TITLE: Open Trial of Heart Rate Variability Biofeedback for Smoking Cessation

NCT05224050

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Document Date: 09/28/2022

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1.1 INTERVENTIONAL

RESEARCH PROTOCOL TEMPLATE

(HRP-503a)

STUDY INFORMATION

- **Title of Project:**

  Open Trial of Heart Rate Variability Biofeedback for Smoking Cessation

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- **Protocol Version and Date:**
  V9, 9.23.2022

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1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of the study is to conduct an open trial assessing the feasibility and acceptability of a refined heart rate variability biofeedback as a smoking cessation treatment adjunct for individuals who smoke cigarettes.

A. Objectives

The present investigation is an open pilot trial assessing the acceptability and feasibility of a heart rate variability (HRV) biofeedback smoking cessation treatment (HRVB-SCT) for individuals who smoke cigarettes. Primary significant findings will support the integration of HRVB as an acceptable and feasible treatment adjunct to standard smoking cessation treatment. Secondary significant findings will support the expansion of HRVB as a transdiagnostic treatment adjunct that alters cardiac vagal functioning to promote smoking cessation outcomes and emotional and behavioral regulation. Together, primary and secondary findings will support changes to the status quo of cognitive-behavioral intervention approaches and decrease the health and economic burden of smokers who suffer from emotional distress.

The goals are to: (a) assess the acceptability and feasibility of the HRVB intervention as an treatment adjunct to SCT (b) assess changes in smoking behavior and emotional distress and (c) collect additional information to assist in further refining the intervention for a larger R01 RCT.

B. Hypotheses / Research Question(s)

1. Primary Analysis: To complete a pilot open trial analyzing the feasibility and acceptability of HRVB-SCT. Intervention feasibility and acceptability will be indexed by measures of i participant attendance and practice adherence, participant self-report ratings of intervention satisfaction, effectiveness, appropriateness, and ease, and therapist reported technological limitations.
2. Secondary Analysis: To examine whether smokers receiving HRVB-SCT evidence improvements in: (1) smoking behavior as indexed by self-reported quit-day abstinence, verified by carbon monoxide breath analysis (CO<8ppm); sustained smoking cessation, verified by CO and salivary cotinine levels (<10ng/mg); and self-reported reductions in smoking rate and (2) emotional distress as indexed by self-reported anxiety, mood, and stress ratings. We expect HRVB-SCT will be associated with significant improvements in smoking and emotional health outcomes.

1.2 Research Significance

Cigarette smokers are disproportionately affected by mood and anxiety disorders (Lawrence, Mitrou & Zubrick, 2009), which impede cessation (Piper, Cook, Schlam, Jorenby & Baker, 2011; Zawertailo & Selby, 2015; Williams, Steinberg, Griffiths & Cooperman, 2013). This Stage II study will further test the feasibility, acceptability, and efficacy of an integrated, biobehavioral, transdiagnostic smoking intervention for individuals who smoke cigarettes. The neurovisceral integration model (Thayer & Lane, 2000; Park & Thayer, 2014) suggests that cardiac vagal functioning plays a critical role in the effective modulation of physiological, emotional, and cognitive processes necessary for self-regulation. Dysregulation in this system is observed across various forms of psychopathology (Moon, Lee, Kim & Hwang, 2013) and cigarette smoking (Thayer & Lane, 2000; Park & Thayer, 2014; Thayer, Åhs, Fredrikson, Sollers & Wager, 2012; Park, Van Bavel, Vasey & Thayer, 2013). Moreover, cardiac vagal activity is associated with emotional disorder severity and recovery (Jain, Cook, Leuchter, et al, 2014; Rottenberg, Salomon, Gross & Gotlib, 2005) as well as smoking onset and maintenance (Ashare, Sinha, Lampert, et al, 2012; Libby, Worhunsky, Pilver & Brewer, 2012; Crane, Gorka, Giedgowd, et al., 2016). HRVB interventions offer a simple and effective means of promoting self-regulation via restoration of the vagal system (Lehrer, Vaschillo E, Vaschillo B, et al., 2003; Lehrer, Vaschillo E, Vaschillo B., 2000; Lehrer & Vaschillo, E, 2004) but have not been applied to smokers with moderate emotional distress. Via the application of HRVB, the current proposal will target the vagal system to improve adaptive and flexible self-regulation (Kashdan & Rottenberg, 2010), thereby supporting smoking cessation and emotional health. Thus, a primary aim of this proposal is to develop and pilot test HRVB as a feasible, acceptable, and effective treatment adjunct for standard smoking cessation treatment (HRVB-SCT) in daily smokers.

Based on a strong body of empirical work demonstrating the benefits of HRVB in reducing anxiety (Henriques, Keffer, Abrahamson, & Horst 2011) and depressive symptoms (Patron et al., 2013; Rene, 2008) a secondary aim of this proposal is to evaluate the efficacy of HRVB-SCT in improving smoking and emotional health outcomes among adults who smoke. Transdiagnostic processes that promote avoidance and escape of emotional distress are implicated in the development and maintenance of cigarette smoking dependence (Baker, Piper, McCarthy, Majeskie & Fiore, 2004), and may also explain why individuals with depressive and anxiety symptoms are more susceptible to cigarette smoking dependence and poor cessation outcomes (Leventhal & Zvolensky, 2015). Existing smoking cessation interventions informed by these models largely rely upon cognitive-behavioral strategies (Gifford, Kohlenberg, Hayes, et al., 2011; Brown, Reed, Bloom, et al., 2013.) However, automatic visceral responses to emotional distress may impede the utilization of intentional self-control strategies. Biobehavioral interventions that directly address transdiagnostic *physiological* processes may offer a more targeted means of improving outcomes, thereby identifying an alternative treatment mechanism. Moreover, the development of biobehavioral interventions may improve smoking cessation outcomes for smokers with moderate emotional distress who are not responsive to, or are less receptive of, cognitive-behavioral interventions.

The proposal will use a staged model for developing and standardizing behavioral interventions, as indicated by NIDA. The first phase (i.e., Phase 1A) of the project has focused on drafting, piloting, and modifying an integrated HRVB smoking cessation treatment (HRVB-SCT). The second phase of the project (Phase 1B) will focus on assessing the acceptability and feasibility of treatment delivery, fidelity, and potential for improving smoking cessation outcomes and reducing emotional distress. Data collected during this time will also potentially inform a larger R01 application of a RCT of HRVB-SCT to evaluate smoking and emotional distress outcomes and explore transdiagnostic physiological and cognitive-affective treatment mechanisms.

1.3 Research Design and Methods

A. Research Procedures

Overview: The current proposal represents the second phase of treatment development and will involve evaluating the acceptability and feasibility of HRVB-SCT treatment deliveryas well as examining whether participants receiving HRVB-SCT evidence improvement in smoking outcomes and emotional health. Individuals enrolled in this pilot clinical trial will include 30 adult daily cigarette smokers..

Recruitment Approach: Smokers interested in receiving free smoking cessation treatment will be recruited from the greater Rutgers, New Brunswick community via posters, leaflets, mailings, online advertisements, community outreach (i.e., meetings with local organizations and treatment providers who work with cigarette smokers), and listservs. We will determine eligibility via completion of a structured phone interview and in-person assessment.

Pre-Study Telephone Screening: Upon interacting with study recruitment materials, prospective participants will be given the option to complete a virtual pre-phone screen via QR code, or to contact the lab in which the pre-phone screen will be conducted verbally. After the initial pre-screen, if prospective participants are deemed eligible for the next steps, they will complete a phone interview where they will be provided with an overview of the study and assessed for detailed inclusion/exclusion criteria (e.g., readiness to quit, current smoking status, and health exclusionary criteria. Participants who remain interested in the study and appear to meet initial study inclusion/exclusion criteria will be scheduled for a remote (i.e., Zoom) completion of the MINI-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998; see ***Table 2***), a semi-structured clinical interview, to confirm inclusion/exclusion diagnostic criteria. If ineligible, the reason for exclusion will be tracked, and they will be referred to the *Rutgers Tobacco Dependence Program*, a free local clinic offering evidence-based pharmacological and individual

and group cessation treatments. Following confirmation of pre-screening eligibility criteria participants will be scheduled for their laboratory visit within one week and sent detailed instructions on behaviors to avoid that may confound physiological assessment (e.g., vigorous physical activity or consumption of caffeine within 2 hours, alcohol use within 12 hours). Lab sessions will be scheduled after 12 PM and at least four hours post-usual waking time. This will help control for high urges and withdrawal and low nicotine plasma levels associated with overnight deprivation.

Baseline and Intervention Session 1 (approximately 190 minutes): In order to expedite their baseline appointment, prior to their visit, participants will be emailed the consent form to review ahead of time as well as well as meet with study personnel to review consent and fill out baseline surveys. Afterwards, if found eligible, subjects will be emailed and asked to complete a battery of self-report measures on Qualtrics, an online survey portal. Questionnaire data will be used to assess self-reported symptoms of depression, anxiety and stress, general health, a range of smoking relevant processes, other substance use, and self-reported and behaviorally indexed distress tolerance (see ***Table 2***). If the participant has not completed the self-report battery via Qualtrics prior to the in-person visit, they will complete it via Qualtrics in the lab before proceeding with the rest of the baseline procedures. At the start of the visit, participants will meet with an independent assessor who will verify smoking status via CO analysis of breath sample, re-confirm study inclusion/exclusion criteria and obtain written informed consent. Participants will next complete a physiological assessment during which electrocardiograph and impedance cardiography recordings will be collected. In addition to recording resting levels of participant physiology, participants will also be asked to complete a series of computerized cognitive tasks while physiological recordings are continuously assessed. An objective measure of the participant's height (inches) weight (lbs) will also be collected using the lab's medical grade scale. Because the baseline session also serves as the first respiratory and SCT intervention session, participants will be offered a 1-hour break and snack after completing all baseline assessments and continuing on to complete the remainder of study visit procedures.

HRVB-SCT Intervention: After completing the baseline procedures, participants will be assigned to work with two trained study personnel for the SCT and HRVB intervention components, respectively..

HRVB Intervention: The initial in-person intervention session will last approximately 60 minutes. All remaining intervention sessions will last approximately 30-40 minutes (see ***Table 1***). The HRVB intervention is designed to maximize respiratory sinus arrhythmia (RSA) by breathing at the resonance frequency of each individual's baroreflex system, which varies around six breaths per minute. When breathing at this frequency, the effects of RSA and the baroreflex interact, producing large increases in low frequency (LF) power, reflecting an increase in both functions, as indexed via LF-HRV. Note that HF-HRV during resonance frequency breathing no longer can be used as an index of vagal activity (i.e., RSA), because RSA is now represented in the LF range (Lehrer et al., 2003). Regular practice of resonance breathing appears to result in long-term improvements in vagus nerve activity that indeed can be indexed via HF-HRV (i.e., RSA) during baseline (i.e., non-biofeedback-period) breathing. Participants will complete 7 sessions of HRVB, two in-lab sessions and five remote sessions, over the course of 6 weeks. Sessions are front-loaded with two sessions occurring during the first week (one in-lab session and one remote session) to ensure accurate training to promote quit day success (see ***Table 1***). Clinicians will be trained in the application of HRVB including identifying and instructing participants to breathe at their resonance frequency using the Inner Balance device by HeartMath software. The Inner Balance provides real time display of HRV and coherence recordings via a photoplethysmograph ear clip sensor that connects to the Inner Balance smartphone application via Bluetooth. This can be viewed by the participant via the Inner Balance smartphone app while simultaneously being shared with their respiratory therapist via Zoom. The combination of these features allow for respiratory therapists to provide participants with ongoing remote instruction including real time corrective feedback intended to maximize HRV. Inter-beat interval data is stored via HeartMath's cloud storage and can be downloaded

by the research team remotely to assess intervention fidelity. HeartMath has a history of working with researchers conducting clinical trials of HRVB. The Inner Balance software was selected for this trial given its usability, portability, and cost-effectiveness.

Homework Practice: Participants will be asked to practice HRV biofeedback 20 minutes daily, in bouts of 5 minutes. Practicing for 20 minutes a day is necessary to most optimally train the reflexes that will help participants control stress response, cravings, and many other symptoms related to the autonomic nervous system (Lehrer, Vaschillo, & Zucker, 2013). In addition to verifying practice outside of intervention sessions, the Inner Balance device allows the investigators to download biofeedback data for quality assessment. Participants will also be prompted via *Metricwire*, a separate web-based platform developed for ecological momentary assessment [EMA], to provide ratings of cigarette craving and withdrawal, as well as relaxation and distress, on a 100-point scale both before and after completing daily respiratory training practice. This system is accessed using a free smartphone app, which allows the study team to acquire daily diary data from a participant's smartphone and is secure, private, and HIPAA compliant. The *Metricwire* app will additionally be used to remind participants to practice on three occasions per day; this reminder will include information regarding their potential compensation for completing their respiratory training practice. Participants will have the option to immediately complete EMA prompts, and subsequently practice, or to complete ratings at a later time. Participants may also open the app on their own (i.e., self-initiated) to complete ratings at their own convenience. The goal of incorporating EMA data collection is to promote homework completion, increase adherence to and engagement with the assigned intervention, and provide quantitative data regarding the relation between breathing practice and craving, withdrawal, relaxation, and distress while minimizing data-entry error or recall bias. All participants will use *Metricwire*. If participants do not have a smartphone which supports the study apps, a smartphone will be loaned to them for the duration of their study participation.

Smoking Cessation Treatment (SCT)*:* All participants will receive six smoking cessation counseling sessions lasting approximately 20-30m each. The first will also occur in-person, after the baseline portion of the initial in-person baseline assessment. In total, participants will complete two in-person SCT sessions (Sessions 1 and 7) and four remote teletherapy sessions via Zoom (Sessions 2-5; see ***Table 1***). Trained research personnel providing SCT will use a protocol adapted from the National Cancer Institute's *Clear Pathways* guide. Each participant will be provided with an adapted version of *Clear Pathways* and be given weekly assignments. Participants will receive an 8-week supply of transdermal Nicotine Replacement Therapy (NRT) patches, at their in-person baseline visit. Smoking cessation counselors will provide remote instruction and feedback on NRT use. Specifically, participants will be instructed to place their first nicotine patch upon waking on their quit day (Fiore et al., 2008). Participants who smoke ≥ 10 cigarettes daily will begin with a 2-week course of 21 mg patch, followed by 4-week taper of 2-weeks of the 14mg and 2-weeks of the 7mg patch. We will recommend that patients who smoke 5-9 CPD begin with the 14 mg patch, as indicated by clinical practice guidelines.

In-Lab Recording Sessions: In-lab physiological recordings will be conducted at baseline and in-person at weeks 6 (i.e., 1-month post-quit) and 15 (i.e., 3-months post-quit). to assess both within and between-session changes in cardiac vagal parameters (i.e., vagal tone and flexibility). An objective measure of the participant's height (inches) and weight (lbs) will also be collected using the lab's medical grade scale. We will use Biopac to obtain five 5-minute recordings of continuous measures of electrocardiograph (ECG), respiration, blood pressure, and impedance cardiograph (IC). Following a 5-minute resting period, participants will complete the Plain Vanilla Task. This is a low cognitive task in which participants are asked to count the number of a particular color rectangle that appear on their screen. Following Plain Vanilla, participants will complete a 5-minute dot-tracking task. While viewing a computer screen, participants are oriented to several yellow circles that appear among many gray circles. The yellow circles then change to gray, and participants are asked to track them as they move around the screen. This cognitively demanding dot-tracking task has reliably been used in the past as an index of vagal flexibility

as indexed by pre- to post-changes in HF-HRV (Muhtadie, 2015). HF-HRV average during the 5-minute baseline will be used as our index of vagal tone.

Remote Intervention Sessions: During sessions 1b, 2, 3, 4, and 5, teletherapy will be used with participants communicating with interventionists remotely (see ***Table 1***), using their personal or a lab provided smartphone, a personal or lab provided computer/tablet, and a HIPAA compliant platform (e.g., Zoom). Due to the ongoing coronavirus pandemic, we will be conducting the intervention primarily through remote means to account for the safety of and to reduce close and direct in-person contact between personnel and participants. Remote sessions are also in place to increase the ecological validity of the intervention. Teletherapy for the majority of intervention sessions will allow for participants to meet with their assigned respiratory and SCT therapists online from a private, internet secure location of their choosing to complete intervention sessions.

Five remote respiratory training sessions and four remote SCT sessions will occur. During HRVB respiratory training sessions, participants will be instructed to use the Inner Balance device and smartphone applications while simultaneously sharing their screen via Zoom while additionally attending the Zoom session on their laptop or tablet. Therapists will provide real time feedback and instruction during the session while assessing their progress via screenshare and while viewing the participant through their laptop/tablet. SCT sessions will also occur via Zoom.

Table 1. Summary of Integrated HRVB-SCT Intervention Protocol by Session

Week	Session	Core Components	Time	Pay
Week 1a^{L} (Baseline)	**Screener**	• Consent, questionnaires, assess abstinence via CO scheduling, set quit date	30	$35 (if ineligible)
	IA	• Recording session: Baseline, Plain Vanilla, Dot Tracking	50	
(Session 1)	**SCT S1**	• SCT program introduction and orientation to *Clear Pathways* • Goals: Understanding why you smoke, health effects of smoking/quitting, reasons to quit, assess and build confidence	30	$10
	HRVB S1	• Intervention Overview • Recording session • Goal: Introduce HRVB Breathing using pacer and Inner Balance	60	
	EMA	• Introduction/enrollment to homework		

Week 1b[V]	**SCT S2**	• Goals: Review quit date, plan for quit day (week 2), troubleshoot potential barriers to quitting • Introduce NRT and instructions on how to use the patch	30	$10
	HRVB S2	• Biofeedback practice session • Goal: Introduce biofeedback • Assign homework: Practice 4x/day for at least 20m	30	
	EMA	• Assess homework compliance and surveys cravings, withdrawal, distress, and relaxation symptoms		
Week 2[V] (Quit Day)	**SCT S3**	• Review homework • Goals: Continue to discuss and revise quit plan, monitor motivation to quit, trouble-shoot/learn from failures	30	$10
	HRVB S3	• Biofeedback practice session • Goal: Review and adjust Inner Balance HRVB • Assign homework: Practice 4x/day for at least 20m	30	
	EMA	• Assess homework compliance and surveys cravings, withdrawal, distress, and relaxation symptoms		up to $105 for HW practice
Week 3[V] (1W post-quit)	**SCT S4**	• Review homework • Goals: Highlight successes, troubleshoot potential barriers to quitting, preventing relapse • Assess NRT use side effects, questions/concerns, adherence	30	$10
	HRVB S4	• Biofeedback practice session • Goal: Review and adjust Inner Balance HRVB • Make post-quit adjustments to HRVB, assess adherence, motivation • Assign homework: Practice 4x/day for at least 20m	30	

	EMA	• Assess homework compliance and surveys cravings, withdrawal, distress, and relaxation symptoms		up to $105 for HW practice
Week 4[V] (2W post-quit)	**SCT S5**	• Review homework • Assess abstinence status, revise quit plan to maintain abstinence or resume cessation, • Provide additional NRT	30	$10
	HRVB S5	• Biofeedback practice session • Goal: Assess adherence, motivation, trouble-shoot • Assign homework: Practice 4x/day for at least 20m	30	
	EMA	• Assess homework compliance and surveys cravings, withdrawal, distress, and relaxation symptoms		up to $105 for HW practice
Week 5[V]	**HRVB S6**	• Biofeedback practice session • Goal: Assess adherence, motivation, trouble-shoot • Assign homework: Practice 4x/day for at least 20m	30	$10
	EMA	• Assess homework compliance and surveys cravings, withdrawal, distress, and relaxation symptoms		up to $105 for HW practice
Week 6[L] (1M post-quit)	**IA**	• 1MFU Survey • Recording session: Baseline, Plain Vanilla, Dot Tracking	50	$35
	SCT S6	• Assess quit status via CO analysis • Goal: Assess abstinence status, offer of support, encourage resumption, provide additional NRT	30	
	HRVB S7	• Recording session • Goal: obtain commitment to continue practice	30	
	EMA	• Assess homework compliance and surveys cravings, withdrawal, distress, and relaxation symptoms		up to $105 for HW practice

Week 15[L] (3M post-quit)	**IA**	• Assess abstinence via CO and cotinine • Recording session: Baseline, Plain Vanilla, Dot Tracking	60	$50 for attending 3 mo F/U $50 bonus for attending 6/7 sessions
	Research Coordinator	• 3MFU survey, Exit interview	30	

[L]In-lab intervention session; [V]Virtual intervention session

Participants will be paid up to $15 each day for past week at-home breathing practice during HRVB sessions 3, 4, 5, 6, and 7, corresponding with weeks 2-6. Specifically, participants will be paid $5 for their first at-home practice lasting at least 5-minutes on a given day, $5 for their second at-home practice lasting 5-minutes, and $5 for any additional at-home practice lasting at least 5 minutes. Practice will be verified via the Inner Balance app, which records practice sessions, and the Metricwire app. In order for participants to be eligible for homework compensation, a practice session must last a minimum of 5 minutes, and they must complete pre- and post-ratings of craving, withdrawal, relaxation and distress.

Table 2. Study Measures Table	**PS**	**BL**	**W**	**Q**	**2W**	**1M**	**3M**
	Phone Screen:						
Interview: The phone screen will be administered prior to study enrollment to help determine whether interested participants are eligible.	**X**						
Readiness to Quit Ladder: Single-item measure that includes ten response options that assess motivation to quit along a continuum. Options range from 10, "I have quit smoking and I will never smoke again", to 1, "I enjoy smoking and have decided not to quit smoking for my lifetime. I have no interest in quitting". As such, higher scores on this measure indicate higher readiness to quit (Biener et al., 2003).	**X**						
Risk Assessment: Study personnel will receive extensive training in risk assessment and follow the attached protocol should a potential participant or consented participant indicate suicidality/homicidality or extreme distress.	**X**						
Covid-19 Screening: Study personnel will assess participants for recent positive Covid-19 test results, developing Covid-19 related symptoms, and recent exposure to others who may have tested positive for Covid-19. This screening is conducted to ensure the health and safety of both participants and study personnel.	**X**						
The Mini International Neuropsychiatric Interview 7.0.0 (MINI): Semi-structured interview guide for making the major DSM-5 diagnoses. Sections C, I, J, and K are administered to screen for Mood, Psychotic, and Substance Use Disorders. The MINI can be used to make diagnoses either categorically (absent or present) or dimensionally (Sheehan et al., 1998).	**X**						
	In Person, Virtual Interview, and Qualtrics Measures:						
Participant Information Sheet: Questionnaire used to confirm		**X**					

inclusion/exclusion criteria.							
Medical Screening Questionnaire: Questionnaire used to confirm inclusion/exclusion criteria.		X					
Participant Contact Info: Used to document best means to contact participant for study communication (includes request for permission to text).		X					
Demographic Information: Used to confirm inclusion/exclusion criteria.		X					
MacArthur Scale of Subjective Social Status: Single-item measure that assesses a person's perceived rank relative to others in their group. Participants view a drawing of a ladder with 10 rungs and identify which rung reflects their perceived status based on the description provided (Adler, Epel, Castellazzo, & Ickovics, 2000).		X					
Smoking History Questionnaire (SHQ): 30-item questionnaire used to assess participants smoking history and patterns of use. Items pertain to smoking rate, age of onset of smoking initiation, and years being a daily smoker (Brown et al., 2002).		X					
Fagerström Test of Cigarette Dependence (FTCD): 7-item scale use to evaluate the quantity of cigarette consumption, the compulsion to use, and nicotine dependence. The measure has both yes/no items (scored as 1 or 0) and multiple-choice items (scored from 0-3). These scores are then summed to give a total score from 1-10 where the higher the score the more intense the subject's nicotine dependence is (Fagerström, 1978 & 2012).		X	X			X	X
Brief Wisconsin Inventory of Smoking Dependence Motives (WISDM-34): 34-item self-report questionnaire which assesses theoretically-derived motivational domains of smoking across 13 subscales that have acceptable internal consistency, are differentially present across levels of smoking heaviness, and have multi-dimensional structure. Participants use 7-point Likert scale(1=not at all true of me to 7=extremely true of me) to indicate nicotine dependence. Its reliability and validity has been proven to be good (Stevens et al., 2010).		X				X	X
Difficulties in Emotion Regulation Scale (DERS): 36-item, self-report scale that assesses multiple aspects of emotional dysregulation. The measure includes 6 subscales, Nonacceptance (*When I'm upset, I feel guilty for feeling that way*), Goals (*When I'm upset, I have difficulty concentrating*), Impulsivity (*When I'm upset, I lose control over my behaviors*), Awareness (*I am attentive to my feelings*; reverse coded item), Strategies (*When I'm upset, I believe that I'll end up feeling very depressed*), and Clarity *(I have difficulty making sense out of my feelings*). All items are score on a 5-point scale, where 1 = *almost never* (0-10%) and 5 = *almost always* (91-100%). The measure also yields a global score (Gratz & Roemer, 2004).		X				X	X
Smoking and Weight Eating Episodes Test (SWEET): 10-item, self-report measure used to assess the extend to which individuals smoke for specific reasons related to eating and weight concerns. Responses are rated on a 5-point Likert scale ranging from (1) *never* to (5) *always.* This scale has demonstrated good psychometric properties and has been validated in male and female daily cigarette smokers (Adams et al. 2011; Farris et al. 2018)		X				X	X
Distress Tolerance Scale (DTS): 15-item scale used to assess participants' perception of their ability to tolerate mental distress. Items		X				X	X

(e.g. "I can't handle feeling distressed or upset") answered on 5-point Likert-type scales ranging from (1) strongly agree to (5) strongly disagree evaluate participants' ability to experience and endure negative emotional states and includes scales that assess appraisal, tolerance, absorption, and regulation. This scale contains good psychometric properties, including high internal consistency (Simons & Gaher, 2005).							
The Urgency, Premeditation, Perseverance, and Sensation Seeking Impulsive Behavior (UPPS-P): 20-item measure used to assess characteristics of personality, such as how rashly participants respond in response to negative moods, and determines how they may contribute to impulsive behavior. Items are rated on a 4-point Likert-type scale (1 = Agree Strongly to 4 = Disagree Strongly) to indicate how much each statement applies to them. The scale demonstrates good internal consistency and convergent and divergent validity (Whiteside & Lynam, 2001; Cyders, Smith, Spillane, Fischer, Annus, & Peterson, 2007).		X				X	X
Somatic Symptoms List (SSL): 30-item measure of fear of non-anxiety-related sensations *(It scares me when I have an earache*). Items are rated on 5-point Likert scale ranging from very little to very much and show good internal consistency (Norton, & Edwards, 2015).		X					X
Nicotine Dependence Syndrome Scale (NDSS): 19-item questionnaire designed to yield continuous measures of multiple theoretically-derived dimensions of dependence. It yields scores for (a) Drive, which captures craving and withdrawal and the subjective sense of compulsion to smoke; (b) Priority, the behavioral preference of smoking over other reinforces; (c) Tolerance, reduced sensitivity to smoking's effects; (d) Continuity, the regularity of smoking; and e) Stereotypy, the rigidity of smoking patterns and tendency to smoke in the same way regardless of circumstances. It also yields a single summary score (NDSS-T) for dependence. The scale has been validated in adult population and treatment samples, and validated variations are available for teen smokers (Shiffman, Waters, & Hickcox, 2004).		X					X
The Pittsburgh Sleep Quality Index Scale (PSQI): 19 item self-rated questionnaire used to assess sleep quality and disturbances over a 1-month time interval. These 19 items are grouped into seven components that reflect standardized areas routinely evaluated in clinical assessments with patients who report sleep/wake complaints: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction. Items are equally weighted and rated on a 0 to 3 scale (0=no difficulty to 3=severe difficulty). The seven component scores are summed to produce a global score (range 0 to 21), with higher scores indicating worse sleep quality. The clinimetric and clinical properties of the PSQI (acceptable internal homogeneity, consistency, and validity) support its use in psychiatric clinical practice and research activities (Buysse et al., 1988).		X				X	X
Multidimensional Assessment of Interoceptive Awareness (MAIA): 32 item measure that assesses multiple dimensions of interoception by self- report (Mehling, Price, Daubenmier, Acree, Bartmess, & Stewart, 2012).		X				X	X
The Intolerance for Smoking Abstinence Discomfort (IDQ-S): 17-		X				X	X

item questionnaire to assess the participants ability to tolerate the acute discomforts of recent smoking abstinence. The subscales measure Withdrawal Intolerance (12-items) and Lack of Cognitive Coping (5-items). Items are rated on a Likert scale ranging from 1= strongly disagree to 5 = strongly agree. The mean of all items is used for the total score for each scale (Sirota, Rohsenow, MacKinnon, Martin, Eaton, Kaplan, & Swift, 2010).							
Body Vigilance Scale: 4 item measure that assesses a respondent's degree of sensitivity to internal bodily sensations such as palpitations or dizziness. Respondents indicate on an 11-point Likert Scale (0 = none to 10 = extreme) (Schmidt, Lerew, & Jackson, 1997).		**X**				**X**	**X**
Boredom Susceptibility Subscale: 10-item yes/no subscale of the Sensation Seeking Scale used to assess susceptibility to boredom (Zuckerman & Link, 1968).		**X**				**X**	**X**
Mindful Attention Awareness Scale: 15-item scale used to assess dispositional mindfulness, specifically, open or receptive awareness of and attention to what is taking place in the present (Brown & Ryan, 2003).		**X**				**X**	**X**
Fagerstrom Test for Nicotine Dependence: 6 item measure that assess the intensity of physical addiction to nicotine. The items measure the quantity of cigarette consumption, the compulsion to use, and dependence. The yes/no items are scored from 0 to 1 and the multiple-choice items are scored from 0 to 3 (Fagerstrdm, 1978).		**X**	**X**				
Sensitivity to COVID-19 Health Symptoms Scale (SCHSS): 14-item scale used to measure physical symptoms Covid-19 related anxiety.		**X**					
Fear of Coronavirus-19 Scale: 7-item scale used to measure physical and psychological symptoms of Covid-19 related fear (Ahorsu et al., 2020).		**X**					
COVID-19 Stress Scales: 36-item measure designed to assess COVID-19 related stress and worry that occurred in the past 7 days. Items are split into 6 sub-scales: Danger (*I am worried about catching the virus*), Socioeconomic consequences (*I am worried about grocery stores running out of food*), Xenophobia (*I am worried that foreigners are spreading the virus in my country*), Contamination *(I am worried that people around me will infect me with the virus*), Traumatic stress (*I had trouble sleeping because I worried about the virus)*, and Checking (*Social media posts concerning COVID-19*). Participants answer along a 5-point Likert scale (Taylor et al., 2020).		**X**					
Pre, Mid, and Post-Intervention Acceptance and Feasibility Ratings (Participant and Therapist versions): Participants will be asked to provide ratings of intervention helpfulness, intervention satisfaction, commitment, negative feelings during session, and degree of difficulty understanding intervention content. Therapists will report incidences of technological issues, distractions in participant remote environment and their respective influence on treatment delivery.			**X**			**X**	**X**
Carbon Monoxide Analysis of Breath Sample: CO analysis will be used to verify eligibility and abstinence status. Analysis will rely on the Bedfont handheld piCO Smokerlyzer and iCOquit Smokerlyzer, which will be used for in-person and remote verification, respectively.		**X**		**X**		**X**	**X**
Daily Information Sheet: Details participants' cigarette use, alcohol consumption, substance use, medications, meals consumed, and NRT-related side effects		**X**	**X**	**X**	**X**	**X**	**X**
Craving/Withdrawal Visual Analog Scale (CW-VAS): Measures craving as well as the severity of withdrawal symptoms ranging from 0			**X**	**X**	**X**	**X**	**X**

(none or non-existent) to 100 (extreme).							
Timeline Followback: Used to assess ongoing cigarette, e-cigarette, patch, alcohol, and other tobacco and substance use (Sobell & Sobell, 1992 & 1995).		X	X	X	X	X	X
Positive and Negative Affect Schedule: Used to assess current emotional states before and after intervention sessions (Watson & Clark, 1988 & 1999).		X	X	X	X	X	X
Felt Arousal Scale (FAS): Used to measure activation on a 6-point scale from low (1 point) to high arousal (6 points) (Svebak & Murgatroyd, 1985).		X	X	X	X	X	X
Distress Intolerance Index: Used to assess participants' perceptions of their ability to tolerate mental distress (McHugh & Otto, 2011).		X				X	X
Short-form Health Survey (SFH): Used to assess quality of life in regard to health (Ware, Kosinski, & Keller, 1996).		X		X	X	X	X
Thoughts about Abstinence: Used to assess commitment to complete abstinence including importance and confidence (Hall, Havassy, & Wasserman, 1991).		X		X	X	X	X
Barriers of Cessation Scale:19-item scale that is made up of three subscales: 1) Addiction Barriers scale ("Fear of failing to quit"), 2) External Barriers subscale ("No encouragement of help from friends"), 3) Internal Barriers subscale ("Feeling less in control of your moods"). The scale also includes a "gaining weight" item. The score scale ranges from 1 to 3, where 0 = not a barrier/not applicable and 3 = large barrier (Macnee & Talsm, 1995).		X		X	X	X	X
Minnesota Nicotine Withdrawal Scale: Used to measure the urge to smoke (craving), depressed mood, anxiety, irritability, frustration, or anger, concentration levels (Cappelleri, Bushmakin, Baker, Merikle, Olufade, & Gilbert, 2005).		X		X	X	X	X
Depression Anxiety Stress Scale (DASS-21): Used to assess past week symptoms of depression, anxiety, and stress (Henry & Crawford, 2005).		X		X	X	X	X
Questionnaire of Smoking Urges: 10-item questionnaire reflecting strong desires or intention to smoke, as well as anticipation of relief from negative affect with desire to smoke (Cox, Tiffany, & Christen, 2001).		X		X	X	X	X
Anxiety Sensitivity Index 3 (ASI-3): 18-item measure that assesses the basic dimensions of anxiety sensitivity: fear of physical symptoms (*When my throat feels tight, I worry that I could choke to death*), fear of cognitive symptoms (*It scares me when I am unable to keep my mind on a task*), and fear of publicly observable symptoms (*I think it would be horrible for me to faint in public*). Responses can range from 0 = *very little*, to 4 = *very much* (Taylor et al., 2007).		X					X
Frustration Discomfort Scale (FDS): 35 item measure to assess participants' intolerance of distress or frustration. Items represent potential beliefs which participants may possess (e.g., "I can't stand having to persist at unpleasant tasks") and are rated on a 5-point Likert-type scale (1 = absent to 5 = very strong). Internal reliability, divergent validity, and discriminative validity are supported (Harrington, 2005).		X					X
Dot Tracking Task: Will be used to manipulate participants' attentional demands. During this task, participants are presented with 12 dots on a computer screen, 3 of which are initially yellow, and 9 of which are gray. The yellow dots subsequently turn gray, and all the dots move at		X				X	X

random around the screen. When they come to a stop, participants are to remember which dots were initially yellow. There are a total of 12 trials that increase in difficulty. During the task, respiration, pulse plethysmograph, heart rate and cardiac output are continually assessed. The change in these parameters from resting to that observed during dot tracking serves as an assessment of change in parasympathetic and sympathetic nervous system activation as a function of attentional demands. The construct indexed, vagal flexibility, is linked to the ability to adaptively respond to stress (Muhtadie, Koslov, Akinola, & Mendes, 2015).							
Smoking Abstinence Expectancies Questionnaire (SAEQ): 28-item self-report questionnaire evaluates the the expected short-term psychological and physiological consequences of abstaining from smoking. Full-scale and subscale (Negative Mood, Somatic Symptoms, Harmful consequences and Positive Consequences) scores exhibit good internal consistency, convergent and discriminant validity, and test-retest reliability (Abrams, K., Zvolensky, M., Dorman, L., Gonzalez, A., & Mayer, M. (2011).		**X**					**X**
Barkley Deficits in Executive Functioning Scale-Short Form (BDEFS-SF): 20-item short form of the BDEFS assessing daily executive functioning, such as self-regulation of emotions and time management. Participants will use a 4-point Likert-type scale (1 = never or rarely to 4 = very often) to indicate how often they experience each statement (e.g., "Make impulsive comments to others"). This scale has demonstrated good reliability and validity (Barkley, R. A. (2011).		**X**					**X**
5-Trial Adjusting Delay Task: a novel method of obtaining a delayed discount rate in less than 1 minute such that participants answer only 5 questions as a result of branch logic which generates individually tailored choice options from 31 possible items (Koffarnus, M. N., & Bickel, W. K. (2014).		**X**					**X**
Adult ADHD Self-Report Screening Scale (ASRS-5): 6-item measure that is short, easily scored, and can detect the vast majority of adult attention-deficit/hyperactivity disorder cases in the general population with high sensitivity and specificity. The scale has excellent cross-validated concordance with blinded clinical diagnoses of *DSM-5* adult attention-deficit/hyperactivity disorder (Kessler, et al., (2005).		**X**					**X**
Perceived Stress Scale (PSS10): 10 item measure designed to assess stress perceptions on a 5-point Likert scale ranging from 0 = *never* to 4 = *very often*. Items were designed to tap how unpredictable, uncontrollable and overloaded respondents find their lives. Construct validity, internal reliability and predictive reliability are supported (Cohen, S., & Williamson, G. (1988).		**X**					**X**
Cigarette Purchase Task (CPT): 26-item measure used to assess trait demand for cigarettes or the behavior-maintaining properties of nicotine. Participants report the number of hypothetical cigarettes they would purchase for consumption across varying prices (i.e. $0.00-9.00). This results in a curve that represents the relationship between the demand for cigarettes and escalating price. The demand curve is comprised of the following indices: intensity (number of cigarettes consumed at unrestricted cost), breakpoint (price at which consumption is suppressed to zero), Omax (peak expenditure for cigarettes), Pmax (the price at maximum expenditure for cigarettes), and elasticity (the degree to which consumption decreases with increasing price)		**X**					**X**

(MacKillop, et al., (2008)							
Exit Interview: Used to collect information about the participant's understanding of the rationale for the intervention, the degree to which the information was applicable and relevant, and their overall feedback and thoughts on the intervention to inform adjustments to the subsequent R01 trial.							**X**
Cotinine Sample: Biochemical verification of smoking abstinence will support point prevalence abstinence at the 3m follow-up via the Salimetrics Enzyme Immunoassay Salivary Cotinine Kit.							**X**
Ratings of Session Protocol Adherence and Examination of Physiological Data for Intervention Accuracy: Recorded sessions will be coded in order to assess accuracy of intervention delivery.							**X**

HRVB and SCT Clinician Training and Supervision: Clinicians will receive a minimum of 8 hours of training from study investigators in the application HRVB and will have to complete a minimum of 5 practice sessions prior to seeing participants. Clinicians will be approved for the study following careful assessment of their protocol adherence, competent application of skills, by the PI. Clinicians will have to demonstrate general knowledge in appropriately modifying HRVB for participants, navigating and addressing common barriers (e.g., discomfort, dizziness), addressing motivation and adherence, instructing and monitoring participants both in-lab and virtually, and will role-play managing several common issues that arise during HRVB before they are assigned participants. Fidelity data will be collected via independent evaluators who will use an HRVB-specific rating scale to assess protocol adherence, implementation of strategies and skills in-session. Designated study assessors will be asked to code audio-recordings, specifically, 25% of the initial eight HRVB sessions provided to participants will be coded (Muse & McManus, 2013). Fidelity will additionally be assessed by Co-I Farris who will review recorded physiological data from baseline and 3-month follow up to rate whether participants, under therapist instruction, received adequate resonance between heart rate and blood pressure, central to the success of the intervention. Measures of treatment fidelity are critical to the current proposal given it has never been applied to smokers and requires ongoing monitoring of participant behavior and physiology. For example, slow-paced breathing is sometimes accompanied by compensatory changes in breath depth, a process that can inadvertently decrease end tidal carbon dioxide ($etCO_2$), which is contraindicated and will not result in desired RSA oscillations; clinicians will need to know how to identify and remedy contraindicated breathing patterns, such as hyperventilation, both during in-lab and remote sessions, to promote accurate HRVB application.

Clinicians will additionally receive at least 5 hours of training in the delivery of SCT. SCT training will include psychoeducation regarding the prevalence of smoking, common beliefs about smoking and cessation, as well as specific training in the co-occurrence of depression and anxiety in smokers and implications for intervention. Clinicians will be trained in the administration of the adapted manual, teaching of skills to participants, conducting the intervention in-lab and virtually, and how to develop personalized smoking cessation plans. Clinicians will complete several role play sessions so that they are equipped with the various issues that commonly impede smoking cessation, and how to appropriately respond. In addition to training, clinicians will be asked to record a minimum of 3 practice sessions. Prior to being approved for the study, the PI will review for adherence to the study protocol and determine if additional training is needed. All clinicians will be provided with additional feedback following review of recorded sessions.

Clinical supervision will occur on a weekly basis with the PI for 2 hours. The first hour will be spent reviewing HRVB sessions, and the second hour will be spent reviewing SCT sessions. The purpose of supervision is to provide additional training and support to clinicians to ensure fidelity of the intervention. In addition, issues regarding homework compliance and participant retention will be addressed.

Potential Problems and Alternative Strategies: Clinicians will be trained to be flexible in HRVB application depending on the needs of the patient. For example, additional use of the pacer or biofeedback may be indicated for an individual who is struggling with appropriate respiratory pacing or achieving maximal oscillations, respectively. Alternatively, both strategies may be abandoned, and the clinician may choose instead to focus on breath depth and quality, if a patient is experiencing difficulty with hyperventilation (e.g., decreases in expired tidal volume of CO_2). Because at-home practice is critical to the promotion of long-term improvements in vagal cardiac activity, the first two weeks will include both an in-person and virtual training session. To address adherence, we have put in place several strategies. Participants who do not have smart phones will be given one for use during the duration of the study. At-home practice will be characterized as a tool that participants may use in place of smoking. In this manner, participants may begin to reduce smoking and conceptualize practice as a helpful skill, rather than a time-consuming task. Such an approach is bolstered by the ease of use of the phone app, which is discreet, on their person, and will serve as a practice cue. To test feasibility of the intervention, without offering additional incentive, our participants will not receive additional adherence reinforcement.

In accord with clinical practice guidelines, participants will begin NRT on the morning of their quit date and will be provided with a full 8-week course (Fiore et al., 2008). This will ensure that assessment of ANS parameters just prior to the quit day is not confounded. Participants will not complete their taper until the end of week 6; this will allow for adequate washout of plasma nicotine, allowing us to biochemically verify abstinence and examine additional cardiac vagal tone changes as a function of treatment.

The ongoing COVID-19 pandemic places all research in an unpredictable situation. We anticipate that we may experience challenges in recruitment and retention associated with illness or safety concerns that could affect both study personnel and participants. We will address these issues on an ad hoc basis, for example, by subbing in respiratory therapists when possible, permitting participants to do make-up sessions, collecting in-person data at modified times, etc., and carefully documenting each adjustment made. Also, a growing body of empirical work has documented the extensive effects of the pandemic on mental health, including emotional distress and substance use. We have added several questionnaires, both validated quantitatively and qualitatively, to obtain information regarding the effects of the pandemic on mental health and functioning, as well as information regarding personal COVID-19 related experiences (e.g., disease contraction by self or close contact). Collection of this data will help the study team glean whether any related effects, or lack thereof, or differences in outcomes between Stage 1A and 1B may be attributable to the pandemic.

Transition to a remote intervention introduces several concerns related to intervention fidelity. Although the Inner Balance device provides relatively reliable real time HRVB feedback, therapists cannot view the participant and their physiology simultaneously. This may introduce challenges in determining whether the participant is practicing the intervention correctly and troubleshooting difficulties they are experiencing, such as feeling breathless or lightheaded. To address these concerns, the baseline appointment includes extensive training in the intervention and orientation to using the Inner Balance device and the Zoom mobile and computer software, so that participants can swiftly move between screens when working with their respiratory therapist remotely. Also, it is possible that the intervention may be disrupted due to connectivity problems. In the event this occurs, a backup plan, including the use of other HIPAA compliant platforms (e.g., Microsoft Teams), will be enacted, or the session will be moved to traditional audio phone call or rescheduled.

Compensation: Participants will receive up to $755 in total study compensation. This includes $10 per week for general participation, $35 for baseline and 1-month follow-up appintments, $50 for their 3-month follow-up appointment, a $50 bonus for attending at least 6 out of 7 sessions. Additionally, subjects will be paid up to $105 each week for at home breathing practice from weeks 2-6.

B. Data Points

Data will be collected over the course of 15 weeks, which include 3 in-person laboratory sessions and 5 remote sessions (see ***Table 1***), and will include interview, self-report, behavioral, and psychophysiological assessment.

C. Study Duration

Following the baseline and first session, which will last 1-3 hours, participants will be asked to complete 6 additional intervention sessions over the course of 6 weeks, lasting 30-60m each. They will also be asked to complete a final follow-up appointment, which corresponds with 3-months post their quit date.

D. Endpoints

N/A

1.4 Preliminary Data

Complete reporting of preliminary data collected during the Pilot Phase IA of this trial can be found under the eIRB protocol Pro2018001848. Of particular relevance for the current protocol, feasibility findings from the preliminary Phase 1A of this study suggest the previous in-person structure could be improved. Primary Phase IA outcome measures assessing intervention feasibility included participant attendance and ratings of the intervention's efficacy, appropriateness of fit, and ease of use in daily life. All scale scores ranged from 0=completely disagree to 4=completely agree. Intervention acceptability also served as a primary outcome and was assessed via participant ratings of intervention satisfaction and liking. Of the seven participants who remained in treatment beyond the first session, an average of 8.71 (SD= 1.49) treatment sessions were attended. At the 3-month follow-up visit, participant average ratings of the intervention's efficacy, appropriateness, ease of use, and acceptability were 3.19 (SD=0.52), 2.87 (SD=0.75), 1.58 (SD=0.32), and 3.52 (SD=0.31), respectively. While the intervention was high in efficacy, appropriateness, and acceptability, these initial results suggest the intervention was not perceived as being easily integrated into participant's daily lives. With this in mind, an intervention protocol modified for predominantly remote instruction may facilitate in addressing this previous feasibility limitations (see Feasibility section 4.3C for further detail).

1.5 Sample Size Justification

Given the developmental nature of the project, our sample size was selected to obtain a reasonable estimate of treatment feasibility, acceptability, and efficacy that would be critical to supporting a future R01 clinical trial. We enrolled n=10 participants for phase 1A and plan to enroll n=30 for phase 1B. Statistical power for phase 1B was determined using G*Power 3.1.9. and based on the analytic approach for examining our secondary outcomes of interest. Separate paired sample t-tests will be used to examine within-subject differences in the number of cigarettes smoked per day and in emotional distress from pre-treatment baseline, 1-month post-quit, and 3-month post-quit, respectively. Paired sample t-tests determined that at a power of 80%, α=0.25, an N=30 is sufficient to detect a small to medium-sized effect (Cohen's d=0.40). A Type I error rate of .25, has been suggested as an adequate error rate for testing preliminary pilot study effects and can be used to inform a more comprehensive study, including sample size planning for a future Stage II R01 (Moore et al., 2011). Given our relatively short assessment phase, this may still be too conservative estimate. Therefore, we will carefully examine effect size estimates and pursue a larger trial if a small to medium effect is observed.

1.6 Study Variables and Outcomes

To inform a subsequent clinical trial, our analytic plan focuses on the use of descriptive and inferential statistics.

Primary Outcomes:

Aims 1.a. and 1.b.: Feasibility and Acceptability:
Descriptive statistics will be used to assess feasibility and acceptability of HRVB (see 1.a. Intervention feasibility and 1.b. Intervention acceptability). Ratings of perceived effectiveness, appropriateness, satisfaction, and ease of the intervention are made on a 5-point Liker-type scale ranging from 0=*completely disagree to* 4=*completely agree.* Descriptive statistics will also be used to assess participant attendance, adherence, indexed by time spent using the intervention. Instances of technological limitations will be indexed both by count as well as qualitative descriptors (e.g., inner balance device failure to pick up recording; Bluetooth connection errors, etc.).

Secondary Outcomes:

Aim 2.a: Changes in smoking behavior:
Descriptive statistics will be used to report total number and percent of participants reporting abstinence on their quit day using the intent-to-treat sample as well as those who remain in treatment.

Sustained smoking cessation will be assessed descriptively using point prevalence abstinence defined by self-reported abstinence verified by both carbon monoxide analysis of breath sample and saliva cotinine. Paired sample t-tests will be used to assess changes in smoking rate within participants from baseline to quit day, two-week, one-month, and three-month follow-up, as a proxy for harm reduction.

Aim 2.b.: Changes in emotional distress:
Paired sample t-tests will be used to assess changes in emotional distress, including depression, anxiety and stress, within participants, from baseline to two-week, one-month, and three-month follow-up.

We will also examine correlations between baseline emotional distress ratings and key outcomes, including feasibility and acceptability ratings, changes in smoking behavior, and emotional distress to evaluate whether the intervention may be particularly beneficial for smokers with elevated emotional distress,

The following list of measures will be used to assess primary and secondary outcomes of interest:

1.a: Intervention feasibility

Outcome	Method	Time Frame
Participant Attendance	Number of attended sessions out of 7 possible sessions	7 weeks
Practice Adherence	Time (in minutes) spent practicing the breathing intervention	7 weeks
Intervention Effectiveness	Participant self-report items assessing how effective the intervention was in helping participants quit and manage emotional distress	Week 1 (i.e., treatment initiation) and Week 16 (i.e., 3-MFU)
Intervention Appropriateness	Participant self-report items assessing intervention comprehension and fit	Week 1 (i.e., treatment initiation) and Week 16 (i.e., 3-MFU)
Intervention Ease	Participant self-report items assessing ease of use and fit into daily lifestyle	Week 1 (i.e., treatment initiation) and Week 16 (i.e., 3-MFU)
Technological Limitations	Interventionist self-report items assessing incidences of technical issues and related effects on intervention delivery	7 weeks

1.b. Intervention acceptability

Outcome	Method	Time Frame
Satisfaction and Liking	Self-report items assessing satisfaction with learning the intervention, liking the intervention, breathing techniques, nicotine replacement, and recommending the intervention to others	Week 1 (i.e., treatment initiation) and Week 16 (i.e., 3-MFU)

2. Secondary Outcome Measures:

2.a. Changes in smoking behavior

Outcome	Method	Time Frame
Quit-day abstinence	Self-reported abstinence on Quit Day, verified with carbon monoxide analysis of breath sample (CO < 8ppm)	Week 3 (i.e., Quit Date)
Sustained Smoking Cessation	Self-reported abstinence, verified carbon monoxide analysis, and salivary cotinine (<10 ng/mL) at study termination	Week 16 (i.e., 3-MFU)
Smoking rate	Timeline Followback interview assessing changes in smoking rate	Week 0 (i.e., Baseline,) Week 3 (i.e., Quit Date), 5 (i.e., 2-WFU), Week 7 (i.e.,1-MFU) and Week 16 (i.e., 3-MFU)

2.b: Changes in emotional distress (i.e., anxiety, depression, and stress)

Outcome	Method	Time Frame
Emotional Distress	Self-report items assessing past 2-week ratings of depression, anxiety, and stress	Week 0 (i.e., Baseline,) Week 5 (i.e., 2-WFU), Week 7 (i.e.,1-MFU) and Week 16 (i.e., 3-MFU)

1.7 Drugs/Devices/Biologics
Nicotine replacement therapy:

NicoDerm Transdermal Patch. The transdermal nicotine patch is an FDA approved treatment for nicotine dependence. Patches are available over-the-counter (OTC) without a prescription. Patches are available in 7,14, and 21mg doses.

Study participants will be provided with information written at a 6th grade level describing the proper use of the nicotine transdermal patch, including a description of common side effects. To minimize adverse events, we are excluding smokers with potential contraindications (see *Participants* section within *Methods* above).

A. Drug/Device Accountability and Storage Methods

1. *Storage and accountability.* We will store nicotine replacement therapy (NRT) in original packaging (patch: box containing 2-week supply) in locked cabinets in a room with locked doors at One Spring Street. We will document temperature of the room weekly using a min/max thermometer.
    a. *Transferring medication.* Trained research staff will arrange to transfer medication between research laboratory sites as needed. Coordinators will be the only people who transfer medication between sites if needed, arranging with one another to pick up or drop off the medication.

2. *Inventory.* We will use an NRT inventory log to document the Lot # and Expiration date of each box of NRT.
3. *Dispensing NRT.* We will use an NRT dispensing log to document which boxes of NRT are provided to which subjects (listed by subject number only), by whom, and on what date. We will not collect unused portions of the NRT because it is not common practice to specify a time limit by which participants are required to use the NRT.

1.8 Specimen Collection

A. Primary Specimen Collection

Cotinine samples collected by study staff for verification of abstinence qualify as human material, and our study follows additional safety guidelines for collection, storage, and transportation, required by the Institutional Biosafety Committee. As part of this, we have a biosafety protocol in place, including a written Exposure Control Plan. In addition, study personnel are required to complete Biosafety Training Certification. In accord with Rutgers policies on biosafety, study staff follow a specific set of procedures when collecting, storing, and transporting samples for analysis off-site, which also serve to maintain completeness and accuracy.

1.9 Data Collection

A. **Primary Data Collection**

All copies of records, behavioral tests, audio and video recordings, and physiological data are linked to an arbitrary 3-digit study ID unrelated to personal information. The file linking participants to their study ID will be stored in a password-protected file, located within a password-protected database on an encrypted computer. Only select trained laboratory personnel will have access to the file. All computer files or printed data used for analysis also will be de-identified and stored separately from the participant ID list. Consent forms and payment forms will be stored in a locked file cabinet separate from data in an office that is locked when not occupied. Participants' confidentiality is also protected by never associating a participant's name with results in any published or otherwise publicly presented report. Demographic information (e.g., age, ethnicity, education, marital status) will be reported using averages and percentages computed over multiple participants and never reported at the level of individual participants. All data gathered during study appointments will be coded by arbitrary study identifiers and stored immediately. This includes paper/pencil, physiological, and audio and video recordings. Audio and video recordings collected using portable devices will be destroyed immediately once stored. Moreover, because audio and video files contain additional identifying information, they will be stored in separate password protected files from other self-report and physiological data, to add an additional layer of confidentiality.

Digital data will be kept indefinitely. The reason for this is that laboratory personnel may wish to engage in secondary data analyses in the future, which may require looking at original raw data. However, to ensure confidentiality, data will remain coded by an arbitrary study number. Data will also continue to be stored in a locked cabinet in a locked office. Data stored on computers will be double password protected.

Data will be stored for all interested participants, regardless of eligibility, to ensure that participants previously deemed ineligible are not mistakenly re-screened. Sessions will include a diagnostic interview completed via Zoom call, the baseline session, we will obtain consent, verify inclusion/exclusion criteria, assess smoking status, obtain physiological measurements to assess baseline autonomic nervous system activity, and ask participants to complete a battery of self-report measures online. The document linking the three-digit identification number to participant contact information will be maintained and stored on a secure computer. Only the PI and the trained study staff will have access to this document. No names or identifying information will

appear in any data or data collection materials for any of the studies. Data will be stored electronically on a secure computer. The only study documents that will contain participants' names and identifying information are the informed consent, payment tracking forms, and excel document used to track interested participants. These forms will be handled exclusively by the project director and coordinator and stored in a locked file drawer in the laboratory, separate from the study ID list. All data will be stored securely for at least five years following any publication of the data. Paper data will be destroyed after 6 years.

1.10 Timetable/Schedule of Events

Due to the impact that the novel coronavirus (COVID-19) had on research, the proposed timetable of the study has changed. We are anticipating entering a no-cost extension, extending the project timeline from 36 months to 48 months.

Table 4. Timeline for Proposed Research
Goals
Phase II recruitment with a target of 3/month. Final enrolled participant by end of March 2023, with 3-month follow-up data obtained by end of June 2023.
Clean and score physiological, behavioral, and self-report data by July 2023. Conduct analyses for Aim 1 and Aim 2. Revise manual based on project findings; begin manuscript draft and R01 application development.

2.0 Project Management

2.1 Research Staff and Qualifications

All study staff have received CITI training, Specific roles are detailed, below:

Graduate Research Assistants: Graduate students from the Ph.D. and Psy.D. programs will receive extensive training in evidence-based smoking cessation treatment and will serve as study clinicians and independent assessors. They will also assist the Research Coordinators in day-to-day activities.

Research Coordinator(s): Isabel Cunha has received training in the protection of human subjects and have obtained extensive research experience working in clinical research settings, including both laboratory and intervention protocols. She and the graduate student Hannah Brinkman will be responsible for coordination of this trial, including the training and supervision of undergraduate research assistance, oversight of participants screening, scheduling, communications, participant compensation, dispensing NRT, data management, informed consent procedures, and collecting in-person assessments.

Key Study Personnel: Drs. Leyro and Farris will be responsible for clinical training and supervision of personnel. They will also provide general project oversight, including training in all study procedures, IRB correspondence, documentation of all adverse events, and data safety monitoring board communication. Consultants, Drs. Hall and McCarthy will provide additional consultation on training, recruitment, and retention strategies. Dr. Bates and consultant Dr. Lehrer will provide additional expertise in data management, in particular, data cleaning, scoring, and analysis of psychophysiological data. All study staff have expertise in conducting clinical trials, working with individuals suffering from mental illness, and substance use disorders.

2.2 Research Staff Training

3 Study staff will undergo extensive (10-15 hours) training on all study procedures. PI will oversee training, which will include verbal description and behavioral demonstration. Staff will then be conducted through the study as mock participants, and then allowed to conduct the PI through the

study to allow for sufficient practicing of necessary procedures. All study staff have previously administered all of the aforementioned techniques during prior investigations.

4 Training will also include careful assessment of clinician adherence, defined as using the correct skills, as well as competence, meaning, and how well the skills are implemented (Fairburn & Cooper, 2011). All clinicians will be required to pass a general knowledge test assessing competency in appropriately modifying HRVB for participants, navigating and addressing common barriers (e.g., discomfort, dizziness), addressing motivation and adherence, navigating both in-lab and remote sessions, and will role-play several common issues that arise during HRVB, before they are assigned participants. In addition, an HRVB-specific rating scale will be used to assess implementation of strategies and skills in-session. Following assessment of implementation strategies, study clinicians will receive additional training and manual adjustments will be made. Measures of treatment fidelity are critical to the current proposal given it has never been applied to smokers and requires ongoing monitoring or participant behavior and physiology. For example, slow-paced breathing is sometimes accompanied by compensatory changes in breath depth, a process that can inadvertently decrease end tidal carbon dioxide ($etCO_2$), which is contraindicated and will not result in desired RSA oscillations; clinicians will need to know how to identify and remedy contraindicated breathing patterns, such as hyperventilation, to promote accurate HRVB application.

5 Study clinicians will receive intensive training from Drs. Leyro and Farris who will provide ongoing clinical supervision and consultation. In addition to prescribed study measures, clinicians will complete progress notes with their qualitative assessment of difficulties they experienced working with their participants, as well as self-report measures of the therapeutic alliance, and sessions will be video recorded. Notes, ratings, and recordings will inform weekly supervision. Participants will be asked to complete weekly pre- and post-session ratings of affect and treatment expectancy and credibility of intervention rationale. Finally, data will be downloaded from the smartphone app to obtain information regarding homework compliance and estimates of HRVB accuracy; participants with low compliance (<75%) will be asked a structured series of questions by their clinician to help determine what is promoting or obstructing adherence.

2.3 Resources Available

Study risks are minimal and may include an increase in distress as a result of topics discussed during SCT; however, the methodologies employed have been utilized in many labs and clinical settings with hundreds of participants suffering from a range of psychopathology and approved by as many IRBs. Participants may also experience temporary discomfort from removal of in-person physiological monitoring equipment; abrasions should not be more distressing than removal of band aids.

2.4 Research Sites

Research will take place in the Principal Investigator's lab space at One Spring Street in downtown New Brunswick, the 5th floor of Tillett Hall located on the Livingston Campus in Piscataway, as well as remotely. Facilities include materials necessary for data collection (e.g., physiological monitoring equipment, laboratory space, sub-zero freezer), and materials and devices needed for remote administration of the study will be provided to participants.

3.0 Multi-Center Research

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

Study advertisements will be posted in the greater New Brunswick area and Central New Jersey through online and community advertisements. Online advertisements via BuildClinical, a digital marketing platform, will be posted via social media platforms and will target potential participants based on demographic criteria including age and gender. We will utilize online recruitment programs to optimize our social media presence as well as expand our recruitment to a wider radius. We will also contact and partner with health-related clinics and institutes in the area to recruit from their patient population. Additionally, we will also attend and host information sessions at events in the New Brunswick community.

B. Recruitment Details

We will consent up to 50 participants from the greater Rutgers, New Brunswick, NJ area with a target of n = 30 who are enrolled in treatment, i.e., meet inclusion/exclusion criteria and who complete at least their first intervention session. Participants will be 50% female. We anticipate that our sample will reflect the race/ethnicity of the greater New Brunswick, NJ area; however, due to the small sample size, it is unlikely that our sample will adequately represent the racial/ethnic diversity of the New Brunswick, NJ area, and we will not recruit/enroll participants with this intent (i.e., 46.4% Caucasian/non-Hispanic, 23% Asian, 19% Hispanic/Caucasian, 11% African-American/non-Hispanic, 0.6 American Indian) (Centers for Disease Control and Prevention, 2014)). Participants will be recruited through March 2023 via posters, leaflets, mailings, online advertisements, community outreach (i.e., meetings with local organizations and treatment providers who work with cigarette smokers), and listservs.

C. Subject Screening

Upon initial contact with the lab, participants will be provided with a detailed description of the study and after providing verbal consent, will undergo a structured clinical phone screen to ensure they are likely to meet study inclusion and exclusion criteria. The phone screen includes sensitive questions related to physical and mental health that are necessary to ensure participants scheduled are eligible to participate in the study. This protects our resources, as well as those of the participant. In accord with lab procedures, we do not store identifying information and phone screen responses that may include PHI together. Instead, potential participant information including name, contact information, date of screening, and status (e.g., eligible, ineligible, scheduled), is stored on a password-protected file on the lab desktop. As an additional safeguard, we do not store this information on a network server; it is only accessible via one designated computer. Screening data will be stored by 3-digit arbitrary study ID number in a separate password-protected file.

- **Inclusion Criteria**

  Inclusion criteria include the following: (1) age 21-50, (2) smoking ≥ 5 cigarettes, daily, for at least two years, (3) expired carbon monoxide analysis of breath sample ≥8 ppm (4) a score of >5 on *the Readiness to Quit Ladder* (desire to quit smoking within the next 6 months) (5) ability to read and speak English fluently, and (6) computer and smartphone proficient.

- **Exclusion Criteria**

  Exclusion criteria include the following: (1) use of other tobacco or nicotine products for recreation or to aid in cessation or use of medication to aid in smoking cessation or currently receiving counseling for smoking cessation, (2) endorsement of current or past psychotic or manic symptoms indicative of bipolar spectrum or schizophrenia spectrum disorders and/or current suicidal or homicidal ideation, (3) inability to provide written informed consent; (4) plan to move from the New Brunswick, NJ area within the next 6 months, (5) inability to provide written informed consent, (6) current evidence of another substance use disorder (≥ 2 DSM-5 symptoms, (7) severe visual or hearing impairments, (8) self-reported medical condition or

medication use that may be contraindicated for participation in a HRVB or confound autonomic parameters: (8a) Being overweight or obese (i.e., body mass index > 35); (8b) Severe asthma or breathing problems (e.g., chronic obstructive pulmonary disease, emphysema, bronchitis); (8c) currently pregnant or lactating or plans to become pregnant in the next 4 months; (8d) Autoimmune disorder (e.g., multiple sclerosis; under or overactive thyroid); (8e) Neurodegenerative disorder (e.g., Alzheimer's disease, Parkinson's disease); (8f) Current use of a psychotropic medication or use of other medication that may affect the cardiovascular system (e.g., mood stabilizers, anti-psychotics, MAOIs, tricyclics, beta blockers, benzodiazepines; patients taking SSRIs or SNRIs will be enrolled if on a stable regimen for at least 6 weeks); (8g) History of heart murmur or arrhythmia; (8h) Pacemaker or other implanted cardiac devices; (8i) Heart disease; or (8j) Abnormal heart or respiratory parameters including respiration rate > 20 breaths per minute, extra systoles, or hypertension (e.g., BP reading ≥ 140/90; this may be determined following baseline assessment. Importantly, the presence of any of these exclusion factors, if unknown to the participant would not put them at any risk if they participated in the study, it would simply make the CV data more difficult (if not impossible) to process and interpret, and (9) self-reported medical issues of potential concern to nicotine patch users (i.e., unstable angina pectoris, myocardial infarction, or significant cardiac arrhythmia (including atrial fibrillation) in the past 90 days.

4.2 Secondary Subjects
N/A

4.3 Number of Subjects

A. Total Number of Subjects
Up to 50 participants will be consented with a target enrollment of n = 30 who will receive a minimal dose of treatment (i.e., at least one intervention session)

B. Total Number of Subjects If Multicenter Study
N/A

C. Feasibility
We have chosen to include participants ages 21-50. Although limited, this allows us to capture a large group of current daily smokers, with recent research indicating greatest declines in smoking prevalence in those ages 18-24 (Centers for Disease Control and Prevention, 2012). This also helps ensure participants have smoked regularly for several years. Research has found that autonomic parameters, including heart rate variability, (Berntson et al., 1997) blood pressure, (Cugini et al., 2003) and the baroreflex, (C. M. Brown, Hecht, Weih, Neundörfer, & Hilz, 2003) are affected by age, with significant decreases occurring in middle age. Therefore, inclusion of individuals older than 50 in this pilot study may confound treatment effects or interpretation of physiological parameters of interest. We have chosen to enroll smokers who smoke at least 5 cigarettes daily. We will exclude non-daily smokers. This will help in both feasibility as well as generalizability with recent research indicating that the proportion of heavy smokers (> 30/day) has declined to 9.1% from 12.5% between 2010 and 2011, whereas the percent who smoke between 1-9/day has increased to 22%, in the same time frame (Centers for Disease Control and Prevention, 2012). This is consistent with other reports indicating that smokers are smoking less per day, and that other indicators such as daily smoking and time to first cigarette may be better indicators of cigarette dependence (Baker et al., 2007).

Based on the preliminary feasibility findings from Phase 1A of this trial, a treatment protocol modified for predominantly remote instruction (as listed here) may yield several feasibility gains. Specifically, the reduced number of in-person study visits will mitigate participant burden (i.e., reduced time

traveling, greater flexibility in scheduling sessions, etc.). Teletherapy also allows participants to learn and practice their assigned breathing interventions in their daily environments potentially increasing the generalizability of the breathing exercises into their daily lives. The use of a portable and user friendly device that is able to connect to a participant's smartphone may also allow for ease of continued use of the intervention.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  Verbal consent will be obtained for the initial phone screen. The PI or RA will first explain the purpose of the phone screen and limits of confidentiality and provide an overview of the study. If potential participants remain interested, they must verbally agree to phone screen completion.
  During the initial virtual meeting study personnel will verbally go over the consent form in a private room.
- **Ongoing Consent**
  Ongoing consent will be confirmed on the basis of ongoing communication and study participation. In addition, participants will explicitly be reminded of study expectations, limitations, compensation, and right to withdraw. Study staff will attempt to contact participants who miss study appointments or follow-up appointments until they provide verbal or written indication that they no longer wish to participate. Details regarding participants who withdraw from the study will be discussed at data safety management meetings with study personnel that will occur every three months following initiation of recruitment to determine adverse event reporting, which will be detailed in all continuing review procedures (see attached DSMP for futher details).
- **Individual Roles for Researchers Involved in Consent**
  PI supervised/trained graduate students and research assistants will complete all aspects of the consent procedures.
- **Consent Discussion Duration**
  Staff will go over details regarding the procedure, time commitment, payment, risks/benefits, and option to discontinue the study at any time without penalty. We anticipate that it will take participants 5 minutes to read the consent and up to an additional 5 for staff to review relevant information.
- **Coercion or Undue Influence**
  During the consent process, staff will make clear to participants that regardless of their ability to make a cessation attempt, they will receive full compensation, and that early termination will result in payment for the portion completed, as detailed in the consent, and will not result in loss of ability to participate in future research.
- **Subject Understanding**
  In addition to providing written informed consent, participants must verbally indicate that they understand the study procedures and that they have no further questions.

B. Waiver or Alteration of Consent Process

- **Waiver or Alteration Details**
  N/A
- **Destruction of Identifiers**
  N/A
- **Use of Deception/Concealment**
  N/A
  a. **Minimal Risk Justification**
     N/A
  b. **Alternatives**
     N/A

c. Subject Debriefing
N/A

C. Documentation of Consent

- **Documenting Consent**
  The PI or supervised/trained study personnel will complete all aspects of the consent procedures. Verbal consent will be obtained for the initial phone screen. The PI or study personnel will explain the study procedure and read the verbal consent form. After the subject's questions are answered, verbal consent will be acquired from the subject. Signed and verbal consent will be used for study participation, in-person, during Week 0.

  During the in-person consent process during Week 0, study personnel will verbally review the consent form and explain what they have read, including the procedure, time commitment, payment, risks/benefits, and option to discontinue at any time without penalty, to check for understanding. Participants will also be provided with their own copy with PI contact information and Rutgers IRB contact information highlighted.

  The informed consent will be provided only in English since the exclusion criteria for the sample include inability to provide written informed consent or non-English speaking

- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**
  N/A

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**
  N/A
- **Non-Parental Permission**
  N/A
- **Assent Process**
  N/A
- **Documentation of Assent**
  N/A
- **Reaching Age of Majority During Study**
  N/A

B. Wards of the State
N/A

- **Research Outside of NJ Involving Minors**
  N/A

C. Non-English-Speaking Subjects
N/A

- **Process for Non-English-Speaking Subjects**
  N/A
- **Short Form Consent for Non-English Speakers**
  N/A

D. Adults Unable to Consent / Decisionally Impaired Adults
N/A

- **NJ Law-Assessment of Regaining the Capacity to Consent**
  N/A
- **Capacity to Consent**

N/A

a. NJ Law-Selecting A Witness

N/A

b. Removing a Subject

Described research staff will work to directly address any concerns participants raise, resulting in their wish to discontinue, while also ensuring participants maintain autonomy in their decision-making and avoiding coercion (e.g., overcoming schedule conflicts, or completing assessments only). If participants decide that they would like to completely withdraw participation, they will not be further contacted. As indicated above, the PI will discuss participant withdrawal with key study personnel to make a determination regarding communicating when and how to communicate information to the IRB or funding agency (NIDA).

4.6 Economic Burden and/or Compensation for Subjects

6. Expenses

Participants may incur costs of transportation to arrive at the study site, however, participants will have the option to travel to the study site via prepaid Uber, Lyft, or taxi.

B. Compensation/Incentives

Participants will receive up to $755 in total study compensation. This includes $10 per session for attendance, $35 for the baseline and 1-month follow-up, $50 for their 3-month follow-up appointment, $50 bonus for attending 6 out of the 7 sessions (see Table 1). Additionally, subjects will be paid up to $105 each week for at-home breathing practice from weeks 2-6. Participants will earn $5 for a single 5-minute practice, $10 for 2 practices, or $15 for 3-4 practices resulting in a total of 20 minutes. Participants will only be compensated for a total of 20 minutes of practice.

C. Compensation Documentation

A signature of participants will be obtained upon the completion of the compensation.

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**
  - *(1) Phone Screen and Questionnaire Completion*: Potential participants may become uncomfortable or distressed when asked certain questions (e.g., regarding illicit substance use; current/past mental health and physical health). However, Dr. Leyro has many years of experience administering these questionnaires in various study protocols and study personnel will receive extensive training in conducting the Phone Screen. Also, participants will be offered an additional layer of protection via a Certificate of Confidentiality.
  - *(2) HRVB*: There are some minimal risks associated with the administration of the proposed breathing intervention. The most often observed risk is discomfort breathing at a pace that is much slower than typical, and worry that one is not inhaling adequate air. To address this potential risk, study clinicians will be carefully trained in providing participants with a clear rationale for the procedure, clinical management of distress associated with the intervention, and appropriate adjustments to ensure participants are able to adhere to the protocol.

- *(3) Physiological Recording*: All of our sensors record responses from the surface of the body and are hence noninvasive, and should not cause the participants any discomfort or physical harm. Patients may experience mild discomfort with the application and removal of passive electrodes to monitor their physiological parameters at in person sessions. However, we do not anticipate this discomfort to be longstanding. To minimize discomfort, all sensors are placed and removed by study staff that will receive training in appropriate placement and removal. Study personnel will train participants in the lab and during remote sessions on proper placement and removal of the Inner Balance ear clip sensor.
- *(4) Assessment Procedures*: No risks are associated with self-report or behavioral assessments other than mild distress due to the sensitive nature of questions or induced distress as a function of difficulty or attention demands on some of the behavioral tasks. Study personnel are experienced and sensitive to this issue and will cease testing if a participant displays excessive frustration during behavioral testing, although the PI has never experienced this in her prior research.
- *(5) Nicotine Replacement Therapy*: The transdermal nicotine patch is available over-the-counter, has been widely used, and its risks are minimal. Possible adverse side effects of the nicotine patch include abnormal redness of the skin, itching, headache, insomnia, diarrhea, indigestion, and nervousness. We minimize risks by screening patients for contraindications of nicotine patch use and requiring physician concurrence. In addition, participants will be queried regarding craving and side effects to ensure adequate dosing and to reduce adverse effects. Participants who are started at 14mg will be moved up to 21mg if they report strong cravings, whereas those started at 21mg will be stepped down to 14 if they report the nicotine to be uncomfortably stimulating.
- *(6) Breach of Confidentiality*: There is a risk that confidential information about a participant may be revealed. Although all technology that is incorporated in the study is encrypted and HIPAA compliant, reliance on teletherapy introduces risks such as: participants not having access to a confidential and isolated location in which to conduct teletherapy sessions and potential identifiable information collected in conjunction with using data from the Inner Balance and iCOquit ® Smokerlyzer devices. This could conceivably result in discriminatory action against participants by insurers, employers, or other groups. However, as an additional layer of protection, a Certificate of Confidentiality has been automatically awarded by NIH.

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**
  N/A

- **Other Foreseeable Risks of Harm**
  Our research team employs standard procedures to ensure confidential information about study participation is not disclosed. All data are linked to an arbitrary 3-digit study ID unrelated to personal information. The file linking participants to their study ID will be stored in a password-protected file, located within a password-protected database on an encrypted computer and maintained separately from de-identified personal data files. Only select trained laboratory personnel will have access to the file. All computer files or printed data used for analysis also will be de-identified. Consent forms and payment forms will be stored in a locked file cabinet separate from data in an office that is locked when not occupied. Participants' confidentiality also is protected by never associating a participant's name with results in any published or otherwise publicly presented report. Demographic information, including information about participants' age, ethnicity, education, marital status and employment status, will be reported using averages and percentages computed over multiple participants

and never reported at the level of individual participants. In addition, all participants will be explicitly instructed to not modify any iCOQuit, Inner Balance, smartphone, and tablet device and application settings or include any identifiable information within these devices and applications (See Section E. Minimizing Risks of Harm for additional detail).

- **Observation and Sensitive Information**
  N/A

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects
N/A

C. Risks of Harm to Non-Subjects
N/A

D. Assessment of Social Behavior Considerations
Study risks are minimal and include a small, temporary increase in distress as a result of the assessments; however, the methodologies employed have been utilized in many labs and clinical settings with hundreds of participants suffering from a range of psychopathology, and approved by as many IRBs.

E. Minimizing Risks of Harm
Participants who indicate psychological distress during participation will be provided with several strategies to reduce distress as needed, including, distraction and deep breathing. Staff will conduct a thorough risk assessment with participants who report suicidal ideation or intent.

Any participants who report suicidal ideation or intent will be provided with information and phone numbers for three local options for mental health care: Rutgers University Behavioral Health Care (800-969-5300), Rutgers Health Psychiatry/Psychology Clinic (732-235-7647), and the Rutgers Psychological Clinic in (848-445-6111). In the unlikely event that a participant reports an imminent intent to harm themselves, we will contact Acute Psychiatric Services (855-515-5700).

- **Certificate of Confidentiality**
  Participants will additionally be protected via a Certificate of Confidentiality issued by the Department of Health and Human Services. The Certificate will protect the investigators from being forced to release research data that contains identifiable information about participants, even under a court order or subpoena. The certificate does not protect the investigators from being compelled to make disclosures that: (1) have been consented to in writing by the participants or the participant's legally authorized representative, (2) are required by the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 201 et seq.) or regulations issued under that Act, or (3) have been requested from a research project funded by NIH or DHHS by authorized representatives of those agencies for the purpose of audit or program review. The Certificate will protect study personnel located at Rutgers University as well as consultants affiliated with the proposed project from disclosing information. The Certificate will additionally protect the privacy of participants by withholding their names and other identifying characteristics from all persons not connected with the conduct of that research.
- **Provisions to Protect Confidentiality on Study Devices**
  All participants will be explicitly instructed to not modify or include any identifiable information within the iCOQuit, Inner Balance, smartphone, and tablet device settings. Upon return, a lab personnel member will connect all used iCOQuit and Inner Balance devices to a lab smartphone to confirm that no identifiable information is present upon device retrieval and will restore all default settings before the devices are provided to a new participant. For lent smartphones and tablets, all identifiable information will be cleared by lab personnel upon device retrieval and will be re-checked again before being given to a new participant. Our lab will also implement a used/clean technology device clearing system. Specifically, returned technology (i.e., iCOQuit, Inner Balance, Smartphone, or Tablet) will be placed in the "used" bucket. Once all protection provisions have been employed, the device will then be placed in the "clean" bucket. This system will increase ease of redistributing reusable tech devices,

identifying those that need to be wiped, and ensureg that redistributed devices are free of PHI.

- **Provisions to Protect the Privacy Interests of Subjects**
  Participants will be asked to engage with trained research staff throughout the course of the study. However, if participants indicate a desire not to work with a particular staff member, we will oblige. In addition, potential participants will not interact with any member of the study team that they have a personal or professional relationship with.
- **Provisions to Protect from Exposure to Contaminants**
  All used iCOQuit, Inner Balance, smartphone, and tablet devices will be thoroughly cleaned with a sanitization wipe upon device retrieval before being given to a new participant to reduce the spread of person-to-person contaminants.

F. Potential Benefits to Subjects

The SCT treatment including the NRT patch is associated with improved smoking cessation outcomes, which may have a long-term positive impact on health and psychological well-being. In addition, though this study is exploratory in nature and benefits of HRVB have not yet been assessed in daily smokers, we are hopeful that participants receiving HRVB will experience additional reductions in anxiety and depressive symptoms, and improved physiological health as determined by indices of autonomic balance.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

N/A

6.3 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

A. Special Populations

B. N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 NJ Access to Medical Research Act (Surrogate Consent)

N/A

6.4 Data Management Plan

6.5 Data Analysis

Primary analyses will use descriptive statistics to assess feasibility and acceptability of HRVB. Ratings of perceived effectiveness, appropriateness, satisfaction, and ease of intervention are made on a 5-point Liker-type scale ranging from 0=*completely disagree* to 4=*completely agree*. Descriptive statistics will also be used to assess participant attendance, adherence, indexed by time spent using the intervention. Instances of technological limitations will be indexed both by count as well as qualitative descriptors (e.g., inner balance device failure to pick up recording; Bluetooth connection errors, etc.) Secondary analyses for Aim 2.a: Changes in smoking behavior will include descriptive statistics used to report total number and percent of participants reporting abstinence on their quit day using the intent-to-treat sample as well as those who remain in treatment. Sustained smoking cessation will be assessed descriptively using point prevalence abstinence defined by self-reported abstinence verified

by both carbon monoxide analysis of breath sample and saliva cotinine. Paired sample t-tests will be used to assess changes in smoking rate within participants from baseline to quit day, two-week, one-month, and three-month follow-up, as a proxy for harm reduction. Secondary analyses for Aim 2.b: Changes in emotion distress will include paired sample t-tests used to assess changes in emotional distress, including depression, anxiety and stress, within participants, from baseline to two-week, one-month, and three-month follow-up. To explore whether the intervention may be particularly beneficial for smokers with elevated emotional distress, we will examine correlations between baseline emotional distress ratings and key outcomes, including feasibility and acceptability ratings, changes in smoking behavior, and emotional distress.

6.6 Data Security

The link between participants and their study ID will be stored in a password-protected file, located within a password-protected database on an encrypted computer. Only select trained laboratory personnel will have access to the file, which will be kept separate from deidentified data. All computer files or printed data used for analysis also will be de-identified. Consent forms and payment forms will be stored in a locked file cabinet separate from data in offices in the PI research space at One Spring Street or Tillett Hall. All research personnel will complete CITI Human Subjects Research training and pass the CITI quizzes.

6.7 Data and Safety Monitoring

Dr. Leyro has developed a detailed data safety and monitoring plan (see attached DSMP file) that has been reviewed and approved by the project's funding agency (NIH/NIDA).

A. Data/Safety Monitoring Plan

Please see DSMP

B. Data/Safety Monitoring Board Details

Please see DSMP. Although this is study qualifies as a clinical trial, no DSMB is required.

6.4 Reporting Results

A. **Individual Subjects' Results**

Individual and aggregate study results will not be shared with subjects. However, participants will be notified via informed consent that this trial will be included on clinicaltrials.gov, in compliance with NIH NOT-OD-16-149. Clinicaltrials.gov provides the public with data regarding clinical trials completion and outcomes.

B. **Aggregate Results**

N/A

C. **Professional Reporting**

It will be made clear to participants that if information from this study is published or presented at scientific meetings, their name and other personal information will not be used.

D. **Clinical Trials Registration, Results Reporting and Consent Posting**

The funding proposal is a Phase I/II clinical trial and is thus subject to the NIH Policy on Dissemination of NIH funded Clinical Trial Information. Upon receipt of award, this study will be registered at ClinicalTrials.gov by the study PI - i.e., Teresa Leyro, Ph.D., the *Responsible Party*. T. Leyro (PI) will additionally be responsible for ensuring that results from this study are submitted to ClinicalTrials.gov as outlined by the NIH policy, effective January 18, 2017 (NOT-OD-16-149), and according to the specified timeline. In accord with the new NIH policy, Rutgers, The State University of New Jersey has an internal policy in place and provides investigators with instructions on how to register and report results, to ensure that clinical trials are registered and results are reported in compliance with NOT-OD-16-149.

Detailed Dissemination Plan:

1. Registration: Our trial will be registered no later than 21 days after enrollment of our first participant. Registration information will include a study description, including the condition to be treated (i.e., tobacco smoking), the intervention/treatment, and study phase. The study design description will include study type, estimated enrollment, allocation, intervention model and description, primary purpose, official title, start date and estimated completion date. We will additionally include study aims and corresponding intervention/treatment, and primary and secondary outcome measures. Finally, detailed eligibility criteria (i.e., inclusion/exclusion), and contacts and locations description of the study aims, approach/protocol, statistical analysis plan, recruitment information, location, and sponsor information will be provided.
2. Consent form language: Our consent form will include language notifying participants that information on the clinical trial, including a description and results, will be posted at ClinicalTrials.gov.
   Results information: In accord with this policy, we will ensure that results are reported at ClinicalTrials.gov within 12 months of the primary completion date – i.e., the date that the final subject follow-up, or final, data collection point. Results to be reported by the indicated policy deadline will include participant flow (e.g., recruitment details), demographic and baseline characteristics (e.g., race/ethnicity, sex/gender, age, cigarettes smoked daily), key outcome measures and analyses, serious and other adverse events, and limitations and caveats.

6.5 Secondary Use of the Data

N/A

7.0 Research Repositories – Specimens and/or Data

N/A

8.0 Approvals/Authorizations

N/A

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