Breath Monitor Study

Protocol

KELLY CARPENTER, PH.D.

Version	Date	Notes	Initials
1.0	**8/6/21**	Version 1 draft	**kc**
1.1	**9/24/21**	Response to IRB feedback	**kc**
1.2	**9/29/21**	Update study name to Breath Monitor	**HB**
1.3	**04/19/22**	Update recruitment to up to 350 from 300	**CC**

SYNOPSIS	
Tracking IDs	OHRA protocol number, 2021-0056
Full Title (Scientific)	Breath Monitor Carbon Monoxide Monitoring Study
Short Title (Public Facing)	Breath Monitor Study
Type of Project Description	Interventional Research
Focus Area/Category	Product Development
Primary Objective	Conduct a 3-arm randomized pilot study to determine the value of adding CO Monitoring (with and without financial incentives) to standard Quit For Life tobacco cessation service offerings.
Anticipated Duration	**Launch**: 10/2021 -- **Publication**: 06/2023
Primary Target Population	Quitline callers who 18+ years old from participating states who are current smokers

PERSONNEL – FULL NAME, CREDENTIALS, AFFILIATION, EMAIL ADDRESS	
Principal Investigator	Kelly Carpenter, Ph.D., Optum Health, Kelly.Carpenter@optum.com
Owner/Primary Contact	Caryn Chalmers, MPH, Optum Health, Caryn.Chalmers@optum.com
Clinical Lead	Etta Short, MS, Optum Health/Rally, etta.short@rallyhealth.com (She will be moving to Optum proper 9/26/21)
Data Scientist	TBD
Operations Architect	NA
Internal Sub-Investigators	Etta Short, MS
External Sub-Investigators	None

COLLABORATING ENTITIES	
Study Sponsor	Quit For Life, Coaching Prevention and Wellness (internally sponsored)
Funding Sponsor	Internally funded with additional funding provided by participating states
Regulatory Sponsor	N/A
Partners	Vincere Health
Vendors	Vincere Health
Research Sites	Conducted remotely via phone by Optum Consumer Wellness Solution's Quit For Life (Tobacco Quitline) Product and Optum Center for Wellbeing Research and via the Vincere Health CO monitoring app.

1. Specific Aims

Aim 1 + Hypothesis 1:

Conduct a 3-arm randomized pilot study to determine the value of adding carbon monoxide (CO) monitoring (with and without financial incentives) to standard Quit For Life tobacco cessation service offerings. We hypothesize that the CO monitoring will be feasible and acceptable to deliver (measured by app download rates and CO compliance rates).

Aim 2 + Hypothesis 2:

Conduct a 3-arm randomized pilot study to determine the value of adding CO monitoring (with and without financial incentives) to standard Quit For Life tobacco cessation service offerings. We hypothesize that the CO monitoring will increase engagement in quitline treatment (measured by calls completed).

Aim 3 + Hypothesis 3:

Conduct a 3-arm randomized pilot study to determine the value of adding CO monitoring (with and without financial incentives) to standard Quit For Life tobacco cessation service offerings. We hypothesize that the CO monitoring will increase tobacco cessation and satisfaction rates compared with treatment as usual (TAU). We will also examine cost effectiveness of the intervention as compared to TAU.

2. Background & Significance

Carbon Monoxide (CO) is an invisible, odorless, but toxic gas that is formed during tobacco smoking and can be measured in the exhaled air of smokers using CO monitors. CO levels, measured as particles per million (ppm), can help distinguish between different levels of smoking, with levels below 10 ppm commonly used as indicators of abstinence. CO testing acts as an objective non-invasive measure of harm from exposure to smoking and conveys more information than that provided by the number of cigarettes smoked alone (e.g., CO levels can be affected by the intensity with which cigarettes are smoked). Exposure to CO via smoking is associated with incidents of stroke and other cardiovascular diseases. CO levels are not affected by concurrent use of nicotine-containing products such as e-cigarettes or nicotine replacement which increases its value as a testing tool for smoking cessation studies and, thus, CO testing is widely used in research as an outcome measurement.

CO testing has also been identified as a valuable monitoring and feedback component of effective stop smoking programs and benefits cessation through making the health impact of smoking more salient. Smaller and more affordable CO monitors have made CO monitoring feasible for home use. The iCOTM Smokerlyzer® manufactured by Bedfont® Scientific Ltd. (Harrietsham, UK) is currently the only such device available for purchase. It connects to smartphones via bluetooth and requires a dedicated app to compute and display CO levels. This provides momentary feedback on behavioral outcomes, which are important self-regulatory and behavior change techniques in smoking cessation. Preliminary research suggests that personal use of CO monitors is acceptable, valued and potentially highly motivating for smokers. No large scale studies of CO monitoring as a component of a comprehensive tobacco cessation program have been published.

Vincere Health (VH; www.vincere.health) is a small business who joined United Healthcare's (UHC) Accelerator program in 2020. VH has developed a proprietary smartphone app that transforms data from the Bedfont CO monitor (cited above) into user-friendly pictorial displays and graphs. The app also connects to coaches, offers notifications/reminders for CO monitoring and can deliver monetary incentives (see below for screenshots). The UHC Accelerator program connected the VH business leads to the Quit For Life (QFL) smoking cessation program operated by Optum. Optum's QFL business has noted competitors who use CO monitoring as a cessation tool (e.g., Carrot, Inc.) and clients have asked why QFL does not offer CO monitoring as part of its program.

While there is preliminary research showing that smartphone-based CO monitoring is feasible, there is limited evidence that adding CO monitoring to a comprehensive cessation program increases cessation rates, engagement or satisfaction. The purpose of the present study is to conduct a pilot study examining the use of the VH monitoring device ("breath pen") and app as an adjunct to the evidence-based QFL program. Results from the pilot will be used to determine the need for further study of CO monitoring and may provide data for a grant application to conduct a larger RCT.

The state of Maryland's tobacco cessation quitline is operated by Optum and the Maryland Department of Health has partnered with Optum to conduct this study with its quitline's participants. They have signed an agreement to that effect. The participant pool for this pilot is Maryland residents who call the tobacco quitline wanting to enroll in a quit smoking program.

This study is funded by Optum's QFL program and participating states (currently Maryland). Scientific oversight is provided by Kelly Carpenter, PhD, Principal scientist at the Optum Center for Wellbeing Research.

3. PRELIMINARY STUDIES

1. *Dallery J, Raiff BR, Grabinski MJ. Internet-based contingency management to promote smoking cessation: a randomized controlled study. J Appl Behav Anal. 2013;46(4):750-764. doi:10.1002/jaba.89*

   Showed that home/internet-based CO monitoring decreased compliance barriers.

2. *Kendzor DE, Businelle MS, Waring JJC, et al. Automated Mobile Delivery of Financial Incentives for Smoking Cessation Among Socioeconomically Disadvantaged Adults: Feasibility Study. JMIR Mhealth Uhealth. 2020;8(4):e15960. Published 2020 Apr 15. doi:10.2196/15960*

   Preliminary evidence of feasibility of smart-phone based CO testing in low income adults.

3. *Herbeć A, Perski O, Shahab L, West R. Smokers' Views on Personal Carbon Monoxide Monitors, Associated Apps, and Their Use: An Interview and Think-Aloud Study. Int J Environ Res Public Health. 2018;15(2):288. Published 2018 Feb 7. doi:10.3390/ijerph15020288*

   Qualitative study of smartphone-based CO monitor use found wide variation among smokers' motivations and preferences.

4. *Shahab L, West R, McNeill A. A randomized, controlled trial of adding expired carbon monoxide feedback to brief stop smoking advice: evaluation of cognitive and behavioral effects. Health Psychol. 2011 Jan;30(1):49-57. doi: 10.1037/a0021821. PMID: 21299294.*

   CO monitoring increased salience to health impacts of smoking but did not impact cessation rates. Those with high self-efficacy did have improved cessation rates with the CO monitoring intervention.

5. *Seijo-Bestilleiro R, Seoane-Pillado T, Pertega-Diaz S, et al. Randomized clinical trial to determine the effectiveness of CO-oximetry and anti-smoking brief advice in a cohort of kidney transplant patients who smoke. Int J Med Sci. 2020;17(17):2673-2684. Published 2020 Sep 23. doi:10.7150/ijms.49401*CO monitoring did not increase cessation rates in kidney transplant patients.

4. Research Design & Methods

4.1. General Design

Quitline registration agents will screen callers for study eligibility criteria during the state quitline enrollment process. Interested and eligible participants will be transferred to a research trained quitline coach who will conduct the informed consent discussion. After giving verbal consent, participants will complete the baseline assessment and be randomized to one of 3 arms: quitline treatment as usual, quitline plus CO monitoring or quitline plus CO monitoring and financial incentives. Participants will complete coaching calls. Approximately 60 days after randomization, participants will complete an outcomes survey and all participants will complete a final CO test to determine smoking status.

Interventions-There will be three treatment arms in this trial:

Arm 1: Standard quitline (treatment as usual: TAU). This arm consists of the state quitline services as offered by participating states (currently MD). These state quitlines offer five proactive coaching calls, mailed support materials, access to text messaging and web-based supplemental programs, plus at least two weeks of free nicotine replacement (NRT). This arm will be mailed a personal CO monitor device and be instructed to download the Vincere Health smartphone app 60 days after randomization in order to complete the final outcome assessment.

Arm 2: TAU plus CO monitoring. Participants in this arm will receive all treatment component of TAU. They will also receive a personal CO monitor by mail immediately after study enrollment and they will be instructed to download the Vincere Health CO Monitoring App. The app will lead participants through a 2x/day CO monitoring program via the Vincere Health Breath Monitor - CO Monitoring device used in conjunction with the smartphone app. The app includes providing CO monitoring results and visualizations of CO results over time as well as reminders and reinforcement for compliance with the CO monitoring program.

Arm 3: TAU plus CO monitoring plus financial incentives. Participants in this arm will received all intervention components described above for Arms 1 & 2. In addition, they will receive financial incentives for engagement with the CO monitoring program. They will receive up to $1.50 for each use of the CO monitor (up to 2x per day for up to 60 days). Incentives will accrue and be visible on the app. Incentives will be delivered by gift card of the participant's choice.

4.2. Study Measures & Methods

SCREENING- Participants will answer questions if interested in study participation. If eligible, participants will be transferred to a research trained coach.
INFORMED CONSENT – If interested and eligible, participant will hear the consent form read to them by the research trained Quit Coach. The participant may ask questions before giving their consent. The coach will note the participant has provided their verbal informed consent.
BASELINE SURVEY – Participant will spend approximately 10 minutes answering baseline assessment questions. Participants will be sent a gift card of their choice for $15 after completing the baseline survey.

Table 2. Measures	Screen	Baseline	Program utilization	2-month follow-up
Demographics (gender, age, race/ethnicity, pregnancy/breastfeeding status)	x			
Tobacco/E-Cigarette/Cannabis use		x		x
Self-efficacy & motivation for quitting tobacco		x		x
Cessation medication use				x
Nicotine dependence (cigarettes per day, time to first cigarette)	x			x
Outcomes				
Program satisfaction and acceptability (usefulness, would recommend the program to others)				x
7- and 30-day point prevalence tobacco abstinence. CO-verified tobacco abstinence				x
Treatment Engagement			x	

Study inclusion/exclusion criteria

Callers to the MD state quitline 18+, daily smokers, not pregnant/post-partum, enrolling into an English quitline program, are not offered or in another study managed by the Optum quitlines, and have not been previously offered this study will be offered study screening.

If callers agree to be screened for the study: inclusion criteria include possession of a smartphone with a data plan (needed for use of the Vincere app), agreement to download the app onto their phone, agreement to use a personal CO monitoring device.

Days 1-55

Tobacco Cessation Coaching Calls 1-5 – Participants will engage in coaching calls about quitting smoking. There will be brief discussion of the CO monitoring program and smartphone app for Arms 2 and 3. Call 1 may take place on Day 1. Other calls will be scheduled as per standard quitline procedures. Participants will be referred to Vincere's technology helpline for questions about the app and CO device.

CO monitoring program (Arms 2 and 3). Participants will be sent a Vincere "breath pen" CO monitoring device and given instructions to download the Vincere Health smartphone app. The app also has an incentive/gift card feature where money earned is tallied and participants will receive a gift card through text message. This is how incentives will be delivered. Arm 2 and 3 participants will be asked to take 2 CO tests per day; only Arm 3 participants will earn incentives for CO monitoring. Participants will receive regular reminders and reinforcement for CO monitoring via the app.

Day 55

Arm 1 receives CO monitoring device and instructions to download Vincere Health smartphone app. They will be asked to try out the Breath Monitor device to make sure they know how to use it and to call Vincere if they experience any issues. On day 60 they will be prompted to complete a CO breath test in the same way as Arms 2 and 3.

Day 60

Follow-up Survey: Participants will be sent information for completing the follow up survey via the Vincere app. $20 will be added to the gift card total on the app after survey is completed.

Biochemical Verification: If participant self-reports being quit from tobacco at follow up, they will be asked to complete a final CO monitoring test (or tests) to verify quit status. Those who complete this final test will be given an additional $20 via the app.

4.3. Drugs & Devices Being Studied

Participants will be provided access to the Vincere Health smartphone app available for Apple or Android devices. The app will be used for CO monitoring and compliance reminders and delivering survey questions (at end of study). Additionally, participants are sent in the mail an iCOquit "Breath Pen" personal Bluetooth CO monitor with a user guide. The device is classified as a low risk 'general wellness device'. As such, we make no claims that the device will help participants quit; it's only used as a (helpful) tool to monitor progress. There are no restrictions on use.

Nicotine replacement (NRT) is provided by participating state quitlines as part of standard services. NRT is not under investigation in this study.

4.4. Intervention or Observation Procedures

All participants will receive the standard quitline coaching intervention. Coaches will review and discuss CO monitoring compliance and readings with participant in Arms 2 and 3. Arm 2 and 3 participants will be asked to take 2 CO tests per day; only Arm 3 participants will earn incentives for CO monitoring. Participants will receive regular reminders and reinforcement for CO monitoring via the app. Voice recording is standard procedure for all quitline calls. Calls are reviewed to ensure coaches are following study protocols.

4.5. Data Sources and Variables

Research Question/Aim/Objective:	Data Variables:	Data Source
• To determine eligibility	• Enrollment screening	• Service utilization (Apollo – Clinical Management System)
• To determine tobacco quit outcomes	• Baseline and follow-up survey • CO readings	• Datstat (Survey software) • VH app & CO monitor
• To determine satisfaction with the program	• Follow up survey • Data from VH App	• Service utilization (Apollo – Clinical Management System) • VH app & CO monitor
• Treatment Engagement	• Call completion	• Service utilization (Apollo – Clinical Management System)

See screening and survey documents for full outline of data variables.

4.6. Justification of Sample Size & Power

For the study there will be ~~300~~ up to 350 individuals per participating Optum state quit line (currently only Maryland is participating). The target recruitment was selected based on estimates regarding how many

participants could be recruited in the given time frame. This pilot study is not powered to detect a significant difference, but outcomes will be used to determine the need for continued study.

4.7. Statistical Methods

For the proposed pilot study we plan to use summary statistics with confidence intervals (CIs), means with standard errors (SE) and graphical displays (histograms, pie charts, Box plots, etc.) as appropriate to describe participant self-reported demographic characteristics, use of tobacco and other variables measured at baseline and at 2 months. We will use logistic or linear regression analyses to compare intervention and control groups on: mean number of calls completed; proportion completing at least two calls and, at 2 months, mean satisfaction ratings, mean change in cigarettes per day (cpd) and smoking cessation rates. We will conduct sensitivity analyses to determine the potential range of treatment effects on abstinence taking into account 1) different assumptions concerning the probability of relapse among survey non-responders, 2) substitution of biochemical results for those who claimed abstinence in the absence of agreement, and 3) the application of biochemical validation confirmation rate of abstinence to individuals who claimed abstinence but did not return their biochemical test results. Our analyses will include independent variables for state and gender to increase precision. We stratified randomization by state because of state variability and by gender because of the impact that gender has on treatment engagement and tobacco cessation. We will address missing values in three ways; 1) we will analyze responders only, 2) we will impute missing tobacco use as ‘smoking’ and 3) we will conduct sensitivity analyses (as discussed above) by modeling the proportion of smokers among non-respondents, and the applying of biochemical validation results to individuals who stated that they were abstinent.

4.8. Control of Bias & Confounding

State quitlines may differ in the services that are provided (e.g. amount of NRT and coaching calls) that are provided. There might also be variability that gender has on treatment engagement and tobacco cessation. Randomization will be stratified by state quitline and gender to address these potential confounding variables.

Follow up survey is collected via the app, so there is no bias in follow up data collection.

4.9. Primary & Secondary Endpoints

Approximately 60 days after randomization, participants will complete an outcomes survey and a final CO test to determine smoking status. Participants will be sent information for completing the follow up survey via the Vincere app and email. Participants will be asked to complete a final CO monitoring test (or tests) to verify quit status.

4.10. Interim Analysis and Stopping Rules

N/A this is a minimal risk study.

4.11. Case Ascertainment for Synthetic Controls

N/A

4.12. Duration

Projected Start of Recruitment Date (month/year) : October 2021

Projected Enrollment Period (days, weeks, months, accrual driven) : Accrual driven

Active Participation time (time for 1 participant to complete activity) : Participation will last about 3 months.

Projected Data Collection Cut off (month/year) : est. Sept 2022 (based on recruitment ending in June 2022)

4.13. Intended Use of Learnings

4.13.1 Internal use of findings plan and relevant enterprise segments: Research findings will be used to inform product development if found compliance and satisfaction rates are high and results indicate a potential for improved tobacco quit rates, treatment engagement, and/or program satisfaction.

4.13.2 External presentation or publication plan: Research findings will be disseminated as peer-reviewed publications and conference presentations. If applicable, findings may be used to secure funding for additional research.

4.14 Future Utilization of Collected Data or Specimens

Data may be used for additional analyses required for product development. Published or unpublished aggregated data may be used for marketing the effectiveness of a product resulting from this research.

5. HUMAN SUBJECTS

5.1. Participant Safety, Risks and Risk Mitigation

The primary risk of participating in this study is the risk of breach of confidentiality. A breach could potentially occur, for example, if an unauthorized individual accesses the study's database records. Quitline calls are recorded as standard procedure. Voice recordings are considered identifiable. Additionally, some participants may experience emotional discomfort that might occur during discussion of smoking and impacts on their own health. Persons who quit smoking may experience temporary discomfort associated with nicotine withdrawal symptoms such as irritability, mood changes, headaches, trouble sleeping, and cravings to smoke.

Risks of NRT. **NRT is provided as part of standard QUITLINE protocol and not specific to the study. These are detailed by the quit coach during coaching calls, and so are not listed in the consent form.** As part of standard service offerings from their state or district quitline, nicotine replacement therapy (NRT) in the form of the nicotine patch, gum or lozenge will be offered to participants in this trial. The study will follow standard NRT protocols as provided through the quitlines. For each participant who opts to use NRT, Optum coaches will assess their medical safety to use NRT and then determine the appropriate dose according to clinical practice guidelines. Optum will then mail the NRT to the participant along with instructions on how to use the medications. The NRT in this trial is being used for its FDA-approved purpose and will be offered to all participants, and therefore, the effect of NRT is not being evaluated as part of the trial, although use of NRT will be assessed at follow-up. As part of standard quitline services, coaches ask about possible side-effects of its use during telephone counseling sessions. According to the FDA-approved product insert, possible side effects associated with the patch include headache, dizziness, lightheadedness, drowsiness, stomach upset, nausea, or flushing the first few days as a user adjusts to the medication. The area around the patch may become red, itchy or irritated. Rarely, users may experience breathing difficulties, chest pain, irregular heartbeat, nervousness, anxiety, or tremors. Very rarely, a user of the patch may experience an allergic reaction such as a rash, itching, swelling, dizziness, or trouble breathing. Side effects will be disclosed in the study consent form. Optum distributes NRT to 65,000 of its 250,000 callers per year and has established protocols for addressing side effects with callers.

Risk of using the Breath Montior (personal CO monitoring device. The device used in this study is the Beford iCOquit® Smokerlyzer®, a personal Bluetooth carbon monoxide monitor that has been in use since 2015 and is a low risk device. **Intended Use**: The iCOquit® Smokerlyzer® breath carbon monoxide (CO) monitor is intended for single patient use by cigarette smoking individuals, notifying the individual user of the amount of CO on their breath produced as a consequence of smoking activity. **Safety Information:** Participant will receive a user manual with their device. The user manual includes the following: "Please do not attempt to modify the equipment in any way or use accessories not specified by the manufacturer. Any attempt to do so will invalidate the warranty and may compromise the safety of the device". For additional safety information and GMP information, participants are referred to the "Safety Information" section located on page 27 of the iCOquit User Manual. https://www.icoquit.com/wp-content/uploads/2021/01/LAB806-iCOquit-manual-issue-2.pdf

Alternatives to these risks include not participating in the study.

Protections against Risk

Protection against breach of confidentiality:

- **Security at Optum.** Optum's quitline business is a HIPAA-covered entity and complies with all HIPAA regulations regarding data security. The Optum offices provide physical and electronic access security, automated backup power for the servers, isolated environmental controls, and fault-warning systems to maintain a stable production environment for their quitline services. Servers, storage appliances and network components are housed in a dedicated server room at the corporate headquarters. All electronic and paper records, including voice recordings, that contain identifiable health information are secured and their use is limited to persons with a direct business-related need for access to this information. All hardware is handled as if it contains protected health information (PHI). Hardware that is no longer used is electronically and physically destroyed. The same security standards that apply to Optum normal business practices will be used to secure data collected for this study. Paper measures will be stored in locked file cabinets. All Service Delivery and Research Staff Members receive biannual Human Subjects training, yearly HIPAA training, sign a confidentiality statement, and are required to adhere to confidentiality and security policies and procedures.
- **Security at Vincere Health.** Vincere Health, Inc. is a HIPAA-covered entity and complies with all HIPAA regulations regarding data security. Of note, Vincere does not physically house any systems used by its Platform in Vincere facilities – all Vincere systems and servers are deployed on secure AWS and Azure Cloud services hosted in AWS / Azure-controlled facilities. Vincere does not store or host PHI on any workstations or mobile devices – all Vincere-maintained PHI is hosted and stored within our private and secure AWS cloud infrastructure as required by Vincere's System Access Policy. All Vincere offices provide physical access security in accordance with Vincere's Facility Access Policy. All electronic records and paper records that contain identifiable health information are secured or stored in locked file cabinets, and their use is limited to persons with a direct business-related need for access to this information according to Vincere's Restricted Internal Access to Protected Health Information (PHI) Policy. All hardware is handled as if it contains protected health information (PHI) – Hardware that is no longer used is electronically and physically destroyed according to Vincere's Disposable Media Policy. The same security standards that apply to Vincere's normal business practices will be used to secure data collected for this study. All Vincere employees receive yearly HIPAA training, sign a confidentiality statement, and are required to adhere to confidentiality and security policies and procedures according to Vincere's Employees Policy. For the purposes of this study, all Vincere Health employees who may see study participant data and any coaches who may talk to a participant have taken Human Subjects training from CITI (certificates available upon request).

Distress due to participation in the study intervention or assessment. It is possible that some participants may be upset or embarrassed by participating in the study intervention. Consent scripts will advise potential participants about the study intervention and their right to terminate participation at any time without risk or penalty. Participants are free to refuse to participate in any element of the study or treatment and to refuse to answer any question during the assessments. Expert clinicians are available to counsel any participant who becomes distressed, including Dr. Carpenter a licensed clinical psychologist, and the clinical supervisory teams at Optum and Vincere Health.

Nicotine withdrawal. Nicotine withdrawal symptoms are temporary and balanced by long term improvements in health. NRT can help mitigate nicotine withdrawal. Coaches are trained to help participants cope with short-term effects of quitting/reducing tobacco and/or adjust their dose of NRT.

NRT side effects (Standard service-Not part of study intervention). Participants enrolled in state quitlines have access to nicotine replacement therapy (NRT). Before recommending any medication or dosage, a participant's health condition is assessed with a series of screening questions. Coaches assess medical safety for NRT use by screening for Use Exclusion (UE) factors. Use Exclusions include: diagnoses of heart attack, stroke, or TIA within the past two weeks; being told by a health care provider within the past 6 months of a rapid or irregular heartbeat that required a change in activities or medication; being told by a health care provider in the past 6 months that they have serious or worsening angina; or a previous reaction to patch medication or adhesive tape that caused a rash or hives over the body, swelling of face or throat, wheezing or shortness of breath, or high fever, or that required the participant to discontinue use, or caused irritation that continued after rotating the patch and/or using hydrocortisone cream. If a participant is not eligible for NRT due to a UE, then a Medical Doctor (MD) Override Letter is sent to the participant. Once Optum receives the completed MD Override form from the participants MD and confirms NRT dosing with the participant, Optum sends the participant's NRT shipment. The screening questions were designed by Optum's medical

team and they are intended for use by non-clinical staff to exclude any individuals with specific conditions. Quit Coaches will also educate participants on the utilization of the products and related side effects. Manufacturers' information about side effects is given to participant in written form and via a 1-800 number that has recorded information. Quit coaches help participants problem solve around minor side effects (such as minor rash at site of the patch) and recommend that participants seek medical help for more serious side effects.

Study Benefits. Study participants may be offered intervention components that are hypothesized to increase success in quitting smoking. Interactions with coaches may facilitate the development of new skills and habits leading to a healthier lifestyle. Participants may also benefit from knowing that they are contributing to the advance of knowledge leading to better understanding of how smokers respond to smoking cessation treatment and may lead to improvement in future cessation programs.

5.2. Recruitment Plan

Optum's participant record/treatment management system will use answers to standard enrollment questions to determine who should receive the study invitations/screening offer. Only daily cigarette smokers from participating quitlines who are 18+ years old, speak English, and are not pregnant/post-partum will be screened for the study. Registration agents will ask three additional screening questions . These questions include: possession of a smartphone with a data plan, willingness to download an app onto their phone, and willingness to use a CO monitor. Eligible participants who have an interest in study participation will be called by a research-trained quitline coach who will describe the study in more detail, obtain informed consent and deliver the baseline assessment and the post-randomization script.

5.3. Enrollment Plan, Consent & HIPAA Authorization

Research-trained coaches will describe the study, read aloud the information/consent document verbatim, answer questions, and obtain verbal informed consent. A copy of the consent form will be sent to participants.

The informed consent will include authorization for use and disclosure of HIPAA protected health information.As all study activities will be conducted remotely, obtaining a signed consent form will not be possible. A partial waiver of HIPAA authorization is requested for this study.

5.4. Eligibility Screening & Medical Clearance

Study participants will be daily tobacco smokers aged 18 and older that are recruited from participating state quitlines who have a smartphone, provide an email address, and agree to download the Vincere Health smartphone app and use a CO monitor. Exclusion criteria include being unable to speak and read English, limited access to a telephone, or enrollment in another study operated by the quitline. Pregnant or post-partum women are also excluded because they are offered a tailored quitline protocol that differs from the standard call program. Participants are only eligible to be screened for the study once.

5.5. Participant Engagement, Results, & Withdrawal

All counseling calls will be attempted at least five times over different days. We will increase retention at the 2 month follow up survey by notifying participants via text message (on the app) that their survey is due. For those who do not complete the survey via the app, we will mail participants a print version of the survey along with a stamped return envelope. Print surveys will be mailed by the OCWR research team and returned to the Vincere Health office in Boston. Incentives will be given for survey completion. Strategies such as these have proven to be effective in our quitline research studies resulting in higher recruitment and retention rates.

Noted previously, participants are free to refuse to participate in any element of the study or treatment and to refuse to answer any question during the assessments with no repercussions. Study participants must request in writing to be withdrawn from the study and/or revoke their authorization to use their data. This information is outlined in the informed consent.

Participants will be restricted from re-enrolling into standard state quitline programs until their study activity is completed (whichever comes first of completion of final assessment and breath test, 90 days, or withdrawal from the study).

5.6. Compensation / Remuneration / Reimbursement

Research Incentives: Participants will receive $15 for completing the baseline survey, $20 for completing the outcome survey and $20 for completing the final CO test (biochemical verification of smoking status). These incentives will be provided to all participants.
Intervention incentives: Participants in Arm 3 will also be able to earn incentives for CO monitoring compliance. They will earn $1.50 for each test and asked to complete 2 tests per day ($3 per day). During the 60 day study period, participants will have about 55 days of CO monitoring in which to earn incentives (we anticipate approximately 5 days for mailing the device). 55 days with $3 per day incentives means Arm 3 participants could earn up to $165 for CO monitoring compliance. This amount is in line with previous financial incentive for tobacco cessation research.

5.7. Diversity Considerations:

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	~~6~~7	45	~~10~~12
Not Hispanic or Latino	~~178~~207	~~112~~131	~~290~~338
Ethnic Category: Total of All Subjects *	~~184~~214	~~116~~136	~~300~~350
Racial Categories			
American Indian/Alaska Native	2	1	3
Asian	~~12~~14	~~8~~9	~~20~~23
Native Hawaiian or Other Pacific Islander	1	1	2
Arab or Arab American	1	~~1~~2	~~2~~3
Black or African American	~~85~~99	~~52~~62	~~137~~159
White	~~84~~98	~~52~~60	~~136~~158
Racial Categories: Total of All Subjects *	~~185~~215	~~115~~135	~~300~~350

These estimates are representative of the target population: existing callers into a single state quitline (Maryland).

5.8. Protected Populations:

The following populations are being targeted for participation and are necessary for this project (Check all that apply):

☐ UnitedHealth Group Employees -- *(Requires Human Capital support during development)*

☐ UnitedHealthcare Members -- (*Requires UHC support. Please specify targeted plan types below. Protocol requires UHC specific intake form*)

☐ Medicare & Retirement Plan Members (M&R)

☐ Employer & Individual Plan Members (E&I)

☐ Community & State Plan Members (C&S)

☐ Global Markets

☐ Children – *(Requires age range justification, assent & parental permission process / materials. OHRA must apply additional regulations)*

☐ Pregnant Women - project is specific to pregnancy or includes intervention that may affect the fetus *(OHRA must apply additional regulations)*

☐ Intellectually / Cognitively / Developmentally Disabled Persons *(requires LAR considerations for recruitment, enrollment & all procedures)*

☐ Economically Disadvantaged Persons *(requires careful consideration of compensation amounts)*

☐ Prisoners *(Requires convened review & must include qualified prisoner representative. OHRA must apply additional regulations.)*

Protected Populations Justifications: *For each population please provide justification for why their involvement is necessary and explain how the project is designed to appropriately accommodate and protect them from undue influence and risk of harm.*

6. Administration, Quality Control, Monitoring & Reporting

6.1. Materials for Internal Development & Procurement

The system used to manage and deliver services to quitline participants will be modified to selectively offer the study to those who answer enrollment questions indicating eligibly and deliver study procedures and coaching calls.

6.2. Research Site Management Plan, Delegation & Training

Service Delivery registration staff, Quit Coaches and all study staff are required to complete the appropriate version of the CITI Human Subjects Research Training. Select coaches will be utilized for research procedures for this project. Breath Monitor coaches will receive additional training in research methods. Study coaches are trained Tobacco Specialists.

Quality assurance protocols. Under the guidance of the principal investigator, OCWR grant managers and research assistants perform regular checks to ensure that all processes are working as intended. This includes reviewing reports to ensure the correct people are being offered screening, reviewing screening calls to ensure enrollment agents are asking questions appropriately and choosing the current answer choice in the participant record system, reviewing consent/baseline/randomization calls to ensure all procedures are being followed correctly, reviewing randomization as it occurs to ensure the system is utilizing randomization tables correctly, and reviewing treatment calls to ensure coaches are following study protocols. Feedback on performance is sent to supervisors of enrollment agents and coaches as needed.

6.3. Deviations & Adverse Events Recording and Reporting

Our research team follows Good Clinical Practice guidelines for documenting research procedures, including the development of a Standard Operating Procedures (SOP) manual to document standard practices and daily processes conducted to assure execution of research tasks in accordance with institutional, state and federal guidelines. During a study, all changes in procedures and deviations are documented in the SOP. Human Subjects training from CITI are also completed (certificates available upon request).

Any participant adverse or health events reported during coaching calls are recorded in the clinical management system as part of the standard or care. Any reported health events that are outside of expected side effects

related to NRT use will be escalated and reviewed by the PI within 2 business days. Any deemed by the PI to be related to the research will be reported to the IRB.

6.4. Data Handling: Security, Protection, Storage and Transfer Plan

Any personal information will be stored as electronic data in password-protected secure computer files, secured from unauthorized access. Data will be kept for at least 6 years after the study ends and related reports are published. Data will be completely destroyed once it is no longer needed.
Any published results will take the form of summary results; they will not report anything that would identify a specific person. The research team at Optum will have access to the study data Only the minimal data required to complete the research will be accessed and analyzed.

Some study data may be shared with research partners and regulatory bodies. This includes:

- Study team at Optum
- Partners at Vincere Health
- Office of Human Research Affairs (OHRA) at United Health Group, who oversees our research, and; the parties named above may need to look at study records for this research study and related quality assurance, survey completion, or data analysis.

6.5. Financial Conflicts of Interest Reporting

Optum employees conducting this research may participate in the Employee Stock Purchase Program. Otherwise, there are no Financial Conflicts of Interest to declare.

7. LIST OF ABBREVIATIONS

Application (App)
Carbon monoxide (CO)
Carbon monoxide monitoring (COM)
Cigarettes per day (CPD)
Confidence intervals (CIs)
Medical Doctor (MD)
Nicotine Replacement Therapy (NRT)
Office of Human Research Affairs (OHRA)
Principal Investigator (PI)
Quit For Life (Q4L)
Research Implementation Unit (RIU)
Standard Operating Procedures (SOP)
Standard Errors (SE)
Treatment as usual (TAU)

7. REFERENCES

Goldstein A.O., Gans S.P., Ripley-Moffitt C., Kotsen C., Bars M. Use of Expired Air Carbon Monoxide Testing in Clinical Tobacco Treatment Settings. Chest. 2017 doi: 10.1016/j.chest.2017.11.002

Middleton E.T., Morice A.H. Breath Carbon Monoxide as an Indication of Smoking Habit. Chest. 2000;117:758–763. doi: 10.1378/chest.117.3.758.

West R., Hajek P., Stead L., Stapleton J. Outcome criteria in smoking cessation trials: Proposal for a common standard. Addiction. 2005;100:299–303. doi: 10.1111/j.1360-0443.2004.00995.x.

Brose L.S., Tombor I., Shahab L., West R. The effect of reducing the threshold for carbon monoxide validation of smoking abstinence—Evidence from the English Stop Smoking Services. Addict. Behav. 2013;38:2529–2531. doi: 10.1016/j.addbeh.2013.04.006.

Beard E., West R. Pilot Study of the Use of Personal Carbon Monoxide Monitoring to Achieve Radical Smoking Reduction. J. Smok. Cessat. 2012;7:12–17. doi: 10.1017/jsc.2012.1.

Jarvis C.M., Russell M.A., Feyerabend C. Absorption of nicotine and carbon monoxide from passive smoking under natural conditions of exposure. Thorax. 1983;38:829–833. doi: 10.1136/thx.38.11.829.

Shahab L., West R., McNeill A. A randomized, controlled trial of adding expired carbon monoxide feedback to brief stop smoking advice: Evaluation of cognitive and behavioral effects. Health Psychol. 2011;30:49–57. doi: 10.1037/a0021821.

8. APPENDICES

N/A