting bear the health risks associated with continued smoking.

Finally, there is a small risk of loss of confidentiality. This could occur through a number of possible avenues, all highly unlikely due to the data security measures in place. UW-CTRI's computer system is linked to the UW network through a firewall, which is managed by the School of Medicine and Public Health network team, via a fiber link which is maintained by the UW Division of Information Technology. No data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. There are rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, which could be taken or lost. In addition, consent forms are obtained in paper copy; these forms contain the participant name and signature. Finally, the University of Wisconsin and the National Cancer Institute may inspect the signed consent forms. Because of this possible need to release information to these parties, we cannot guarantee absolute confidentiality.

Adequacy of Protection Against Risks

*Recruitment and Informed Consent.* To ensure that our findings are maximally relevant to real-world healthcare application, we will screen smokers presenting to 18 primary care clinics (PCCs) in two participating health systems located throughout Southern Wisconsin. Participants will be recruited via two methods. 1) Participants will be recruited by the clinic's roomers (e.g., Medical Assistants) with methods similar to methods used in our prior research. Prompted by the electronic health record (EHR), roomers will screen all patients for smoking status and then will ask all smokers if they are interested in learning about treatments to help them quit now or in the future or reduce their smoking. They will also describe standard of care services their clinic has available. If the patient is interested, a one-click referral will send an EHR-generated Smoker Interest Form, containing patient contact information, to the research office. The roomer will also flag the patient's chart so that the physician will know that the patient's smoking has already been addressed and will not offer a smoking cessation intervention or study participation in the upcoming clinical encounter. 2) In the second recruitment method, smokers at participating clinics will receive direct recruitment information via mailings and EHR-specific messaging as part of the Smoker Registry. The direct recruitment messages will encourage smokers to learn more about the study by either providing their contact information so the study can contact them or by calling the research office directly.

The EHR-generated messages about interested patients or telephone messages left by interested patients will prompt a screening call from our research personnel within 48-72 hours to introduce the study options, assess interest and screen for eligibility. If the person is interested in one of the studies and is eligible, an in-person appointment at their referring clinic with a study staff member is set up. At this visit, the smoker will learn about general requirements for participation (e.g., need for follow-up, participation in assessments) as well as



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risks associated with nicotine toxicity, nicotine withdrawal, and the pharmacotherapies. The health counselor will then provide each study candidate with an IRB-approved informed consent document corresponding with the study which they have chosen. Study candidates will read the informed consent document and be given an opportunity to ask any questions regarding study participation. A research staff member will read the consent form to the study candidate if needed or desired. The consent form will include necessary HIPAA language. Participants will be required to sign the consent form. Case managers will provide participants with a copy of the consent form.

*Protection Against Risk.* Risks related to medications are minimized through close monitoring. The leader for each study (Project Leaders), working in consultation with the Program Project’s physician (Dr. Fiore), will be responsible for routine monitoring of unanticipated health events. This risk protection includes procedures for contacting the emergency physician or psychologist and monitoring of all events through scheduled biweekly meetings with study staff and review of written documentation. Unanticipated health event assessment, recording, reporting and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The Project Leaders and the Program Project Co-Principal Investigators have ultimate responsibility for ensuring that unanticipated health events are detected and reported in a timely manner. Health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity, significant change in mood, suicidal ideation) will be immediately reported to the study physician who will determine an appropriate course of action.

To facilitate safety, participants who may not be medically appropriate to take NRT will not be included in the study (e.g., hospitalized within the past month for a stroke, heart attack, congestive heart failure or diabetes). Once enrolled, follow-up protocols will assess for medication side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend NRT dosage/use alterations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects once they begin medication treatment. We will refer participants to their referring physician as needed. Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

In terms of confidentiality risk, the UW-CTRI Information Technology Administrator manages the hardware, data, security, and infrastructure below the firewall. Access to the network is limited to only UW-CTRI owned and actively managed devices. All devices automatically lock and are password protected after 15 minutes of inactivity. All portable devices are encrypted for data security and no PHI is stored on local devices. All data stored on the network file server is limited by the principle of least privilege.

As stated above, no data are stored on individual computer hard drives. All data are transmitted from the point of collection to the UW-CTRI server through secure, encrypted web connection. On those rare occasions when, due to a loss of internet access or computer hardware failure, data are collected in paper forms, these forms will be stored securely in the clinic and transported personally by the case manager to UW-CTRI. No identifying data other than a participant ID number is entered on any data form. Any paper collected data are entered

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into the computer immediately upon receipt at UW-CTRI and the paper document is disposed of securely. Consent forms are obtained in paper copy; these forms contain the participant name and signature. These are retained in secure files at the clinic where they are collected and then transported to the UW-CTRI office, where they are securely stored.

Finally, no publications or presentations resulting from this research will contain any identifying information about individual participants.

Potential Benefits of the Proposed Research to the Participants and Others

The potential benefits for smokers participating in the Motivation Study include the chance to reduce their smoking and make a quit attempt sooner than they otherwise would have. Benefits for all research participants include the chance to receive smoking cessation counseling and pharmacotherapy at no cost—two evidence-based treatments which can double a smoker’s odds of quitting successfully. Considerable research has demonstrated that, whenever a smoker quits successfully, health benefits occur. In addition, quitting smoking reduces the burden of secondhand smoke exposure to others. Finally, the benefit of reduced healthcare costs, morbidity and mortality related to smoking is a societal benefit from quitting smoking.

The health and economic benefits to the individual and society greatly outweigh the risks in terms of discomfort, side effect of medication and loss of confidentiality.

Importance of the Knowledge to be Gained

These research studies will develop new treatments and determine whether treatment packages engineered using Phase-Based intervention components and the MOST approach are more effective and more cost-effective than usual care treatment for smoking cessation. This information could lead to the provision of tested treatment packages that a health system can implement for smoking cessation, as the cornerstone of a chronic care treatment for smoking. Further, this research will identify treatment mechanisms via which the treatments exert their effects. Such knowledge could be helpful in developing new treatment packages and for personalizing treatment based on which treatments work for various groups of smokers. Finally, the studies will test methodologies designed to more rapidly develop effective interventions, test them and bring them into clinical use, considerably shortening and improving the methodology for research translation into practice.

As outlined above, the risks of this study are minimal and limited to the discomfort of quitting smoking, generally mild side effects of medication and small risk of breach of confidentiality. The potential study impact on increased numbers of smokers across clinical settings nationally far outweigh these risks.

Data and Safety Monitoring Plan

The following Data and Safety Monitoring Plan (DSMP) pertains to all research to be supported under the National Institute of Health (NIH) Program Project Award. This plan comprises not only the research conducted directly by the University of Wisconsin Center for Tobacco Research and Intervention (UW-CTRI) researchers, but also research conducted by other investigators who are supported by these funds. All investigators must agree to comply with the procedures outlined in this DSMP. This DSMP does not reduce any investigator’s obligation to comply with the requirements of the UW Institutional Review Board (IRB) or the IRB of any collaborating organizations.

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*Monitoring the progress of trials and the safety of participants.* The PIs of the Program Project will be responsible for routine monitoring of the progress of the research. This monitoring includes scheduled biweekly meetings with study staff and review of written documentation of all research projects. Data that are reviewed at these meetings include the number and type of participants enrolled, the number and reasons for exclusions from enrollment, the number of participants treated and the stage of intervention, a summary and an individual review of any unanticipated health events, and outcome data.

To facilitate participant safety, study participants must meet study inclusion and exclusion criteria. Once enrolled, follow-up protocols will assess the presence of medication side effects and unanticipated health events at all study visits and follow-up contacts. We will recommend dosage/use alterations as per good clinical practice if the patient experiences symptoms of nicotine toxicity or other troublesome side effects. We will refer patients to the study physician and/or their referring physician based on defined, regularly administered medication safety protocols. Any unanticipated health events that raise concerns (e.g., allergic reaction, symptoms suggestive of nicotine toxicity) will be immediately reported to the study physician. Such symptoms typically result in dosage changes or medication stoppage. Should either excessive risk to study participants and/or lack of measurable benefit to study participants be determined, the study will be stopped and all participants notified in a manner appropriate to the nature of the risk and/or lack of benefit.

*Plans for the reporting of unanticipated health events.* This DSMP requires that investigators notify NIH and the University of Wisconsin IRB in a timely manner of the occurrence of any unanticipated health events, which are severe, unanticipated, and possibly related to study medication or protocol.

Because this study involves pharmaceutical agents, in the event of an unanticipated health event that might be related to drug use, both the FDA and the manufacturer will also be notified within 5 days of investigators becoming aware of the event. Examples of a serious unanticipated health event would be untoward occurrences related to study participation 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 health events would also include less serious problems that merit reporting because they are severe, unanticipated, and possibly related to study participation. All serious unanticipated health events, including those reported during scheduling and follow-up calls, will be examined within 72 hours and reported as required by IRB, NIH and/or FDA rules. The PIs will be responsible for the accurate documentation, investigation, and follow-up of all study-related unanticipated health events.

Unanticipated health event assessment, recording, reporting, and investigation will be accomplished through staff training, structured/standardized assessments of untoward occurrences/events, and regular monitoring by study physicians and other study investigators. The Project Leaders and the Program Project Co-Principal Investigators have ultimate responsibility for ensuring that unanticipated health events are detected and reported in a timely manner. Additionally, the IRB will receive an annual report of all serious unanticipated health events and unanticipated health events meeting the criteria listed above.

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

*Plans for assuring data accuracy and confidentiality and protocol compliance.* The Project Leader, supported by staff, will refine and monitor existing protocols for assuring data accuracy and protocol compliance. Data from their compliance reviews will be shared with the Program Project PIs. Such protocols will include data verification and protocol compliance checks. The Data Manager and IT Manager will also be responsible for ensuring that the data for the project are securely stored, that storage is in compliance with University and federal regulations and that no unauthorized persons have access (electronic or physical) to any participant-identifiable data. The PI's will ensure that HIPAA regulations and guidelines are currently implemented and all study staff have completed approved human subjects and HIPAA training programs. The.

Safety Review Committee

In addition to the protections outlined in the Program Project-wide DSMP (above), all three studies conform to the NIH definition of a clinical trial. All of the trials in this P01 application are Phase IV clinical trials that are not multicenter in nature (the projects are testing existing interventions delivered through new methods to determine population effectiveness). The DSMP specifies overall monitoring that will be conducted by the PIs for all projects. Their responsibilities include timely reporting of unanticipated health events and serious unanticipated health events. Every 6 months, the Program Project-wide Safety Review Committee will convene to review the overall safety data, as well as data on safety summarized by treatment condition. The objective of these reviews will be to determine whether continued conduct of the trial poses no undue risk for participants.

The Program Project-wide Safety Review Committee will be chaired by Dr. James Cleary, leader of the Palliative Care and Supportive Oncology Group at the UW Carbone Cancer Center. Dr. Cleary is a very experienced physician and clinical trial researcher with no involvement in any of this P01's research activities. Dr. Cleary will be joined on the committee by Dr. James Sosman and Dr. Burke Richmond. Dr. Sosman is a practicing general internist and has collaborated on clinical trials with UW-CTRI in the past. Dr. Richmond has served on independent Data and Safety Monitoring Boards for Phase II and III trials involving a nicotine vaccine. Neither has direct involvement with any of this P01's research activities. UW-CTRI's data staff will provide support for these reviews including summaries of safety data by treatment condition. The PIs will participate in these reviews and take lead responsibility for implementing any recommended changes in procedure or protocol.

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**Appendix 1: Sample Representativeness/Study Recruitment Aggregate Data Request\***

**\* obtained for Active Intervention study clinics only**

**Subjects:**

- ~100000 patients who had visits at clinics during the project recruitment period at each participating clinic plus all smokers connected with these clinics who were not seen

**Consent Procedures:**

- Patients will not be asked to provide consent or specific HIPAA authorization for this anonymous data reporting

**Data Collection for Patients Visiting the Clinic During the Recruitment Period**

- Medical Assistants (MAs) complete EMR-recorded tobacco use screening. The following visit record information will be analyzed from the EMR during specified recruitment time periods in each clinic:
  - Number of unique adult patients (18 years and older) with visits during the recruitment period
  - Number of visits by those unique patients
  - Clinic
  - Smoking status: not asked, never, current, former
  - Study referral: yes/no
- UW-CTRI research staff send the following data to EMR data staff via secure server for all those sent for consenting to study participation and contact with their health clinic (by clinic subsequent to the close of the recruitment period):
  - Name
  - Date of visit where referral took place
  - MR #
  - Clinic
- EMR data staff sends the following group data to research staff via secure server for 7 different groups for each clinic participating in the study: (1) those not asked about smoking at all visits (2) those indicating they are a never smoker at any visit; (3) those indicating former smoker at any visit, (4) those indicating smoking at any visit but not invited to study by attending medical staff (5) those indicating smoking at any visit not interested in being referred at any visit, (6) those referred but not enrolled in the study and (7) those enrolled in the study.
  - Gender distribution
  - Ethnicity distribution (African American, white, other)
  - Age distribution (5 year increments, over 80 as a single group)
  - Types of insurance (commercial, Medicaid, self-pay, etc.)
  - Diagnosis (ICD-9, grouped into categories)
  - Visit type and level
  - Number of clinic visits during the study period (1, 2, 3, 4 or more)
  - Visit at which study invitation was accepted (groups 5 and 6 only)

**Data Collection for Patients NOT Visiting the Clinic During the Recruitment Period**

- EMR data The following information will be analyzed from the EMR during specified recruitment time periods in each clinic for those who had no visits:
  - Number of unique adult patients (18 years and older) with no visits during the recruitment period
  - Clinic
  - Smoking status: unknown, never, current, former

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- Outreach performed: letter, mychart, none
- UW-CTRI research staff send the following data to EMR data staff via secure server for all those contacting the study directly. (Note: the purpose of this transmission is to enable the health clinic to differentiate between groups 6 and 7 below. By providing a list of the study participants, the clinic can provide essential aggregate comparative data on the group of individuals who they referred but did not enter the study.
  - Name
  - Clinic
  - EMR number
- EHR Data Department staff members at Aurora and Dean Health systems will perform necessary database queries that will allow them to send the following group data to research staff via secure server for 7 different groups for each clinic participating in the study for all those not having a clinic visit: (1) those never asked about smoking (2) those indicating they are a never smoker; (3) those indicating former smoker, (4) those indicating smoking at any visit but not receiving any outreach (5) those indicating smoking but not contacting the study, (6) those referred but not enrolled in the study and (7) those enrolled in the study.
  - Gender distribution
  - Ethnicity distribution (African American, white, other)
  - Age distribution (5 year increments, over 80 as a single group)
  - Types of insurance (commercial, Medicaid, self-pay, etc.)
  - Diagnosis at latest visit (ICD-9 [or -10], grouped into categories)

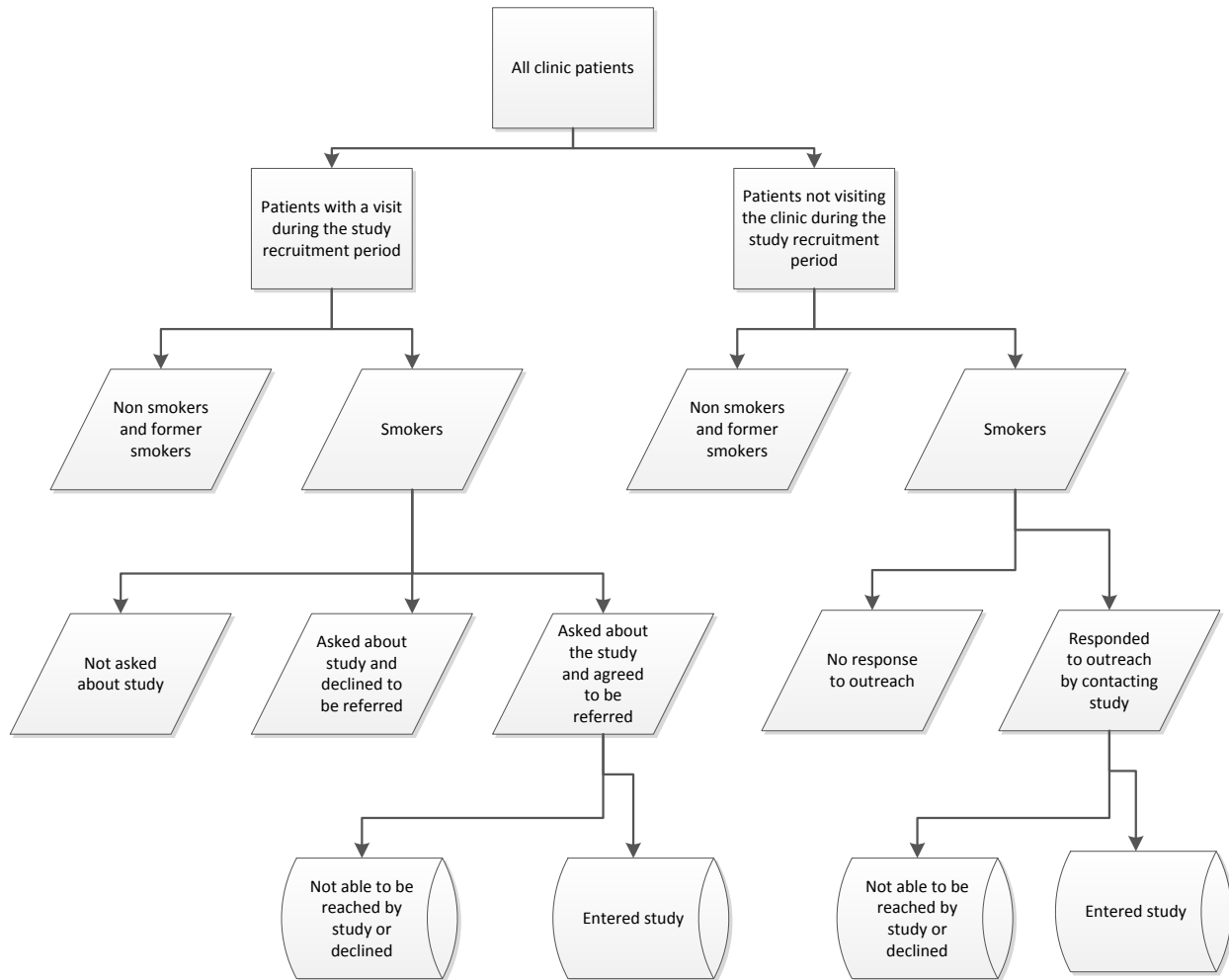
**Data Storage:**

- Research staff will maintain a cumulative anonymous dataset received from the health system EMR provider until 7 years after completion of the study, when the dataset will be destroyed
- Health system Data Department staff will securely maintain a record of data provided by the study until data verification is performed by the researchers. Following that time, these data will be destroyed in a HIPAA compliant manner in accord with health system policies.

“Breaking Addiction to Tobacco for Health (BREATHE) Study”  
 PI: Michael Fiore, MD, MPH, MBA; UW-CTRI Center Grant: 1P01CA180945-01.

**Appendix 2: Consort Diagram**

Optimized Chronic Care for Smokers: Aggregate Clinic Recruitment Data Needed for Study CONSORT Diagram



In order to just the effectiveness of the study approach, relevant aggregate “demographic” information is being sought on each of the groups in the above chart, as outlined in the EMR data summary document appended to the protocol

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