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INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE
(HRP-503a)

INSTRUCTIONS

This template should be used by biomedical and social-behavioral researchers conducting research which subjects are assigned to receive one or more interventions so that the researchers can evaluate their effects. (e.g. clinical trials, CBT, Behavioral Modification studies, or randomized outcome studies)

Sections in red may not be applicable to your research: you may replace the instructional text with "N/A".

As you are writing the protocol, remove all instructions in blue italics so that they are not contained in the final version of your protocol.

STUDY INFORMATION

Title of Project: Development and Pilot Investigation of Heart Rate Variability Biofeedback for Smoking Cessation

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1.0 Research Introduction

1.1 Purpose/Specific Aims

The purpose of the study is to conduct a pilot trial to examine the effects of heart rate variability biofeedback as a smoking cessation treatment adjunct for smokers with moderate anxiety and/or depression symptoms.

A. Objectives

The present investigation is an uncontrolled pilot study of a heart rate variability (HRV) biofeedback smoking cessation treatment (HRVB-SCT) or smokers with moderate levels of anxiety or depression. This study is designed to develop, refine, and pilot test HRVB-SCT for daily, nicotine dependent smokers, with elevations in anxiety and depression symptoms. Findings will be used to further develop and refine patient and clinician manuals for HRVB-SCT to be used in a subsequent randomized clinical trial.

The goals are to: (a) develop and refine patient and clinician manuals for HRVB-SCT in smokers with comorbid emotional psychopathology; (b) understand unique concerns in this patient group that may affect treatment fidelity and participant adherence; and (c) complete two open trials of 5 smokers each with moderate levels of affective distress in each (n=10) and use observations to inform a subsequent randomized clinical trial.

B. Hypotheses / Research Question(s)

The main study hypothesis is that HRVB-will be a feasible and acceptable accompaniment to standard SCT in smokers with elevated emotional distress. We hope to identify and address processes that may affect treatment delivery fidelity and patient adherence. We expect that information gleaned from the open pilot trial will lead to changes in patient and clinician manuals. Finally, we expect that participants will make a quit attempt while enrolled in the open trial, and will report reductions in anxiety and depressive symptoms.

1.2 Research Significance *(Briefly describe the following in 500 words or less):*

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 I study will develop and pilot test an integrated, biobehavioral, transdiagnostic smoking intervention for smokers with moderate emotional distress (i.e., elevated mood/anxiety symptoms). 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 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.

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) the current proposal seeks to develop and pilot test HRVB as a treatment adjunct for standard smoking cessation treatment (HRVB-SCT) in daily smokers with moderate emotional distress. The proposal will use a staged model for developing and standardizing behavioral interventions, as indicated by NIDA. The first year of the project will focus on drafting, piloting, and modifying an integrated HRVB smoking cessation treatment (HRVB-SCT) and assessing feasibility of treatment delivery, fidelity, and potential for improving smoking cessation outcomes and reducing emotional distress. Data collected during this time will inform the next stage of the study, which will involve completion a two-arm pilot randomized controlled trial (RCT) of HRVB-SCT versus a breath awareness training (BAT-SCT) sham to evaluate smoking and emotional distress outcomes and explore transdiagnostic physiological and cognitive-affective treatment mechanisms.

1.3 Research Design and Methods

Overview: The current proposal represents of the initial phase of treatment development and will involve writing, pilot testing, and refining the HRVB-SCT patient and clinician treatment manuals. We will pilot test the manual in two open trials including 5 participants each (n=10) to assess feasibility in preparation for a subsequent pilot randomized clinical trial, to be conducted at a later date.

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. All participants will receive HRVB-SCT.

Pre-Study Telephone Screening: Upon initial contact of the ABUSA lab, prospective participants will complete a phone interview to assess current smoking status, history, screen for key health exclusionary criteria (e.g., substance use, cardiac health, and history of psychotic spectrum symptoms), and assess current depression, anxiety and stress, using the DASS-21. Participants who appear to meet study inclusion/exclusion criteria will be scheduled for a baseline appointment to occur within the next week. Reason for exclusion will be tracked for ineligible participants, 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. 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.

HRVB Intervention: Intervention sessions will last between 30 and 60 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 10 sessions of HRVB over the course of 7 weeks. Sessions are front-loaded with two sessions occurring before homework assignment to ensure accurate training, and four prior to the quit date, to promote quit day success (see **Table 1**). Clinicians will be trained in the application of HRVB including instructing participants in how to breathe with a pacer and using *Thought Technology* software to teach participants how to follow a cardiotachometer to achieve breathing at their resonance frequency (i.e., biofeedback), which provides real time display of resonance, peak and trough amplitude of heart rate, inter-beat-interval, and respiration data. Clinicians will also be trained in the use of a smartphone application, that will be used for at-home practice and recording. This app uses the phone camera light as a pulse plethysmograph to obtain estimates of heart rate data. Data will be used primarily for homework compliance and in-session to build confidence in home practice. While breathing at the prescribed pace, participants will view a waveform on the phone that reflects their heart rate, similar to that observed in biofeedback sessions. While following the waveform and practicing learned resonance breathing, they are instructed to try to increase the amplitude of heart rate oscillations, which will

increase heart rate variability (HRV). Participants will be asked to practice HRV biofeedback 40 minutes daily, in bouts of 5-20 minutes. Practicing for 40 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 at-home practice, the device allows the investigators to download biofeedback data for quality assessment. 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)*:* As indicated by clinical practice guidelines ((Fiore et al. 2008; Jaen et al., 2008), participants will receive transdermal (NRT) patches and counseling for smoking cessation. Counseling will be integrated into HRVB sessions. To standardize treatment between-groups, independent assessors, who are blind to treatment randomization, will be trained in providing the SCT using the National Cancer Institute's *Clear Pathways* (NCI, 2013) guide. Each participant will be provided with *Clear Pathways* and be given weekly assignments. SCT will be provided for 20 minutes at weeks 1a, 2a, 3a, and 5 (see ***Table 1***). Participants will receive 8 weeks of NRT and will be instructed to place their first nicotine patch upon waking on their quit day (Fiore et al. 2008). Dosage Schedule: Individuals smoking >10 cigarettes/day will receive the 21 mg/day NRT patch for 4 weeks, followed by the 14 mg/day NRT patch for 2 weeks, and complete their course of NRT treatment with the 7 mg/day NRT patch for 2 weeks. Individuals smoking ≤10 cigarettes/day will receive the 14 mg/day NRT patch for 6 weeks followed by the 7 mg/day NRT patch for 2 weeks. To increase compliance, dosing will be monitored and adjusted as needed to ensure adequate dosing and minimize adverse effects.

Week 0 Visit (Baseline): At Week 0, potential participants will come to the lab and meet with an independent assessor who will verify smoking status via CO analysis of breath sample, confirm study inclusion/exclusion criteria, and obtain written informed consent. To ensure participants do not meet criteria for exclusionary bipolar, psychotic spectrum disorders, or severe substance use disorders, the independent assessor will use a short diagnostic structured interview. Next, participants will complete a battery of self-report measures on Qualtrics, an online survey portal. In addition to core inclusion/exclusion criteria, questionnaire data will be used to assess general health, a range of smoking relevant processes, other substance use, and self-reported and behaviorally indexed distress tolerance. Following Week 0, participants who remain eligible will be scheduled for their first intervention session the following week.

Recording Sessions: During sessions 1, 4, 8, and 10, we will record several 5-minute physiological segments in order to assess both within and between-session changes in cardiac vagal parameters (i.e., vagal tone and flexibility). Data will be collected via two methodologies. First, participants will be hooked up to Mindware's integrated psychophysiological system to obtain continuous measures of electrocardiograph (ECG) and impedance cardiograph (IC), which allows for the extraction of respiration data necessary to compute HF-HRV (BioNex 8SLT Biolab Acquisition Application, MindWare Technologies, Gahanna OH). Following a 5-minute resting period, 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. Mindware software will be used to score data, and

digitized ECG signals will be examined to correct misidentified R spikes. 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.

During HRVB training, participants will be connected to *Thought Technology Infiniti System* (www.thoughtechnology.com) to obtain continuous respiration and ECG data during several 5-minute rest and HRVB periods. HF-HRV data will be scored using Cardiopro software. This data will supplement our core indices of vagal tone and flexibility that will be obtained using Mindware. During each session, participants will be asked to complete several measures to assess pre- and post-session positive and negative affect, substance use, importance of quitting and confidence ratings, and smoking withdrawal craving. In addition, both participants and therapist will provide ratings to assess acceptability and feasibility of the intervention.

Weekly Assessments: During each session, participants will again be asked to complete several measures to assess pre- and post-session positive and negative affect, substance use, importance of quitting and confidence ratings, and smoking withdrawal craving. Also, participant and therapist ratings to help assess acceptability and feasibility of the intervention will be made.

Follow-up Assessments: Post-quit assessments will occur during sessions eight and ten (2-weeks and 1-month, post quit), and 3-months post quit date. Abstinence will be verified via self-report and carbon monoxide analysis of breath sample and confirmed by saliva cotinine.

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

Week	Session	Core Components	Time	Pay
Week 1a	**HRVB S1**	• Intervention Overview • Recording session[R] • Goal: Introduce HRVB Breathing using pacer	40	$25 $15 app practice
	SCT	• SCT program introduction and orientation to *Clear Pathways* • Goals: Understanding why you smoke, health effects of smoking/quitting, set quit date (week 3)	20	
Week 1b	**HRVB S2**	• Biofeedback practice session[B] • Goal: Introduce cardiotachometer biofeedback • Assign homework: Practice 2x/day for at least 20m	30	
Week 2a*	**HRVB S3**	• Biofeedback practice session[B] • Goal: Cross-reference Camera HRV and cardiotachometer	30	$25

		• Assign homework: Practice 2x/day for at least 20m		$15 app practice
	SCT	• Review homework • Goals: Increase motivation to quit, plan for quit day, introduce NRT and provide instructions	20	
Week 2b	**HRVB S4**	• Recording session[R] • Assign homework: Practice 2x/day for at least 20m	40	
	SCT	• Plan for quit day, introduce NRT and provide instructions		
Week 3a (Quit day)	**HRVB S5**	• Biofeedback practice session[B] • Goal: Assess adherence, motivation, trouble-shoot • Assign homework: Practice 2x/day for at least 20m	30	$10 $15 app practice
	SCT	• Assess quit status via CO analysis[101] • Highlight successes, trouble-shoot/learn from failures • Promote quit resumption if failed • Assess NRT use side effects, questions/concerns, adherence	20	
Week 3b	**HRVB S6**	• Biofeedback practice session[B] • Goal: Make post-quit adjustments to HRVB, assess adherence, motivation • Assign homework: Practice 2x/day for at least 20m	30	
Week 4*	**HRVB S7**	• Biofeedback practice session[B] • Goal: Assess adherence, motivation, trouble-shoot • Assign homework: Practice 2x/day for at least 20m	30	$10 $15 app practice
Week 5 (2w post quit)	**HRVB S8**	• Recording session[R] • Assign homework: Practice 2x/day for at least 20m	40	$25 $15 app practice
	SCT	• Goal: Assess abstinence status, revise quit plan to maintain abstinence or resume cessation, provide additional NRT	20	
Week 6*	**HRVB s9**	• Biofeedback practice session[B] • Goal: Assess adherence, motivation, trouble-shoot • Assign homework: Practice 2x/day for at least 20m	30	$10 $15 app practice

Week 7 (1m post-quit)	**HRVB S10**	• Recording session[R] • Goal: Obtain commitment to continue practice	40	$25 $15 app practice
	SCT	• Goal: Brief assessment abstinence status, offer of support, encourage resumption, provide NRT	20	
Week 16 (3m post-quit)	**HRV**	• Recording session[R]	40	$50 $15 for every week of app practice
	SCT	• Assess abstinence via CO and cotinine	10	

[R]Recording session (respiration, ECG, blood volume sensor, skin temperature, and skin conductance);
[B]Biofeedback practice session (respiration and ECG)

Participants will be paid up to $15 each week for at-home breathing practice during weeks 1-15. Participants will be paid $1 per each 20-minute at-home breathing practice session as recorded with the app. Participants should practice twice daily, for a total of up to $2 per day. If participants complete 2 sessions per day for all 7 days, they will receive a $1 bonus, for a total possible of up to $15 weekly.

*At the discretion of the study team, participants may be given the option to complete sessions 3 (week 2a), 7 (week 4), and 9 (week 6) at home with therapist support via teleconferencing (e.g., via computer, phone, etc.).

Table 2. Study Measures Table
Phone Screen:
1) **Interview**: The phone screen will be administered prior to study enrollment to help determine whether interested participants are eligible.
2) **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.
3) **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.
In Person and Qualtrics Measures:
Participant Information Sheet to confirm inclusion/exclusion criteria
Medical Screening Questionnaire to confirm inclusion/exclusion criteria
Participant Contact Info to document best means to contact participant for study communication *includes request for permission to text*
Demographic Information[B] to confirm inclusion/exclusion criteria.

Short-form Health Survey[133] to assess quality of life in regard to health.
Credibility and Expectancy Questionnaire[B] [134] to assess treatment expectancy and credibility of intervention rationale (modified for the purposes of this study).
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 provide ratings of participant engagement, comfort in applying intervention, confidence in applying intervention, and perceived accuracy of intervention.
Exit interview
Smoking History Questionnaire (SHQ) [B][135]–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.
Fagerström Test of Cigarette Dependence (FTCD)[B] [136-138] –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 (scoredas 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.
Thoughts about Abstinence [W][139-141] to assess commitment to complete abstinence including importance and confidence.
Minnesota Nicotine Withdrawal Scale [W] [142]
Questionnaire of Smoking Urges [W,] [143]
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.
Smoking Abstinence Questionnaire (SAQ)--55-item self-report questionnaire which assesses expectancies related to smoking abstinence. Participants usea7-point Likert scale (0=not likely at allto 6=extremely likely) to indicate perceived feelings, thoughts, behaviors that will be experienced as a result of quitting. The psychometric properties and reliability of this scale have been reported.
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.
Wisconsin Inventory of Smoking Dependence Motives (WISDM-68)--68-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-dimesnional 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 proved to be good.

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.
Timeline Followback [W]interview[144-146] will be used to assess ongoing cigarette, e-cigarette, patch, alcohol, and other tobacco and substance use.
Depression Anxiety Stress Scale (DASS-21) [W] [116] to assess for past week symptoms of depression, anxiety, and stress.
Positive and Negative Affect Schedule [W] [147,148] to assess current emotional states before and after intervention sessions.
Distress Intolerance Index (McHugh & Otto) [B, R] [149] to assess participants' perceptions of their ability to tolerate mental distress.
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.[106]
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*.[107]
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.
Distress Tolerance Scale (DTS) -- 15-item scale used to assess participants' perception of their ability to tolerate mental distress. Items (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.[127]
Frustration Discomfort Scale (FDS) -- 35 items 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.[128]

Perceived Stress Scale (PSS10) – 10 items designed to measure 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.
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.[139,140,141,142]
Adult ADHD Self-Report Screening Scale (ASRS-5) 6 items 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.
The Urgency, Premeditation, Perseverance, and Sensation Seeking Impulsive Behavior (UPPS-P) -- 20-item measure assesses characteristics of personality, such as how rashly participants respond in response to negative moods, and determines how they may contribute to impulsive behavior.[134] 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[135] and convergent and divergent validity.[136]
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.
Cigarette Purchase Task (CPT) is a 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).
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 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. [131] 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.[132]
Ratings of Session Protocol Adherence and Examination of Physiological Data for Intervention Accuracy: To assess treatment fidelity.

HRVB Clinician Training: Training will include careful assessment of clinician adherence, defined as using the correct skills as well as competence, i.e., 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, and will role-play managing 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. Designated study assessors will be asked to code 25% of the initial eight HRVB sessions provided to first cohort (n=5) of participants (Muse & McManus, 2013). Fidelity will additionally be assessed by Co-Is E. Vaschillo and P. Lehrer who will review recorded physiological data from sessions 1, 4, 8, and 10 to rate whether participants, under therapist instruction, received adequate resonance between heart rate and blood pressure, central to the success of the intervention. 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 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, to promote accurate HRVB application.

HRVB Training and Manual Refinement: Study clinicians will receive intensive training from our team who will provide ongoing clinical supervision and consultation. In addition to prescribed study measures, study 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 (completing <75% of at-home practice sessions; and/or at-home sessions average < 10m of practice) will be asked a structured series of questions by their clinician to help determine what is promoting or obstructing adherence. Together, a combination of qualitative, interview, objective, and self-report data will be consolidated and provided to the research team and will be used to adapt HRV-SCT intervention accordingly.

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 two in-person training sessions, and homework will not be assigned until after the second

session. We hope that this prevents formation of bad habits and increases the likelihood of adherence. To address adherence, we have put in place several strategies. Participants who do not have iPhones 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 10; 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.

Compensation: Participants will receive up to $455 in total study compensation. This includes $10 to $25 per week, depending on whether they include a recording session, $50 for their 3-month follow-up appointment, and a $50 bonus for attending all sessions. Additionally subjects will be paid up to $15 each week for at home breathing practice from weeks 1-15.

B. *What data points will be collected including long-term follow-up?*
Data will be collected over the course of 16 weeks, which include ten in-person laboratory sessions (Tables 1), and will include interview, self-report, behavioral, and psychophysiological assessment.

C. *Define the duration of the study and the length of time each subject will participate in the study.*
Following the baseline session, which will last 1-3 hours, participants will be asked to complete 10 intervention sessions over the course of 7 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. *Describe any primary and secondary study or safety endpoints*
N/A

1.4 Preliminary Data
N/A

1.5 Sample Size Justification
The goal of this study is for n=10 to complete at least one intervention session. We will consent up to n=15 participants for this study as we anticipate that a portion of individuals attending a Week 0 appointment will not be eligible for the intervention, based upon our extensive inclusion/exclusion criteria. The target sample size of n=10 for the current project was selected to allow our study team to develop, refine, and test, via open trial, HRVB-SCT on two cohorts of 5 participants, prior to scaling the intervention for a larger randomized clinical trial. Data will not undergo rigorous statistical testing and will instead be examined qualitatively, and used to adjust our study protocol.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

All participants will receive the active intervention, HRVB-SCT as part of this uncontrolled open trial. Please see ***1.3 Research Design and Methods*** for details.

B. Dependent Variables or Outcome Measures

The following list of measures will be used to assess therapist credibility, treatment fidelity and acceptability, and participant adherence. We will also examine treatment utility via examination of whether participants make a quit attempt, as well as changes in withdrawal, urges, overall use of cigarettes, and anxiety and depression symptoms.

Credibility and Expectancy Questionnaire to assess treatment expectancy and credibility of intervention rationale.
Post-Intervention Acceptance Ratings (Participant and Therapist versions): To assess treatment acceptability.
Ratings of Session Protocol Adherence and Examination of Physiological Data for Intervention Accuracy: To assess treatment fidelity.
Minnesota Nicotine Withdrawal Scale
Questionnaire of Smoking Urges
Timeline Followback interview will be used to assess ongoing cigarette, e-cigarette, patch, alcohol, and other tobacco use.
Depression Anxiety Stress Scale (DASS-21) to assess for past week symptoms of depression, anxiety, and stress.

1.7 Drugs/Devices/Biologics

Nicotine replacement therapy. The nicotine patch is an accepted, FDA approved treatment for nicotine dependence. Patches are available over-the-counter (OTC) without a prescription. Study participants will be provided with information written at a 6th grade level describing the proper use of the nicotine 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) *Storage and accountability.* We will store nicotine replacement therapy (NRT) in original packaging (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.

b) *Inventory.* We will use an NRT inventory log to document the Lot # and Expiration date of each box of NRT.

c) *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 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 Interviews, Focus Groups, or Surveys

N/A

1.10 Timetable/Schedule of Events

The proposed timeline is based on project completion within three years.

Table 4. Timeline for Proposed Research

Months	Goals
1-3	Draft initial manual; obtain feedback from consultants; revise manual; conduct staff training, begin recruitment.
4-5	Conduct open trial for cohort 1 (n=5) through quit week.
6	Initial revisions to protocol. Update IRB of proposed revisions, if applicable.
7-8	Cohort 2, open trial (n=5) through week 6.
9-10	Finalize protocol revisions, prepare IRB submission for subsequent randomized clinical trial. Open trial participants complete 3-month follow-up.

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: Min-Jeong Yang, Mark Versella, and Allison Borges have each completed extensive training in evidence-based smoking cessation treatment and will serve as study clinicians and independent assessors.
Research Coordinator: Amy Gong has participated in several studies in our lab. She will be responsible for study coordination, including scheduling, compensation, dispensing NRT, and randomization.
Key Study Personnel: Drs. Leyro, B. Vaschillo, and Lehrer will be responsible for clinical training and supervision of personnel and Dr. Leyro will provide general project oversight, including training in all study procedures, IRB correspondence, documentation of all adverse events, and data safety monitoring board communication. Drs. Bates and E. Vaschillo 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.
Undergraduate Research Assistants: Undergraduate RAs will undergo extensive training in addition to their prior experience in the lab and will assist in screening potential participants, scheduling appointments, recording physiological data and communicating select study information to participants.

2.2 Resources Available

A. Facilities

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

B. Medical Or Psychological Resources

Study risks are minimal and include an increase in distress as a result of the speech tasks; 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 physiological monitoring equipment; abrasions should not be more intensive than removal of bandaids.

C. Research Staff Training

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.

Training will also include careful assessment of clinician adherence, defined as using the correct skills, as well as competence, meaning, 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, 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.

Study clinicians will receive intensive training from Drs. Leyro, Lehrer, and B. Vaschillo 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. Together, a combination of qualitative, interview, objective, and self-report data will be consolidated and provided to the research team, and be used to adapt HRV-SCT intervention accordingly prior to the Phase II RCT.

3.0 Multi-Site Research Communication & Coordination

N/A

3.1 Outside Research

N/A

4.0 Research Data Source/s

4.1 Primary Data-Subjects and Specimens

N/A

4.2 Subject Selection and Enrollment Considerations

A. Recruitment Details

We will consent up to 15 participants from the greater Rutgers, New Brunswick, NJ area with a target of n=10 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 over the course of six months through posters, leaflets, mailings, online advertisements, community outreach (i.e., meetings with local organizations and treatment providers who work with cigarette smokers), and listservs.

B. Source of Subjects

Community participants in the greater New Brunswick and Central New Jersey area.

C. Method to Identify Potential Subjects

Study advertisements will be posted in the greater New Brunswick area and Central New Jersey. Online advertisements will be posted via social media platforms and will target potential participants based on demographic criteria including age and gender. Advertisements will also be posted in health-related clinics and institutes in the area.

D. 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) ability to read and speak English fluently, and (4) computer 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) self-reported pending legal issue with potential to result in incarceration; (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 > 30); (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.

E. Recruitment Materials

Prospective participants will be recruited from the greater Rutgers University area in New Brunswick, New Jersey via posting flyers in the community and via social media. In addition, information on our study will be printed in local and University print and online papers, forums, and listservs.

F. Lead Site Recruitment Methods

N/A

4.3 Subject Randomization

N/A

4.4 Secondary Subjects

N/A

4.5 Number of Subjects

A. Total Number of Subjects

Up to 15 participants will be consented with a target enrollment of n=10.

B. Total Number of Subjects If Multicenter Study

N/A

C. Require Number of Subjects to Complete Research

N/A

Please see the response in 4.5.A above.

D. Feasibility of Recruiting

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 (e.g., Baker et al(Baker et al., 2007)).

4.6 Consent Procedures

A. Consent

- **Documenting Consent**

The PI or supervised/trained RAs will complete all aspects of the consent procedures. Verbal consent will be obtained for the initial phone screen. The PI or RA 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, procedure, 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**

  N/A
- **Waiver or Alteration of Consent Process**
  - **(i) Waiver or Alteration Details**

    N/A
  - **(ii) Destruction of Identifiers**

    N/A
  - **(iii) Use of Deception/Concealment**

    N/A

B. 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 in-person meeting at our research offices, or at the agency at which the participant is associated, 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 with the DSMB to determine adverse event reporting, and will be detailed in all continuing review procedures.

- **Individual Roles for Researchers Involved in Consent**

PI supervised/trained graduate students and research assistants will complete all aspects of the consent procedures.

1. 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.

2. 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.

3. 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.

4.7 Special Consent/Populations

A. Minors-Subjects Who Are Not yet Adults

- **Criteria for Consent of Minors**

N/A

- **Wards of the State**

N/A

- **Parental Permission**

N/A

- **Non-Parental Permission**

N/A

- **Assent Process**

N/A

- **Non-English Speaking Subjects**

N/A

1. Process for Non-English Speaking Subjects

N/A

- **Short Form Consent for Non-English Speakers**

N/A

B. Adults Unable to Consent / Cognitively Impaired Adults (*for interventional studies*)

- **NJ Law-Assessment of Regaining the Capacity To Consent**

N/A

- **Capacity To Consent**

N/A

- **NJ Law-Selecting A Witness**

N/A

- **Removing a Subject**

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 the designated DSMB to make a determination regarding communicating when and how to communicate information to the IRB or funding agency (NIDA).

4.8 Economic Burden and/or Compensation for Subjects

A. Expenses

Participants may incur costs of transportation to arrive at the study site. Travel and transportation costs will not be reimbursed. 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 $455 in total study compensation. This includes $10 to $25 per week depending on whether they include a recording session, $50 for their 3-month follow-up appointment (see Table 1), and a $50 bonus for attending all sessions. Additionally subjects will be paid up to $15 each week for at home breathing practice from weeks 1-15.

C. Compensation Documentation

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

4.9 Risks to Subjects

A. Description of Subject Risk

(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 interventions. 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. 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.

(5) 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.

(6) 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.

(7) Breach of Confidentiality: There is a risk that confidential information about a participant may be revealed. 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.

B. Procedures for Risks to Embryo, Fetus, and/or Pregnant Subjects

N/A

C. Risks 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.

- **Risk Of Imposing An Intervention On Subject With Existing Condition**

N/A

- **Other Foreseeable Risks**

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.

- **Observation And Sensitive Information**

N/A

E. Minimizing Risks

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 themself, we will contact Acute Psychiatric Services (855-515-5700).

F. 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.

G. 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 assigned to HRVB will experience additional reductions in anxiety and depressive symptoms, and improved physiological health as determined by indices of autonomic balance.

H. 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.

I. Research Team Access to Subject Data

Only IRB approved staff will have access to participant data. All data will be coded by arbitrary study number to ensure confidentiality and will be stored in a locked filing cabinet or stored on the lab server where access will be password-protected. Data collected online will be de-identified (e.g., associated with an arbitrary study ID number) and only accessible to trained study personnel. Consent forms with identifying information (names) will be filed separately from actual study data in a separate locked filing cabinet. The list linking participant ID with name will be kept in a separate locked cabinet from de-identified data, and a digital copy will be maintained locally in a password-protected file, located within a password-protected database on an encrypted computer. Locked cabinets and the locked office in which they are kept will ensure that all data also double-locked.

4.10 Secondary Data – Records/Chart Reviews/Databases/Tissue Banks/etc.

N/A

4.11 Chart/Record Review Selection

N/A

4.12 Secondary Specimen Collection

N/A

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

N/A

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 NJ Access to Medical Research Act

N/A

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

A. "Special" Classes Of Subjects

N/A

6.0 Research Data Protection and Reporting

6.1 Data Management and Confidentiality

All copies of records, behavioral tests, audio and video recorded, 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 the baseline session, we will obtain consent, verify inclusion/exclusion criteria, assess smoking status, complete a diagnostic interview, 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.

A. *Data analysis plan*

The current study is underpowered for statistical examination of intervention effects, which are not the primary study aims. Instead, fidelity, adherence, and acceptability of the intervention will be examined using data acquired via self-report, physiological, and phone app data from participants, therapist report of session quality and ease, and rating of recorded sessions. We will also assess whether participants engage in a quit attempt and report decreases in withdrawal, urge, cigarette use, and anxiety and depression symptoms.

B. *Power analysis*

N/A The goal of this project (N=10) is to provide preliminary data to examine the feasibility and acceptability of a novel smoking cessation intervention.

C. *Securing data*

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.

D. *Quality control*

Qualtrics and Excel databases will be created in such a way as to not allow for out of range data.

In addition, the following strategies will be employed to minimize study attrition and maximize data collection: Randomized participants will begin treatment within one week of consent. During the first visit, study staff will emphasize the participant's responsibility for engagement and commitment to their quit program and our intervention, reiterate confidentiality, and work to establish strong rapport with participants, including discussing their training, expressing enthusiasm to work with the participant, and addressing questions and concerns. Study staff will follow a detailed protocol to address participant lateness or absenteeism based on work by Hall et al,(Hall et al., 2011; Hall et al., 2009; Hall, Humfleet, Reus, Muñoz, & Cullen, 2004; Hall, Muñoz, & Reus, 1994; Hall et al., 1996; Hall et al., 1998) whose extended smoking cessation interventions boast retention rates of nearly ~90%.

Specifically, participants will complete a tracking form to obtain names and contact information, including telephone numbers, home, and email addresses of four individuals who may be contacted by study staff if we are unable to reach the participant.

Participants will not be considered lost to follow-up at any data point until they: (1) fail to return three calls when messages are left; (2) fail to attend three appointments; and (3) refuse an outreach visit by staff.

If this occurs, we will attempt to obtain smoking data by telephone verification from contacts, and encourage completion of questionnaire data via online survey link or mail. Participants will be contacted for all assessments independent of whether or not they continued treatment. In addition, at each visit, participants will receive a written reminder of their next appointment, and reminder calls/texts will be placed 48 and 24 hours prior to study visits that occur one-week apart, and one- and two-weeks prior to the 3-month follow-up.

We anticipate that the majority of study attrition will occur early in treatment or during the follow-up period. Accordingly, we have front-loaded intervention sessions during weeks 1 and 2 (see ***Table 1***), where clinicians will build rapport and implement psychoeducation strategies and provide a credible treatment rationale. In addition to promoting HRVB practice during treatment, we will provide ongoing monetary compensation for routine practice during weeks 7 through 16.

E. *Data handling*

Study data will be linked to an arbitrary study number. Data will not be linked to protected health information. Data will only be accessed and handled by IRB approved study personnel and kept in password protected databases.

Data will be kept indefinitely to allow for future secondary data analyses, which may require looking at original raw data. However, to ensure confidentiality, data will remain coded by an arbitrary study number. Data will continue to be stored and a locked office and locked cabinet. Data stored on computers will be double password protected.

Dr. Leyro, the study PI, is responsible for the receipt and transmission of data.

Data will not be transported or shared with any individuals aside from named study staff without explicit IRB approval. Data will only be accessible on password protected laboratory computers.

6.2 Data Security

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 separately 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. 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.

6.3 Data and Safety Monitoring

Dr. Leyro has developed a detailed data safety and monitoring plan and board that can be found in the attachment. Please note that the DSMP, submitted to the funding agency (NIH/NIDA) was designed to be used for both the open and randomized clinical trial (to be submitted to IRB for approval at a later date) phases of the study.

A. Periodic Data Evaluation
Please see DSMP
B. Type of Data Evaluated
Please see DSMP
C. Collection of Safety Information
N/A
D. Frequency of Data Collection
Please see DSMP
E. Reviewer of Data
Please see DSMP
F. Schedule of Review of Cumulative Data
Please see DSMP
G. Tests for Safety Data
Please see DSMP
H. Suspension of Research
Please see DSMP

6.4 Reporting Results

A. Sharing of Results with Subjects

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. Individual Results

N/A

C. Aggregate Results

N/A

D. 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.

E. ClinicalTrials.Gov Registration and Data Reporting

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, masking 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.
3. 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, reporting groups, and randomization assignment), demographic and baseline characteristics (e.g., race/ethnicity, sex/gender, age, cigarettes smoked daily; total and separated by randomization), key outcome measures and analyses, serious and other adverse events, and limitations and caveats.

6.5 Data Sharing

Please see section 6.4.E. We will follow data sharing mandates in accord with registration on clinicaltrials.gov. Our consent form will detail requirements associated with this policy to ensure participants are aware of this policy.

7.0 Data and/or Specimen Banking

N/A

8.0 Other Approvals/Authorizations

N/A

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