PROTOCOL TITLE:

Addressing Psychological Factors Underlying Smoking Persistence in COPD Patients: The Fresh Start Study

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1.0 Purpose of the Study:

Chronic Obstructive Pulmonary Disease (COPD) is caused primarily by smoking and smoking cessation is the first-line treatment for slowing disease progression. Despite this, nearly 50% of COPD patients continue to smoke following diagnosis. Smokers with COPD report high rates of co-occurring conditions – nicotine dependence, depression, and anxiety – which serve as barriers to quitting. The proposed research will develop and pilot test a behavioral intervention designed to target the common psychological factors underlying these co-occurring conditions and foster smoking cessation among COPD patients. Specific aims are:

Aim 1: Refine behavioral treatment components. We will conduct a series of semi-structured qualitative interviews with COPD providers (pulmonologists, nurses, and respiratory therapists) that will elicit feedback on key elements of treatment design (components, methods, and milestones) and implementation (safety, tolerability, and acceptability) to guide treatment tailoring and foster engagement.

Aim 2: Develop a multi-component behavioral treatment to address psychological risk factors among COPD patients. We will conduct a component analysis using single case design experiments with 15 participants to a) examine the contribution of each treatment component to the behavioral target of smoking for affect regulation, and b) establish proof-of-concept on the clinical endpoint of initial cessation (≥24 hours abstinence). **Hypothesis**: Behavioral treatment components will produce a) clinically significant reductions in smoking for affect regulation (≥ 30%), and b) achievement of initial cessation in ≥ 60% of participants.

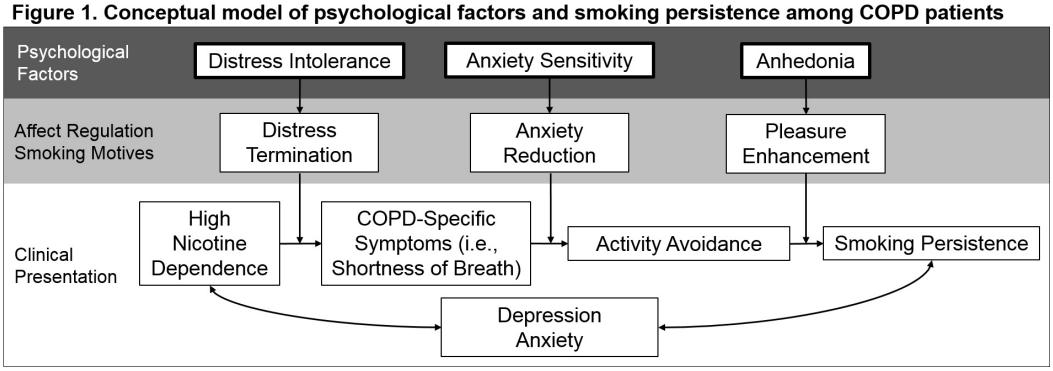
Aim 3: Examine effects of psychological risk factor reduction on smoking outcome. Informed by Aim 2, we will conduct a pilot trial in which 62 participants are randomized to the multi-component behavioral treatment (9 weekly sessions) or self-guided treatment (mailing of printed self-help materials). Each participant will make a quit attempt at week 4. The primary outcome is number of days abstinent for 2 weeks post-quit (range = 0-14 days); secondary outcomes are smoking status at 3 months post-quit, COPD functioning, activity avoidance, and depression and anxiety symptoms. **Hypothesis**: Participants in the behavioral treatment vs. self-guided treatment will demonstrate a) greater number of abstinent days, and b) longer latency to smoke during the quit attempt.

2.0 Background / Literature Review / Rationale for the study:

Chronic Obstructive Pulmonary Disease (COPD) is the third leading cause of death in the United States, responsible for 135,000 deaths each year.[1,2] COPD is caused primarily by smoking and approximately 47% of those with COPD are current smokers.[3]

Smoking cessation is imperative for COPD patients. Quitting smoking is the most effective and cost-effective therapy for COPD[4,5]. As compared to smokers in the general population, COPD patients are equally motivated to quit[6] and attempt to quit at equal rates,[3,7] but are less responsive to smoking cessation treatment,[8,9] with only 12% abstinent at 12 months.[10] COPD patients commonly have co-occurring conditions – high nicotine dependence,[11,12] depression, and anxiety[13,14]

Figure 1. Conceptual model of psychological factors and smoking persistence among COPD patients



– that maintain smoking for negative reinforcement (i.e., reduction of withdrawal-related distress).[15] To improve upon stagnant quit rates among COPD patients, novel, targeted treatment strategies are needed.

Psychological factors are a promising treatment target. Guided by recent systematic reviews[16,17] and our preliminary, human laboratory-based work, we propose three core psychological factors that commonly underlie nicotine dependence, depression, and anxiety: *distress intolerance* (DI; inability to withstand distressing states), *anxiety sensitivity* (AS; fear of anxiety-related sensations), and *anhedonia* (Anh; diminished sense of pleasure or interest). As shown in Figure 1, we propose that each of these factors interacts with clinical symptoms specific to COPD to drive smoking persistence. First, DI promotes smoking for distress termination (i.e., during frequent bouts of acute withdrawal caused by high nicotine dependence) and results in exacerbation of COPD-specific symptoms. Second, AS promotes smoking for anxiety reduction especially when COPD patients experience distressing symptoms such as shortness of breath[18] and leads to avoidance of activities that may increase these symptoms (i.e., physical exercise, engagement in pulmonary rehabilitation). Third, as activity avoidance cuts off contact with natural rewards in the environment, Anh promotes smoking for pleasure enhancement. Lastly, all three factors contribute to smoking persistence and perpetuate depression and anxiety symptoms, creating a cycle which serves as a powerful barrier to quit even among highly motivated individuals. In summary, these psychological factors index an individual's tendency to smoke to regulate affect (i.e., to enhance pleasure or reduce distress) in response to COPD-specific states and underlie smoking persistence among COPD patients.

Behavioral treatment can address psychological factors and promote cessation. Cognitive-behavioral treatment strategies have been shown to effectively reduce these psychological factors among a general population of cigarette smokers[19,20] as well as individuals with chronic illness,[21] elevated depressive symptoms,[22] and substance use disorders.[22-25] These treatment strategies reduce reliance on smoking for affect regulation[26,27] and improve cessation rates.[26,28,29] Ours will be the first study to adapt a behavioral treatment to specifically target these psychological factors among COPD patients. Effectively addressing psychological conditions is also shown to increase COPD patients' exercise tolerance, engagement in pulmonary rehabilitation, and quality of life.[30,31] Thus, this intervention has potential to obviate a large number of health burdens among COPD patients.

3.0 Inclusion and exclusion criteria:

For COPD patients in Phases 2-3, study eligibility will be determined as follows: Inclusion criteria: Eligible participants will be males and females who are 1) diagnosed with COPD (as documented in electronic health record [EHR]), 2) daily cigarette smokers (≥ 5 cigarettes per day over past 30 days), 3) intend to quit smoking within the next 60 days, 4) report at least moderate level of smoking for affective regulation (SMQ-R[32,33] coping subscale score ≥30), 5) have access to a smartphone, tablet, or computer, and 6) are able to communicate fluently in English. Exclusion criteria: We will exclude based on presence of any concurrent medical or psychiatric condition which would preclude ability to provide informed consent or perform study procedures (e.g., moderate to severe dementia and/or severe, uncontrolled schizophrenia), as determined by the treating physician or study PI.

We will not include adults unable to consent, pregnant women, prisoners, or individuals under the age of 18. Socioeconomically disadvantaged persons will be included in this study, but not targeted for recruitment. It is possible that Rush University employees or students may choose to participate. However, status of participation in the study will be independent of the participant's work or school activities.

4.0 Procedures Involved:

Overall Study Design

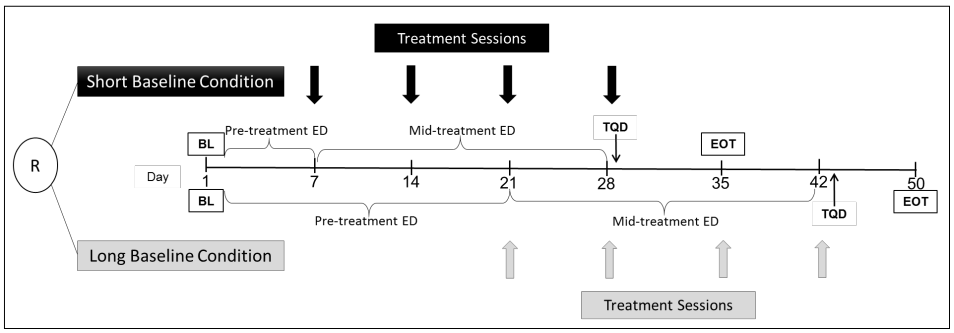
The project includes a total of three phases that will each recruit an independent sample of participants, as shown in Table 1 below. A total of 97 participants will be recruited for the current study. First, Phase 1 will

involve qualitative interviews with COPD healthcare providers (N=20). In Phase 2, we will conduct a series of single case design experiments in which COPD patients (N=15) will complete behavioral treatment components before an attempt to quit smoking. Lastly, Phase 3 consists of a pilot randomized, controlled trial comparing the behavioral intervention to minimally-enhanced usual care (N=62).

Phase 2: Single Case Design Experiments

Procedure. Single case design experiments offer a rigorous and methodologically-sound procedure to test within-subject change across conditions (i.e., baseline to active treatment) in a replication context to efficiently evaluate interventions.[34,35] Specifically, we will conduct a component analysis using a series of 15 single-case design experiments. As shown in Figure 2, a non-concurrent multiple baseline design (1-3 weeks in length) will be used across participants to observe if change in the behavioral target occurs when, and only when, a treatment module is introduced, thus controlling for the effects of extraneous factors.[34] The overall goal of Phase 2 is to examine whether each treatment component in isolation follows the hypothesized pathway in Figure 3.

Figure 2. Phase 2 Study Design



Length of Study Participation. As shown in Figure 2, participants who are randomized to the short baseline condition will be enrolled in the study for approximately 35 days; participants randomized to the long baseline condition will be in the study for approximately 50 days.

Pre-Screening and Baseline Session. Participants will complete an initial pre-screening questionnaire administered by telephone or computer, using surveys developed in REDCap software, version 6. Eligible participants will be scheduled for an in-person baseline session approximately 1.5 hours in length. The following procedures will be completed at the baseline session:

1. Informed consent/HIPAA forms will be reviewed with participants, during which they will hear a description of all study procedures, risks, benefits, and information about the study medication. Participants' questions will be answered. Following this discussion, the combined informed consent and HIPAA form will be completed.
2. A carbon monoxide (CO) breath assessment will be used to measure recent tobacco exposure. The handheld device uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about three minutes to administer.
3. Participants will complete questionnaire measures of smoking-related variables, psychological factors, and COPD-related variables, as described below.
4. Following a randomization scheme programmed in REDCap, participants will be randomized to baseline length (long or short) and treatment condition (Mindfulness, Interoceptive Exposure, or Behavioral Activation, described below).
5. Lastly, participants will be provided with instructions on electronic diary completion. The study team member will provide each participant with written instructions on how to complete the REDCap questionnaires via smartphone, tablet, or computer. All participants will be provided with contact information for the research team should they have any questions about the electronic diary questionnaires.

Electronic Diary (ED) Assessment. ED assessments have demonstrated high compliance rates (>80%) among older adults, including those with chronic illness.[36,37] Thus, we believe these methods are feasible for the current study. Participants will be prompted to complete nightly ED assessments via REDCap each evening (between 7:00 and 10:00 pm) during both baseline phase and treatment phase of the study. This will yield up to approximately 29 assessment timepoints for participants in the short baseline condition and 43 assessment timepoints for participants in the long baseline condition. In order to allow for the five-week treatment session

window described below, we will provide compensation for up to 36 assessment timepoints in the short baseline condition and up to 50 assessment timepoints in the long baseline condition.

Treatment Sessions. Each treatment component consists of 4 weekly in-person, individual sessions of 45-60 minutes each with a trained study therapist. We will attempt to schedule treatment sessions on the same day of each week, but will allow for a five-week window to complete all four sessions, to accommodate some rescheduling of sessions if needed. Session content is described in the Behavioral Treatment Components subsection below.

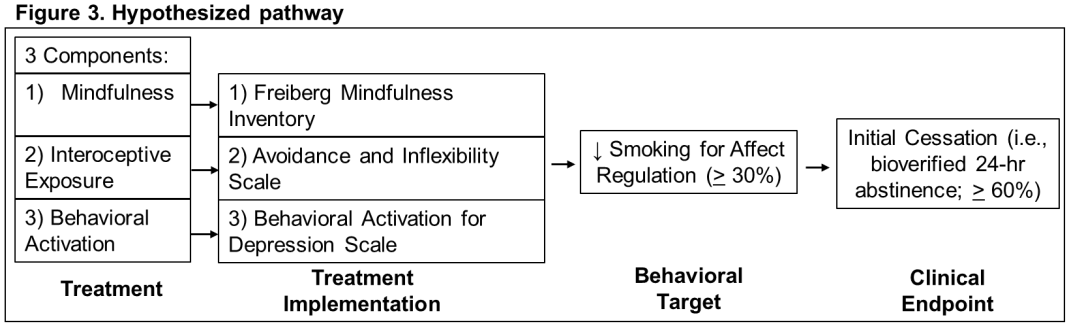
Target Quit Date. Each participant will set a target quit date on the day following the final treatment session. They will be instructed not to smoke starting at midnight (12:00 am) on their designated quit date.

Remote CO Assessment. At the final treatment session, participants will be provided with a carbon monoxide (CO) monitor and trained to submit a breath CO sample via REDCap at 24-hours post-QA (i.e., upon waking on Day 30 for the short baseline condition or Day 44 for the long baseline condition). This procedure will be used to conduct remote bioverification of smoking status. Developed by Dr. Dallery, a study collaborator at the University of Florida,[38-43] this method has demonstrated feasibility among a variety of populations, including older adults.[44] We will provide each participant with written instructions and contact information for the research team should they have any questions about the CO monitor.

End-of-Treatment Session. Participants will return for an end-of-treatment (EOT) study assessment approximately one week following their target quit date. At this assessment, participants will complete a final set of questionnaire measures on smoking-related variables, treatment implementation variables, and the behavioral target of smoking for affect regulation, described below. Participants will also return the CO monitor device and receive compensation for all completed ED assessments.

Behavioral Treatment Components. Treatment components are cognitive-behavioral strategies adapted from the Unified Protocol (UP) for the Transdiagnostic Treatment of Emotional Disorders[45]. For the current study, we will evaluate only the three modules that have been shown to reduce reliance on smoking for affect regulation before a QA[26,27] and provide skills to cope with acute nicotine withdrawal after quitting:[26,28,29] Mindfulness, Interoceptive Exposure, and Behavioral Activation (described below).

Figure 3. Hypothesized pathway



Behavioral counseling strategies for smoking cessation, drawn from current US Public Health Service guidelines[46], are incorporated in each treatment module. All participants will be provided with the American Lung Association Freedom from Smoking guide to aid in their quit attempt.

Component 1: Mindfulness. This module introduces mindfulness training skills, with the goal of cultivating nonjudgmental, present-focused experience of emotions, thoughts, and physical sensations related to cigarette smoking. By progressing though a series of experiential exercises (e.g., awareness of the breath, anchoring in the present), this module seeks to reduce maladaptive attempts to control negative emotions and facilitate tolerance of the physical and emotional symptoms of nicotine withdrawal.

Component 2: Interoceptive Exposure (Practice Quitting). This module introduces interoceptive exposure, a technique in which participants purposefully and systematically complete exercises to evoke physical sensations typically associated with anxiety and distress, in order to reduce fear and avoidance of these sensations. Interoceptive exercises will focus on a gradual exposure to nicotine withdrawal symptoms, through a series of 'practice quit attempts' (i.e., brief periods of smoking abstinence without intention to permanently quit).

Component 3: Behavioral Activation (Countering Emotional Behaviors). Lastly, this module introduces behavioral activation, which seeks to increase positive emotions by systematically introducing greater

engagement with natural rewards. Treatment sessions focus on the identification of avoidance strategies, including cigarette smoking as a coping strategy for negative emotions. The goal of this treatment module is to replace smoking with adaptive coping strategies to facilitate contact with and enjoyment of reinforcing activities that are incompatible with smoking.

Treatment Fidelity. All treatment sessions will be delivered by trained study counselors, supervised by the PI, a licensed clinical psychologist. Dr. Mathew has extensive experience in cognitive-behavioral therapy for mood and anxiety disorders, as well as behavioral counseling for smoking cessation. She obtained specialized training in delivery of the proposed intervention at the Unified Protocol Institute at Boston University in October, 2017. Sessions will be audio recorded, with 20% of sessions reviewed by an independent evaluator using standardized fidelity ratings for each UP module.

Measures.

Psychological Factors. Anhedonia will be assessed with the Environmental Reward Observation Scale (EROS),[47] which measures amount of pleasure experienced from daily activities. Anxiety sensitivity will be assessed with the Anxiety Sensitivity Index (ASI-3),[48] a measure of tendency to fear body sensations. Distress intolerance will be assessed with the Distress Tolerance Scale (DTS),[49] which assesses perceived tolerance of negative physical or emotional states.

Smoking-Related Variables. We will administer a Smoking History Questionnaire to assess baseline smoking characteristics. We will administer validated PROMIS measures of nicotine dependence[50] and smoking coping expectancies.[51] We will administer the Cessation Fatigue Scale,[52] a measure of perceived tiredness of trying to quit smoking. Smoking status will be assessed with timeline follow-back methods, and will be supplemented with an assessment of expired carbon monoxide (CO) at in-person assessment sessions to provide bioverification of smoking status. Lastly, an outside-study treatment review will be conducted to identify any pharmacotherapy or behavioral therapy for smoking cessation received outside of the study.

COPD-Related Variables. We will conduct a chart review to identify participants' most recent six-minute walk test[53] and spirometry (FEV_1) values prior to COPD hospitalization. The chart review will also be used to supplement participants' self-report of any hospitalization for COPD at the time of the 3-month follow-up assessment. COPD symptom impact will be assessed with the COPD assessment test (CAT),[54] an 8-item questionnaire measuring the global impact of dyspnea on health status. PROMIS measures will be used to assess task avoidance and emotional response to dyspnea symptoms.

Table 2. Phase 2 Study Measures	**Timepoint Assessed**		
	Baseline	**Treatment Sessions**	**End-of-treatment**
Demographic Questionnaire	X		
Contact Form	X		
Psychological Factors			
Anxiety Sensitivity Index	X		X
Environmental Reward Observation Scale	X		X
Distress Tolerance Scale	X		X
Smoking-Related Measures			
Smoking Motives Questionnaire-Revised	X		
Smoking History Questionnaire	X		
PROMIS-Nicotine Dependence	X		X
PROMIS-Coping Expectancies	X		X
Cessation Fatigue Scale	X		X
Smoking timeline follow-back	X		X
CO assessment	X	X	X
Outside-study treatment review	X	X	X
COPD-Related Measures			
Six-minute walk test	X		
Spirometry (FEV1)	X		
Charlson Comorbidity Index	X		
COPD Assessment Test	X		X
PROMIS- Dyspnea Task Avoidance	X		X
PROMIS- Dyspnea Emotional Response	X		X
Depression and Anxiety Measures			
PROMIS- Depression short form	X		X
PROMIS- Anxiety short form	X		X
Treatment-Related Measures			
Freiberg Mindfulness Inventory	X	X	X
Avoidance and Inflexibility Scale	X	X	X
Behavioral Activation for Depression Scale	X	X	X

Depression and Anxiety Symptoms. PROMIS short forms will be used to assess past-7 day depression and anxiety symptoms.[55,56]

Treatment Implementation. To assess treatment implementation, participants will complete process measures at each treatment session assessing skill acquisition specific to each module (i.e., Freiberg Mindfulness Inventory,[57] Avoidance and Inflexibility Scale,[58] and Behavioral Activation for Depression Scale,[59] respectively).

Behavioral Target. The behavioral target will be smoking for affect regulation, as measured by 13 items from the Smoking Motives Questionnaire-Revised (SMQ-R).[33,60] Items are adapted from a measure of drinking motives and have been validated to assess coping motives across classes of substance use.[32,60,61] SMQ-R items can be modified to assess within-subject, state-like motives for use via ecological momentary assessment[62] and have demonstrated good internal consistency.[63] Further, these items are sensitive to treatment-related change (i.e., reduced as a function of a brief behavioral intervention)[64,65] and specifically related to reductions in substance use and associated problems, above and beyond non-affective motives.[64,65] Responses are scored from 0 (not at all) to 100 (extremely) and averaged to index the overall tendency to smoke for affect regulation. Threshold of clinically-significant change is set at $\geq$ 30%, as this change magnitude was associated with substance use outcomes in prior studies.[64,65] Specific items which index smoking for distress termination (e.g., "To turn off negative thoughts about myself"), anxiety reduction (e.g., "Because it helped me when I was feeling nervous"), and pleasure enhancement motives (e.g., "To help me feel more positive about things in my life") will be examined separately in follow-up exploratory analyses.

Clinical Endpoint. The clinical endpoint will be achievement of 24-hour smoking abstinence at end-of-treatment, as verified by CO < 5 ppm,[66,67] for at least 60% of participants (i.e., 3 of the 5 participants receiving each module), as this is consistent with rates of initial abstinence achieved by established smoking cessation treatments.[68,69] We chose this endpoint because it is highly sensitive to treatment effects,[70] strongly predictive of long-term abstinence,[69,71] and especially relevant for smokers with elevated psychological risk factors who are vulnerable to early lapse.[72,73]

Procedures to Minimize Risk

Throughout the study phases, we will implement procedures to minimize risk to participants. First, the risk of participant distress will be minimized through ongoing training and supervision of study staff to maintain a good working relationship with participants, thoroughly explain all procedures and address participant questions, and consult with the PI, a licensed clinical psychologist, as needed. The PI will respond to all situations of participant distress or worsening of mental health symptoms, and will provide appropriate psychiatric referrals.

Second, participants will be thoroughly debriefed on common symptoms of nicotine withdrawal. In Phases 2-3, these symptoms will be monitored throughout the active treatment phase and coping with nicotine withdrawal symptoms will be addressed in treatment (either through behavioral counseling or provision of self-help smoking cessation materials).

Third, the risk of potential loss of confidentiality will be minimized through supervision of study staff, storage of all private health information on a secure network drive and the use of numeric code identifiers. Only the study staff will have access to the master list of participants' names and codes. Dr. Mathew will provide oversight of the maintenance of patient confidentiality and will report any breaches of confidentiality to the IRB. All staff with access to the data with have completed Rush University requirements for the responsible conduct of research including Collaborative Institutional Training Initiative (CITI) training.

5.0 Multiple sites:

N/A

6.0 Incomplete Disclosure or Deception:

N/A

7.0 Recruitment:

Participants will be recruited from the Departments of Internal Medicine and Pulmonary Medicine at Rush University Medical Center, under the supervision of study co-investigator Dr. Zimmermann. The Department of Internal Medicine provides approximately 87,000 primary care visits per year at 10 sites in the medical center and community-based clinics in the Chicago area. The department sponsors more than 50 active clinical trials and interfaces with the Electronic Data Warehouse to facilitate clinic-based recruitment. We expect that 40% of patients with COPD identified through clinic-based recruitment are current cigarette smokers.[3,74]

Trained study personnel will identify potential participants through reviewing Epic data requests, screening outpatient clinic schedules, and provider referral. Potentially eligible patients who are identified through chart review process will be mailed a recruitment letter to describe the research study and inform them that study staff will be calling them within the next week. Patients will have the opportunity to 'opt out' by calling the study team if they are not interested in being contacted.

Study recruitment will also be supplemented by partnerships with Rush University organizations such as the Tobacco Oversight Committee and Rush Lung Institute, and community organizations, including the Respiratory Health Association (RHA) and American Lung Association (ALA). Dr. Mathew will share IRB-approved recruitment materials with these organizations through multiple communication channels (i.e., newsletters, e-newsletters, website postings) to reach potentially eligible COPD patients and providers. She and other study team members will also attend events and meetings hosted by these organizations and post sign-up sheets where interested individuals may provide their contact information. The study team will call and/ or email these individuals to describe the study and assess interest in participating and eligibility, if applicable.

8.0 Consent Process:

We will obtain electronic informed consent via the REDCap e-consent template. After completing the phone screener, those who remain interested and eligible for the study will be immediately emailed or texted a link to the appropriate IRB-approved online consent form in REDCap. Study staff will discuss the consent form while on the phone with the participant following the screening process. If the participant does not have time for this discussion, a second phone call will be arranged. We will attempt to conduct the signature process in one continuous session with the participant. If this is not possible (e.g., the participant uses a cell phone as their only connected device, and is unable to simultaneously talk on the phone and view the REDCap e-consent), study staff will follow the consent process below to obtain verbal consent. Study staff will then follow up with the participant by email/ text to obtain an electronically signed copy of the consent form as soon as possible after the phone call has ended.

Consenting procedures will follow Rush IRB guidance for the use of electronic informed consent to ensure best practices are followed in remotely obtaining informed consent. Study staff will first verify that: 1) the form the participant received is the currently approved version, 2) all pages of the consent were received, and 3) the participant can read all pages of the consent. Study staff will verify the identity of the participant by asking their date of birth. Study staff will then review all information in the consent form, similarly to how this discussion would be conducted in an in-person format. Participants will be provided with ample time to review the consent and ask any questions they may have. Those who remain interested will provide an online signature on the REDCap consent form. A PDF version of the consents will be emailed or texted to the participant. Informed consent will be obtained prior to any data collection or study procedures. There is no waiting period between informing the prospective subject of

their eligibility and obtaining the consent. Non-English speaking individuals, individuals under the age of 18, cognitively-impaired adults, and adults unable to consent will not be included in the current study.

9.0 Process to Document Consent:

Documentation of the consent process will occur within the REDCap e-consent project (i.e., eConsent form with electronic signature for each study participant, Consent Collection Form, and Consent Process Documentation Form).

10.0 Risks to Participants:

First, participants will be asked to report on their smoking, COPD symptoms, and symptoms of psychological disorders. As a result, they may experience discomfort or distress from providing self-report of private, potentially embarrassing information. Second, participants may experience nicotine withdrawal-related distress as a result of smoking cessation in Phases 2 and 3. Third, while we will make every effort to protect privacy and keep data confidential, a risk of potential for loss of confidentiality also exists.

11.0 Potential Benefits to Participants:

Participants may not directly benefit from the proposed research, but will contribute to the research literature on improving smoking cessation treatment for individuals with COPD. The risk/benefit ratio is seen as highly favorable, as the potential benefits of quitting smoking for improving COPD functioning and preventing the development of other smoking-related illnesses greatly outweigh the potential of temporary withdrawal discomfort and frustration associated with quitting.

12.0 Financial Compensation:

Participants will be provided with financial compensation for completing study assessments, as shown in table below. They will be paid $10 to offset travel costs for each in-person study visit. Participants are only eligible for payment if all study procedures at a given assessment are completed. For Study Phase 3, payments will be provided in the form of a mailed check or reloadable debit card (Greenphire ClinCard). Participants will not be responsible for any costs associated with participating in the research.

Table 4. Financial Compensation per Participant by Study Phase

	Visit Compensation	**Travel Compensation**	**Total**
Phase 2			
Baseline assessment	$20	$10	$30
Electronic diary assessment	$2 x up to 50 total	N/A	Up to $100
Treatment sessions	N/A	$10 x 4 total	$40
CO assessment	$10	N/A	$10
End-of-treatment assessment	$20	$10	$30
TOTAL			**Up to $210**

13.0 Provisions to Protect the Privacy Interests of Participants:

The risk of potential loss of confidentiality will be minimized through training and ongoing supervision of study staff as well as storage of all private health information on a secure network drive (detailed in section 14.0 below).

14.0 Confidentiality and Data Management:

Data Management

Sources of data include a) consent forms, b) self-report questionnaires, c) expired CO values, d) digital audio recordings, and e) chart review variables. Data will be stored for a minimum of 7 years after study completion on a secure Rush University network drive and in a double-locked office suite within the Department of Preventive Medicine. At the conclusion of the study, all data will be stripped of identifiers and archived for future analysis.

Procedures to secure the data include training and ongoing supervision of study staff; use of an encrypted, digital recording device; storage of all private health information on a secure network drive; and the use of numeric code identifiers. Digital audio recordings will be identified by numeric code only, and submitted to the transcription service via their secure, cloud-based Exavault server. Dr. Mathew will be responsible for data and safety monitoring activities. She will provide oversight of the maintenance of patient confidentiality and will report any breaches of confidentiality to the IRB. She will report any changes to the study's risk/benefit ratio to the IRB. Only the study investigators will have access to the master list of participants' names and codes. All co-investigators and study personnel have completed CITI training in human subjects research.

All questionnaire measures will be completed using REDCap data management software, which allows real-time data quality control measures (e.g., requiring fields to be completed, restricting ranges of acceptable values). We will also complete data quality checks by automatically setting each form status to 'Unverified' upon initial entry. Study staff will click on each unverified record, check for data quality and completeness, and select either 'Complete' or 'Incomplete.' They will then lock the form to prevent further changes, with administrative privileges set to unlock forms only for the study investigators. REDCap data will be downloaded and backed up on the secure Rush University network drive on an ongoing, monthly basis.

Data Analyses

Phase 2 Data Analyses. We will examine change scores in the behavioral target over the course of treatment (i.e., with visual interpretation and calculation of non-overlapping parameters) and rates of achieving 24-hour abstinence by treatment module. Only those treatment components that demonstrate effects as specified in the hypothesized pathway on both milestones across participants will be included in a finalized treatment manual for use in Phase 3. We will secondarily examine magnitude of effect size for each treatment component on the behavioral target, relative to baseline, with Shadish's d,[75] a measure of effect size specifically for single-case designs and equivalent to Cohen's d. If all effect sizes are medium or greater (≥ 0.5), we will include all 3 components in the multi-component treatment in Phase 3; otherwise, we will select the two components with the highest effect sizes.

15.0 Data Monitoring Plan to Ensure the Safety of Participants:

In collaboration with Dr. Hitsman and co-mentors, Dr. Mathew has developed a data safety and monitoring plan for this project that is commensurate with the with the risks, nature, size, and complexity of the study. The proposed study has been designated as a minimal risk study by the Rush University IRB, consists of a behavioral intervention only (no medication), and will occur at a single site. Further, pilot trial procedures have been updated to be conducted on a fully remote basis, with all study contacts occurring via phone or online assessment, to facilitate social distancing. Given these study characteristics, a Data Safety Monitoring Board will not be convened. As detailed below, data and safety monitoring for the pilot trial (i.e., Study 3 of the current project) will consist of oversight by the PI, in coordination with the Rush University Institutional

Review Board (IRB). The PI will be assisted by study Co-Investigator, Dr. Laura Zimmermann, a board-certified Internal Medicine physician and Medical Director of the Rush University Prevention Center.

Data Acquisition and Maintenance

Data will be collected using REDCap (Research Electronic Data Capture) electronic data capture tools hosted at Rush University. REDCap is a secure, web-based software platform designed to support data capture for research studies. REDCap provides 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for data integration and interoperability with external sources.

The PI will be responsible for maintaining the security of the data stored both in REDCap and on the secure network server. Data will only be identified with the study ID of the participant. The codes that link the name of the participant and the study ID will be kept confidential by the PI on a secure network drive, with permissions set on an as needed basis. All data will be stored on the Department of Preventive Medicine's MS SQL server relational database. Rush data network security and availability on DMC servers is supported by Rush Information Services servers. Rush University has two data centers on our Chicago campus at 1700 W. Van Buren St. and 711 S. Paulina St. All servers are located in the locked data centers, with access limited to authorized personnel via a biometrics access system. Data centers each have Sinorix™ 227 and Ecaro-25™ Clean Agent Chemical Fire Suppression Systems, redundant backup diesel generator and uninterruptible power supply (UPS) systems, and redundant chillers for cooling.

The Rush data network is segmented and protected from the internet by a Palo Alto Networks® firewall. Access to the network from the internet requires multi-factor authentication. All network users are required to have a unique login and password. The passwords must be changed every 180 days and must be complex (i.e., must have: a capital letter, small letter, number, special character, and be at least 8 characters in length). Change management policies and procedures are in place to protect the integrity of the systems. A Change Management Review Board meets once each week to review all proposed software and hardware changes. Systems are backed-up nightly and the data is duplicated and sent to an offsite storage facility.

Monitoring of Data Quality

We will embed data validation checks within each questionnaire (i.e., required items, allowable ranges of response values) to ensure valid data is entered by participants at the time of data collection. Study staff will complete a verification process for each questionnaire record before 'locking' the record to prevent further changes. Only the PI will have administrative privileges to unlock completed records. Our study database will also include a scheduling program that tracks when research contacts occur and when visits or calls need to be scheduled based on the participants' condition.

Monitoring of Safety Data

Overall framework. The PI will be responsible for monitoring the safety and efficacy of the project, executing the Data and Safety Monitoring (DSM) plan, and complying with the reporting requirements. She will be assisted by Dr. Laura Zimmermann (study Co-Investigator), a board-certified Internal Medicine physician and Medical Director of the Rush University Prevention Center. The PI will provide a summary of the DSM report to NHLBI on an annual basis as part of the progress report. The DSM report will include the participants' sociodemographic characteristics, expected versus actual recruitment rates, retention rates across all study assessments, any quality assurance or regulatory issues that occurred during the past year, summary of Adverse Events (AEs) and Serious Adverse Events (SAEs), and any actions or changes with respect to the protocol. The DSM report to NHLBI will also include, when available, the results of any data analyses conducted. No interim analyses of the data are planned.

The PI will ensure the project is conducted according to the protocol. She will oversee data quality checks on a regular basis to ensure completeness and accuracy of ongoing data collection. Through weekly meetings with project staff, the PI will discuss issues related to progression of the project and factors that may

affect outcome including review of data quality and security, recruitment, and retention. The PI will be available for meetings with project staff outside the weekly allotted time to discuss any issues that may arise, including AEs or unanticipated problems. The PI will ensure all project staff have completed research ethics training as required by the IRB and are thoroughly trained on study procedures.

Adverse events. Adverse events are defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (e.g., abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. At all assessment points (i.e., Days 0, 28, 42, 56, and 120), we will monitor participant reports of adverse events related to: 1) nicotine withdrawal symptoms; 2) COPD symptoms, including COPD exacerbation, defined as an acute worsening of symptoms of COPD requiring new or increased doses of systemic corticosteroids, antibiotics, and/or emergency treatment or hospitalization; 3) utilization of outside study treatment (e.g., smoking cessation, mental health services, pulmonary rehabilitation, and medication use); and 4) any other symptoms participants believe may be related to study participation. Procedures for identifying and reviewing adverse events, including SAEs, are as follows: The research assistant will review each assessment to identify symptoms of moderate or greater severity, indicated by 1) Minnesota Tobacco Withdrawal Scale score $\geq$ 24, 2) COPD Assessment Test score $\geq$ 20, 3) any report of acute COPD exacerbation since the prior assessment, and/ or 4) any other symptom identified by participants to be of moderate or greater severity. In all cases of an assessment indicating symptoms of moderate or greater severity, an assessment summary will be emailed to the PI and study Co-I Dr. Zimmermann within 24 hours. Drs. Mathew and Zimmermann will review the assessment summary and respond within 24 hours to advise on appropriate actions to be taken. Actions may include continuing to monitor symptoms, contacting the participant for further assessment, advising that the participant contacts his or her healthcare provider, or advising that the participant presents to the Emergency Room.

Serious adverse events. A serious adverse event is defined as follows: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or a medically significant event that may require medical or surgical intervention. Risks of participation will be continually monitored and appropriate measures implemented in cases of unforeseen adverse events. If a serious adverse event occurs, the study PI will notify the IRB and the appropriate NHLBI program official. These events will be reported regardless of whether they appear to be related to study procedures. A summary of the SAEs that occurred during the previous year will be included in the annual progress report to NHLBI and the IRB Continuing Review.

Unanticipated problems. All unanticipated problems will be reported to the PI and study Co-I Dr. Zimmermann within 24 hours by research staff. The PI will notify the Rush University IRB and the appropriate NHLBI program official within five (5) business days of discovering any unanticipated problems involving risks to participants and others.

Trial Registration.

This project includes an applicable trial which requires registration on ClinicalTrials.gov. The PI will be responsible for compliance of registration and reporting of trial outcomes.

16.0 Data and if applicable, Specimen Banking:

N/A

17.0 Qualifications to Conduct Research and Resources Available:

The primary investigator, Dr. Mathew, is a licensed clinical psychologist with expertise in human laboratory-based and clinical research within the field of smoking cessation. All study staff will be directly supervised by Dr. Mathew and have been trained in human subjects research and current study procedures.

Ms. Chelsea Cox, study counselor, is an advanced graduate student in the Clinical Psychology Program at the University of Illinois-Chicago. She will conduct all study-related activities as a Rush University Independent Contractor. Ms. Cox has received training in cognitive-behavioral therapy, and will be trained and supervised by Dr. Mathew to deliver the study intervention.

Dr. Laura Zimmermann, study co-investigator, is a board-certified internal medicine physician (PCP) and medical director of the Rush University Prevention Center. Dr. Zimmermann will primarily assist the study PI with eligibility determination and medical oversight of study participants.

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